Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 1937–1940

# NMR study of 1-aryl-1,2-dicarba-*closo*-dodecaboranes: intramolecular C–H···O hydrogen bonding in solution

Kiminori Ohta, Hiroto Yamazaki and Yasuyuki Endo*

*Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1, Komatsushima, Aoba-ku, Sendai 981-8558, Japan*

Received 15 December 2005; revised 13 January 2006; accepted 16 January 2006
Available online 2 February 2006

**Abstract**—Dicarba-*closo*-dodecaborane(12) (carborane) has recently received much attention as a building block for supramolecular assemblies and bioactive compounds. Among carborane isomers, 1,2-dicarba-*closo*-dodecaborane(12) (*o*-carborane) has unique chemical properties, including the ability of the *o*-carborane C–H hydrogens to form hydrogen bonds. To evaluate intramolecular hydrogen bond formation between the *o*-carborane C–H hydrogen and various hydrogen bond acceptors in solution, we have designed and synthesized 1-aryl-*o*-carboranes **2**. Intramolecular hydrogen bonding ability was evaluated by means of $^1$H NMR measurement of the *o*-carborane C–H hydrogen signal of **2**. The 1-(2-methoxyphenyl)-*o*-carborane derivative **2m** appeared to form an intramolecular hydrogen bond between *o*-carborane C–H hydrogen and the oxygen atom acting as a hydrogen bonding acceptor. In this study, we present evidence for hydrogen bond formation in solution between the *o*-carborane C–H and hydrogen bond acceptors positioned with appropriate geometry.


The potential utilization of 1,2-dicarba-*closo*-dodecaborane, *o*-carborane, as a building block for bioactive compounds, supramolecular assemblies and macrocyclic molecules containing carboranes (carboracycles) has recently been the subject of many reports.[1] The C–H protons of *o*-carborane are highly acidic ($pK_a = 22.0$), owing to the electron deficiency of the carborane cage, and consequently have the potential for hydrogen bond formation.[2] Thus, supramolecular structures utilizing *o*-carborane are mainly generated by hydrogen bonding via the acidic *o*-carborane C–H vertices.[3] *o*-Carborane C–H hydrogens interact with various substituents, such as halogens[4] and π systems,[5] as well as hydrogen bond acceptors.[6] It is especially interesting in relation to the potential of *o*-carborane C–H hydrogen for hydrogen bond formation that 3-iodo-*o*-carborane forms a beautiful zigzag network structure through intermolecular C–H···I interactions in the X-ray crystal structure.[4b] Interactions involving *o*-carborane C–H hydrogen in crystal structures have been studied in detail, but there are only two reports concerning solution structures.[7]

Most drugs interact dynamically with receptors in vivo,[8] and hydrogen bonding plays an important role in the process. The key factor in the utilization of *o*-carboranes in medicinal chemistry and other fields is therefore an understanding of dynamic interactions in solution, rather than static interactions in crystals. Thus, we focused on developing an understanding of the interactions between *o*-carborane C–H hydrogen and various substituents in solution.

To examine hydrogen bond formation between *o*-carborane C–H hydrogen and various hydrogen bond acceptors in solution, we designed 1-(2-substituted phenyl)-*o*-carboranes, which appear to form an intramolecular hydrogen bond between *o*-carborane C–H hydrogen and various substituents introduced onto the *ortho* position of the benzene ring. We also designed various 1-aryl-*o*-carboranes with substituents at *meta* or *para* positions as negative controls for evaluation of intramolecular hydrogen bond formation (Fig. 1). These designed compounds **2** were readily synthesized by a conventional method, that is, cyclization of acetylene derivatives with decaborane(14) in the presence of acetonitrile as a Lewis base (Scheme 1).[9]

Table 1 shows the $^1$H NMR chemical shift values of C–H hydrogen of *o*-carborane in various 1-aryl-*o*-carborane derivatives. The $^1$H NMR measurements were carried

*Keywords*: Intramolecular C–H···O interaction; *o*-Carboranes; Supramolecular chemistry.
* Corresponding author. Tel.: +81 22 234 4181; fax: +81 22 275 2013; e-mail: yendo@tohoku-pharm.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.072

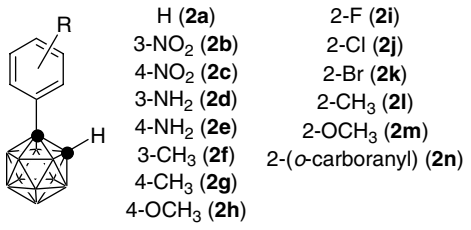
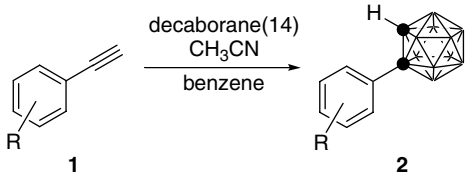



**Figure 1.** Structures of various compounds designed for examination of intramolecular hydrogen bond formation.




**Scheme 1.** Synthesis of 1-aryl-*o*-carboranes.

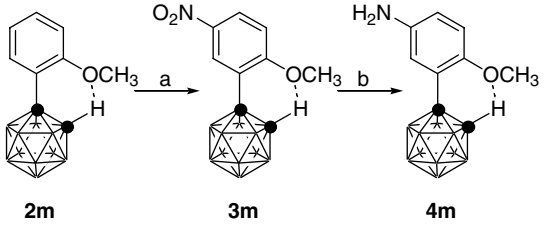
**Table 1.** The $^1$H NMR chemical shift values of *o*-carborane C–H hydrogen in various 1-aryl-*o*-carborane derivatives

| Compound | Chemical shift $CDCl_3$ (ppm) | Compound | Chemical shift $CDCl_3$ (ppm) |
|---|---|---|---|
| **2a** | 3.97 | **2i** | 4.67 |
| **2b** | 4.03 | **2j** | 5.50 |
| **2c** | 4.02 | **2k** | 5.74 |
| **2d** | 3.93 | **2l** | 4.57 |
| **2e** | 3.83 | **2m** | 5.36 |
| **2f** | 3.97 | **2n** | 4.95 |
| **2g** | 3.92 | | |
| **2h** | 3.85 | | |

out at 25 °C in $CDCl_3$ with a 270 MHz NMR spectrometer. The chemical shift value of C–H hydrogen in phenyl-*o*-carborane **2a**, which was taken as a standard compound in this study, was 3.97 ppm. The introduction of a nitro group as an electron-withdrawing group onto the benzene ring of **2a** shifted the C–H hydrogen signal to lower field, the values for 3-nitrophenyl-*o*-carborane **2b** and 4-nitrophenyl-*o*-carborane **2c** being 4.03 and 4.02 ppm, respectively. When electron-donating groups, such as amino, methyl, and methoxyl groups, were introduced onto the phenyl ring, the C–H hydrogen signal remained the same as in **2a** or was shifted to higher field (Table 1; **2d**–**h**). The changes of the chemical shift values of the C–H hydrogen can be explained in terms of the changes of electron density of the C–H bond caused by the substituents introduced onto the phenyl ring. These observations are consistent with the well-known anisotropic effect, which relates the effect of an external magnetic field and the electron density of the C–H hydrogen.[10]

On the other hand, the introduction of substituents at the *ortho* position to *o*-carborane resulted in downfield shifts of the *o*-carborane C–H hydrogen signal, presumably owing to a steric repulsion effect: substituents introduced at the *ortho* position disturb the electron cloud of the *o*-carborane C–H hydrogen.[10] Here, we paid particular attention to the chemical shift values of 1,2-bis(*o*-carboranyl)benzene **2n**, 2-bromophenyl-*o*-carborane **2k** and 2-methoxyphenyl-*o*-carborane **2m**. Recently, we reported that the central benzene ring of **2n** is distorted by the steric repulsion between the two neighboring bulky *o*-carborane rings.[11] Though **2n** is the most sterically hindered of the present derivatives, it is noteworthy that the chemical shift values of C–H hydrogen of **2k** and **2m** were remarkably larger than that of **2n**. Moreover, it is also noteworthy that the chemical shift value of 2-fluorophenyl-*o*-carborane **2i** was larger than that of **2l**, even though the van der Waals radius of the fluorine atom, 1.47 Å, is smaller than that of carbon, 1.70 Å.[12] We considered that these findings were consistent with the presence of hydrogen bonding between hydrogen bond acceptors in substituents introduced at the *ortho* position and *o*-carborane C–H hydrogen.

Next, we examined the effect on the chemical shift value of *o*-carborane C–H hydrogen caused by the changes of electron density on the oxygen atom in **2m**. The effects of nitration and subsequent reduction of **2m** is shown in Figure 2.[13] Interestingly, the introduction of a nitro group as an electron-withdrawing group at the *para* position to the methoxyl group in **2m** led to a remarkable upfield shift of the *o*-carborane C–H hydrogen $^1$H NMR signal (Fig. 2; **3m**) in spite of the introduction of the electron-withdrawing group, which should induce a downfield shift of the C–H hydrogen signal owing to the anisotropic effect (Fig. 2; **2b** and **2c**). In addition, the introduction of an amino group into **2m** induced a slight downfield shift of the C–H hydrogen (Fig. 2; **4m**) in opposition to the general electronic effect (Fig. 2; **2h**). These fascinating results can be accounted for as follows: since the electron density of the two unshared electron pairs on the oxygen atom of the methoxyl group was decreased by the introduction of a nitro group, hydrogen bonding between *o*-carborane C–H hydrogen and the oxygen atom of the methoxyl group became weaker, while in the case of the amino group as an electron-donating group, the hydrogen bond became stronger owing to an increase of the electron




| compound | chemical shift $CDCl_3$, (ppm) |
|---|---|
| **2m** | 5.36 |
| **3m** | 5.18 |
| **4m** | 5.38 |

**Figure 2.** Effect of nitration and subsequent reduction on the *o*-carborane C–H hydrogen signal. (a) $HNO_3$, c.$H_2SO_4$, $CH_2Cl_2$; (b) Pd/C, $H_2$, EtOH.

density on the oxygen atom. Therefore, we suggest that these results imply the formation of an intramolecular hydrogen bond between *o*-carborane C–H hydrogen and the oxygen atom in solution.

To seek further evidence of hydrogen bond formation between the oxygen atom in the methoxyl group and *o*-carborane C–H hydrogen in solution, we evaluated the change of the chemical shift values of *o*-carborane C–H hydrogen in **2a** and **2m** in various solvents labeled with deuterium and estimated the differences between the highest value and the lowest value of **2a** and **2m**, respectively (Table 2). The chemical shift value of the C–H hydrogen in **2a** was the smallest in benzene-$d_6$, 2.92 ppm, and the largest in DMSO-$d_6$, 5.79 ppm. There was a remarkable solvent effect on the $^1$H NMR spectra of **2a** and the difference (Δ ppm) was 2.87 ppm. In general, aromatic solvents cause an upfield shift of the hydrogen signal due to the shielding effect.[10] Compound **2a** also showed a remarkable upfield shift of the *o*-carborane C–H hydrogen signal in aromatic solvent. In DMSO-$d_6$, some hydrogens often show a downfield shift owing to hydrogen bond formation with oxygen of DMSO. The C–H hydrogen of **2a** exhibited a remarkable downfield shift, which we ascribed to intermolecular hydrogen bond formation between the C–H hydrogen and oxygen of DMSO. The C–H hydrogen of **2a** may also hydrogen bond with the solvent oxygen in $CD_3OD$. These results indicate that *o*-carborane C–H hydrogen may exhibit C–H$\cdots\pi$ interaction as well as hydrogen bond formation.

On the other hand, we were surprised to find hardly any solvent effect in **2m**. The C–H hydrogen of **2m** exhibited remarkable downfield shifts in all solvents examined. The difference was small (e.g., 0.76 ppm), although there should be a shielding effect of the aromatic ring in benzene-$d_6$. We concluded from the results that the C–H hydrogen of **2m** forms a hydrogen bond at all times; that is, the solvent effect could not be observed because the C–H hydrogen of **2m** forms an intramolecular hydrogen bond with the oxygen atom of the methoxyl group. Moreover, the difference of the chemical shift value of the C–H hydrogens between **2a** and **2m** in DMSO-$d_6$ is the smallest (0.19 ppm), and we suggested that the C–H hydrogens of **2a** and **2m** form a similar hydrogen bond in solution.

In summary, we have designed and synthesized 1-aryl-*o*-carboranes, and evaluated their ability to form a hydrogen bond in solution between *o*-carborane C–H hydrogen and hydrogen bond acceptors, by means of $^1$H NMR spectral measurements. We found that the 1-(2-methoxyphenyl)-*o*-carborane **2m** forms an intramolecular hydrogen bond between *o*-carborane C–H hydrogen and the oxygen atom of the methoxyl group in solution. This information should aid the application of *o*-carborane to supramolecular chemistry, medicinal chemistry and materials chemistry, and it should become possible to design and create novel interesting molecules by utilizing the hydrogen bonding ability of *o*-carborane C–H hydrogen, as well as the high hydrophobicity of *o*-carborane cage.

**Table 2.** The change of chemical shift value of C–H hydrogen of the *o*-carborane of **2a** and **2m**

| Solvent | Chemical shift (ppm) of **2a** | Chemical shift (ppm) of **2m** | (Δ ppm) **2m** − **2a** |
|---|---|---|---|
| Benzene-$d_6$ | 2.92 | 5.22 | 2.30 |
| $CDCl_3$ | 3.97 | 5.36 | 1.39 |
| $CD_3OD$ | 5.09 | 5.67 | 0.58 |
| DMSO-$d_6$ | 5.79 | 5.98 | 0.19 |
| (Δ ppm) max. − min. | 2.87 | 0.76 | |

## Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (B) (Nos. 13470468 and 16390032) from the Ministry of Education, Culture, Sports, Sciences and Technology, Japan.

## References and notes

1. (a) Grimes, R. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1289; (b) Hawthorne, M. F.; Zheng, Z. *Acc. Chem. Res.* **1997**, *30*, 267; (c) Songkram, C.; Yamasaki, R.; Tanatani, A.; Takaishi, K.; Yamaguchi, K.; Kagechika, H.; Endo, Y. *Tetrahedron Lett.* **2001**, *42*, 5913.
2. (a) Kruglyak, L. I.; Kalinin, V. N.; Rys, E. G.; Zakharkin, L. I.; Shatenstein, A. I. *Zh. Obshch. Khim.* **1972**, *42*, 2670; (b) Leites, L. A. *Chem. Rev.* **1992**, *92*, 279.
3. (a) Harada, A.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1352; (b) Kusukawa, T.; Fujita, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3142; (c) Hardie, M. J.; Raston, C. L. *Chem. Commun.* **1999**, 1153; (d) Frixa, C.; Scobie, M.; Black, S. J.; Thompson, A. S.; Threadgill, M. D. *Chem. Commun.* **2002**, 2876.
4. (a) Lee, H.; Knobler, C. B.; Hawthorne, M. F. *Chem. Commun.* **2000**, 2485; (b) Barbera, G.; Vinas, C.; Teixidor, F.; Rosair, G. M.; Welch, A. J. *J. Chem. Soc., Dalton Trans.* **2002**, 3647.
5. (a) Blanch, R. J.; Williams, M.; Fallon, G. D.; Gardiner, M. G.; Kaddour, R.; Raston, C. L. *Angew. Chem., Int. Ed.* **1997**, *36*, 504; (b) Hardie, M. J.; Raston, C. L. *Eur. J. Inorg. Chem.* **1999**, 195; (c) Hardie, M. J.; Godfrey, P. D.; Raston, C. L. *Chem. Eur. J.* **1999**, *5*, 1828.
6. (a) Davidson, M. G.; Hibbert, T. G.; Howard, J. A. K.; Mackinnon, A.; Wade, K. *Chem. Commun.* **1996**, 2285; (b) Godfrey, P. D.; Grigsby, W. J.; Nichols, P. J.; Raston, C. L. *J. Am. Chem. Soc.* **1997**, *119*, 9283; (c) Harakas, G.; Vu, T.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1998**, *120*, 6405; (d) Macias, R.; Rath, N. P.; Barton, L. *J. Organometal. Chem.* **1999**, *581*, 39.
7. (a) Alekseyeva, E. S.; Batsanov, A. S.; Boyd, L. A.; Fox, M. A.; Hibbert, T. G.; Howard, J. A. K.; MacBride, J. A. H.; Mackinnon, A.; Wade, K. *J. Chem. Soc., Dalton Trans.* **2003**, 475; (b) Cappelli, A.; Giorgi, G.; Anzini, M.; Vomero, S.; Ristori, S.; Rossi, C.; Donati, A. *Chem. Eur. J.* **2004**, *10*, 3177.
8. *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Academic Press: UK, 1996.
9. (a) Heying, L. T.; Ager, J. W., Jr.; Clark, S. L.; Mangold, D. J.; Goldstein, H. L.; Hillman, M.; Polak, R. J.; Szymanski, J. W. *Inorg. Chem.* **1963**, *2*, 1089; (b) Paxson, E. T.; Callahan, P. K.; Hawthorne, M. F. *Inorg. Chem.* **1973**, *12*, 708.

10. *Spectrometric Identification of Organic Compounds*, 4th ed.; Silverstein, R. M., Bassler, G. C., Morrill, T. C., Eds., John Wiley & Sons: USA, 1981; p 181.
11. (a) Endo, Y.; Songkram, C.; Ohta, K.; Kaszynski, P.; Yamaguchi, K. *Tetrahedron Lett.* **2005**, *46*, 699; (b) Endo, Y.; Songkram, C.; Ohta, K.; Yamaguchi, K. *J. Organometal. Chem.* **2005**, *690*, 2750.
12. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
13. Ohta, K.; Iijima, T.; Kawachi, E.; Kagechika, H.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5913.