Pergamon

Tetrahedron Letters 40 (1999) 9073–9076

TETRAHEDRON LETTERS

# Electronic effects of icosahedral carboranes. Friedel–Crafts acylation of 1-phenyl-1,2-, 1,7-, and 1,12-dicarba-*closo*-dodecaboranes

Yasuyuki Endo * and Yoshiyuki Taoda

*Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Received 8 September 1999; revised 27 September 1999; accepted 1 October 1999

**Abstract**

Friedel–Crafts acylation of the benzene nucleus of 1-phenyl-1,2-, 1,7- and 1,12-dicarba-*closo*-dodecaboranes (phenylcarboranes) proceeded in the presence of trifluoromethanesulfonic acid. In spite of the strong electron-withdrawing effect of the carborane skeleton, *para*-acylated products predominated. However, substitution of a methyl group at the 2-position of 1-phenyl-1,2-carborane resulted in a change of isomer distribution. 

*Keywords:* carboranes; electronic effects; Friedel–Crafts reactions.

Icosahedral *closo* carboranes have been described as three-dimensional aromatic systems, and the implications for electronic interaction with substituents have been of particular interest since the first synthesis of these compounds.[1] Investigations of the $pK_a$s of carboranylbenzoic acids and carboranylanilinium ions,[2] and of the $^{19}F$ NMR chemical shifts of carboranylfluorobenzenes,[3] showed that the icosahedral carboranes behave as strongly electron-withdrawing groups in the sequence *ortho*>>*meta*>*para* towards carbon substituents. These investigations also showed that the electron-withdrawing inductive effect of the carborane cage is similar to that of the halogens, and that ground-state cage-ring-π interaction is not important. In spite of the strong inductive electron-withdrawing effect, nitration of the benzene ring of 1-phenyl-1,2-dicarba-*closo*-dodecaborane (1-phenyl-*o*-carborane) predominantly afforded the *para*-nitrophenyl derivative.[2] Other extensive investigations of electrophilic substitution reactions of the benzene ring of 1-phenyl-1,2-, 1,7- and 1,12-dicarba-*closo*-dodecaboranes (1-phenyl-*o*-, *m*- and *p*-carboranes) have shown that the reactions take place with difficulty on account of the strong inductive electron-withdrawing effect of the carborane cage.[4,5] Friedel–Craft acylation of 1-phenyl-*o*-, *m*- and *p*-carboranes with acyl halides in the presence of aluminum chloride did not take place at all.[6] We have focused on the design, synthesis and biological evaluation of carborane-containing biologically active molecules in order to utilize carboranes as a hydrophobic pharmacophore.[7–9] For these studies,

* Corresponding author. Tel: +81 3 5841 4734; fax: +81 3 5841 4768; e-mail: yendo@mol.f.u-tokyo.ac.jp

0040-4039/99/$ - see front matter 
*PII:* S0040-4039(99)01911-5

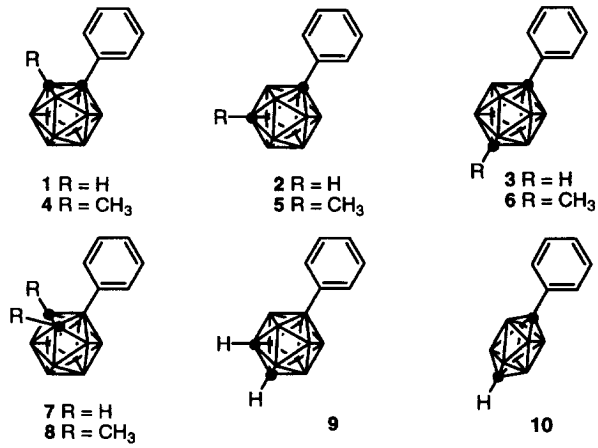


Figure 1. In the cage structure ● represents a carbon atom and other vertices represent BH units

a functionalization method for 1-phenylcarboranes is required so that we can introduce carboranes as a component of the designed molecules. In this paper, we describe the Friedel–Crafts acylation of 1-phenyl-*o*-, *m*- and *p*-carboranes and the isomer distributions of the products.

Trifluoromethanesulfonic acid, TFSA is an effective catalyst for Friedel–Crafts acylation.[10] It has been demonstrated that the major active species of the acylation in the reaction with deactivated benzenes in TFSA is the protonated acyl cation.[11] The carborane cage has been reported to be stable under acidic conditions, at least at room temperature.[12] We therefore performed model acylation experiments, initially using 1-phenyl-*o*-, *m*- and *p*-carboranes (**1**, **2**, **3**) with acetyl chloride in an excess of TFSA. The structures of the substrates are shown in Fig. 1 and the results are summarized in Table 1. Reaction of **2** and **3** with acetyl chloride (10 equiv.) in the presence of TFSA (100 equiv.) at 60°C smoothly proceeded to give the corresponding *meta*- and *para*-acetophenone derivatives (approximately 1:3) in yields of more than 95%.[13] Acetylation of **1** did not proceed effectively under the same conditions while, when acetyl cholide (10 equiv.) was added twice more at intervals of 12 h in the presence of TFSA (200 equiv.), the *meta*- and *para*-acetophenone derivatives (39:61) were obtained in 53% yield after 36 h. However, substitution of the 2-position of **1** by a methyl group (**4**) decreased the reaction rate and the ratio of *m*-:*p*-isomers changed to 63:37. A methyl group at CH on the carborane cage did not affect the reactivity or isomer distribution of the other methylated 1-phenyl carboranes (**5**, **6**). A similar alteration of isomer distribution has been reported in the case of nitration of **1**[2] and 2-substituted-1-phenyl-*o*-carborane,[14] although a systematic investigation was not performed.

Reaction of 3-phenyl-*o*-carborane (**7**)[15] under the same conditions as in the case of **2** and **3** also proceeded effectively to give *meta*- and *para*-acetophenone derivatives (58:42) in 82% yield. The methyl group at CH on the carborane cage did not affect the reactivity or isomer distribution in the case of 1,2-dimethyl-3-phenyl-*o*-carborane (**8**). 9-Phenyl-*o*-carborane should readily undergo electrophilic substitution because of the electron-donating effect ($\sigma I$ −0.16) of the 9-*o*-carboranyl group, and does undergo Friedel–Crafts acetylation with aluminum chloride.[6] Reaction of 9-phenyl-*o*-carborane (**9**) using the present TFSA condition proceeded effectively to give *meta*- and *para*-acetophenone derivatives (24:76) in 86% yield. The compound bearing the 10-vertex carborane, 1-phenyl-1,10-dicarba-*closo*-decaborane (**10**) also reacted with acetyl chloride in the presence of TFSA to give *meta*- and *para*-acetophenone derivatives (5:95) in 92% yield.

The order of reactivity of these phenylcarboranes is consistent with their inductive constant ($\sigma I$) values in the sequence *ortho*>>*meta*>*para* carboranyl towards carbon substituents. The results of the product

Table 1
Friedel–Crafts acetylation and electronic constants of 1-phenyl-1,2-, 1,7- and 1,12-dicarba-*closo*-dodecaboranes and related carboranes

| | | Yield (%)[a] | *meta* (%) | *para* (%) | σI[c] | σR⁰[c] |
|---|---|---|---|---|---|---|
| 1-phenyl-*o*- | 2-H (**1**) | 16 | 38 | 62 | +0.38 | 0 |
| | | 53[b] | 39 | 61 | | |
| | 2-$CH_3$ (**4**) | 5 | 63 | 37 | +0.38 | +0.04 |
| 1-phenyl-*m*- | 7-H (**2**) | 96 | 26 | 74 | +0.21 | -0.02 |
| | 7-$CH_3$ (**5**) | 97 | 25 | 75 | +0.19 | -0.04 |
| 1-phenyl-*p*- | 12-H (**3**) | 95 | 23 | 77 | +0.14 | -0.02 |
| | 12-$CH_3$ (**6**) | 90 | 25 | 75 | | |
| 3-phenyl-*o*- | 1,2-H (**7**) | 82 | 58 | 42 | +0.11 | +0.07 |
| | 1,2-di $CH_3$ (**8**) | 96 | 63 | 37 | +0.18 | +0.04 |
| 9-phenyl-*o*- | 1,2-H (**9**) | 86 | 24 | 76 | -0.16 | -0.03 |
| 1-phenyl-1,10-dicarba-*closo*-decaborane | 10-H (**10**) | 92 | 5 | 95 | +0.05 | -0.01 |

a) Condition: 100 eq of $CF_3SO_3H$, 10 eq of $CH_3COCl$, 60°C, 7 h.
b) Condition: 200 eq of $CF_3SO_3H$, 30 eq of $CH_3COCl$ (added 3 times at intervals of 12 h), 60°C, 36 h.
c) lit. 4 and 6

distribution seem to be compatible with the values of $\sigma R^0$. The orientations of the present reactions are presumably related to the fundamental electron-delocalizing effect of the icosahedral carboranes. The formation of *p*- as well as *m*-nitrophenyl derivatives in nitrations of *C*-phenylcarboranes has been reported,[2] while the *m*-nitrophenyl derivative formed predominately in nitrations of trifluoromethylbenzene,[16] which has a purely inductive electron-withdrawing group. An explanation has been proposed in terms of the electron density changes in the radial *sp* hybrid bond of the antipodal atom, which do not affect the NMR chemical shifts.[1] On the other hand, the difference of the product ratios between the acetylation of **1** and **4** may be affected by the difference of their structural geometries[17,18] and closely related to the electronic bonding structure of the two cage carbons in *o*-carboranes, which still remains ambiguous.

In summary, we have developed a Friedel–Crafts acylation of the benzene nucleus of phenylcarboranes, which behave as strongly electron-withdrawing groups. The present findings should be helpful for preparing biologically active molecules and polymers containing a carborane cage, and for theoretical studies of carboranes.

## References


1. Fox, M. A.; MacBride, J. A. H.; Peace, R. J.; Wade, K. *J. Chem. Soc., Dalton Trans.* **1998**, 401–411.
2. Hawthorne, M. F.; Berry, T. E.; Wegner, P. A. *J. Am. Chem. Soc.* **1965**, *87*, 4746–4750.
3. Zakharkin, L. I.; Kalinin, V. N.; Rys, E. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, 2632–2635.
4. Zakharkin, L. I.; Kalinin, V. N.; Snyakin, A. P.; Kvasov, B. A. *J. Organomet. Chem.* **1969**, *18*, 19–26.
5. Kalinin, V. N.; Teplyakov, M. M.; Gelashvili, Ts. P.; Savitskii, A. M.; Dmitriev, V. M.; Zakharkin, L. I. *Dockl. Akad. Nauk SSSR* **1977**, *236*, 367–370.
6. Zakharkin, L. I.; Ol'shevskaya, V. A.; Antonovich, V. A. *Z. Org. Khim.* **1987**, *23*, 1691–1695.

7. Endo, Y.; Iijima, T.; Ohta, K.; Kagechika, H.; Kawachi, E.; Shudo, K. *Chem. Pharm. Bull.* **1999**, *47*, 585–587: Iijima, T.; Endo, Y.; Tsuji, M.; Kawachi, E.; Kagechika, H.; Shudo, K. *Chem. Pharm. Bull.* **1999**, *47*, 398–404.
8. Endo, Y.; Iijima, T.; Yamakoshi, Y.; Yamaguchi, M.; Fukasawa, H.; Shudo, K. *J. Med. Chem.* **1999**, *42*, 1501–1504.
9. Endo, Y.; Yoshimi, T.; Kimura, K.; Itai, A. *BioMed. Chem. Lett.* **1999**, *9*, 2561–2564.
10. Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 151–171.
11. Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037–3043.
12. Brown, D. A.; Colquhoun, H. M.; Daniels, J. A.; MacBride, J. A. H.; Stephenson, I. R.; Wade, K. *J. Mater. Chem.* **1992**, *2*, 793–804.
13. A typical procedure of Friedel–Crafts acylation was as follows: 1-Phenyl-1,12-dicarba-*closo*-dodecaborane (**3**) (0.5 mmol) was diluted with 0.1 ml of dichloromethane and added to a mixture of acetyl chloride (5 mmol) and TFSA (50 mmol) at room temperature with vigorous stirring. The mixture was heated at 60°C (bath temperature) and stirring was continued for 7 h under Ar. The mixture was poured into ice-water and extracted with dichloromethane (3×30 ml). The organic layer was washed with saturated $NaHCO_3$ solution, and brine and dried over $Na_2SO_4$. The solution was concentrated and passed through a silica gel column giving a mixture of 3- and 4-(1,7-dicarba-*closo*-dodecaboran-1-yl)acetophenone (125 mg, 95%). Purification by silica gel column chromatography and recrystallization from *n*-hexane afforded 3- and 4-(1,12-dicarba-*closo*-dodecaboran-1-yl)acetophenone. 3-Isomer: colorless fine needles, mp 102–103°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 3H), 2.82 (s, 1H), 1.6–3.3 (br m, 10H), 7.28 (t, 1H, *J*=8.0 Hz), 7.41 (m, 1H), 7.79–7.81 (m, 2H); HRMS calcd for $C_{10}B_{10}H_{18}O$: 262.2361; found: 262.2341. 4-Isomer: colorless plates, mp 162–163°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3H), 2.83 (s, 1H), 1.6–3.3 (br m, 10H), 7.30 (d, 2H, *J*=8.8 Hz), 7.75 (d, 1H, *J*=8.8 Hz); Anal. calcd for $C_{10}B_{10}H_{18}O$: C, 45.78; H, 6.92; found: C, 45.56; H, 6.63.
14. Maurer, J. L.; Berchier, F.; Serino, A. J.; Knobler, C. B.; Hawthorne, M. F. *J. Org. Chem.* **1990**, *55*, 838–843.
15. Hawthorne, M. F.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 896–901.
16. Coon, C. L.; Blucher, W. G.; Hill, M. E. *J. Org. Chem.* **1973**, *38*, 4243–4248.
17. Brain, P. T.; Cowie, J.; Dononoe, D. J.; Hnyk, D.; Rankin, D. W. H.; Reed, D.; Reid, B. D.; Robertson, H. E.; Welch, A. J. *Inorg. Chem.* **1996**, *35*, 1701–1708.
18. McGrath, T. D.; Welch, A. J. *Acta Cryst.* **1995**, *C51*, 646–647.