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Closo → *nido* cage degradation of 1-(substituted-phenyl)-1,2-dicarbadodecaborane(12)s in wet DMSO under neutral conditions

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Abstract—1-(2-Nitrophenyl)-1,2-dicarba-*closo*-dodecaborane(12) shows C–H···O intramolecular hydrogen bonding in chloroform. The reaction of isomeric 1-(nitrophenyl)-1,2-dicarba-*closo*-dodecaborane(12)s and of 1-(4-fluorophenyl)-1,2-dicarba-*closo*-dodecaborane(12) with wet DMSO causes the removal of 3-B or 6-B, leading cleanly to *nido*-carboranes. The rank order of rates of these deboronations is consistent with developing negative charge in the rate-determining step.

The icosahedral 1,2-dicarba-*closo*-dodecaborane(12) is of current interest in medicinal chemistry as a water-, air- and bio-stable multi-boron entity, which can be attached to tumour-targetting systems.[1,2] Such agents are being designed to address a major issue in boron neutron capture therapy (BNCT) of cancer, that of delivery of sufficient boron (specifically ^{10}B) selectively to tumours, while keeping the concentration of ^{10}B in adjacent normal tissues low.[3] When tumours containing ^{10}B are irradiated with low-energy ('thermal') neutrons, the boron captures the neutrons efficiently (neutron capture cross-section for ^{10}B 3836 barns, cf. 0.0034 barns for ^{12}C). An (n,α) reaction ensues to give a ^{7}Li nucleus and an α-particle with sufficient kinetic energy to propel the α-particle by one cell diameter in tissue. Thus the DNA-damaging and cytotoxic effects of the therapy are limited to the cells in which ^{10}B had been located. Carboranes have been linked to nitroimidazoles,[4–6] porphyrins,[7–9] antibodies[10] and nucleosides,[11] *inter alia*, for tumour-targetting of the boron cluster.

This neutral cluster is notoriously insoluble in water. Several tactics have been adopted to increase the solubility of candidate BNCT agents in biocompatible solvents. These have variously included polyethers[8] and polyols,[12] but the most usual approach to soluble BNCT agents is to degrade the neutral *closo*-carborane cage to the corresponding anionic *nido*-carborane (a C_2B_9 cluster).[13,14] This deboronation has been achieved using several sets of reagents and conditions. The most common is hydroxide ion at elevated temperatures,[15] but amines[14,16] and fluoride[7,17,18] are also used. The disadvantage with these methods is that it is often necessary to use harsh conditions to the potential detriment of other functional groups.

In 1999, Schaeck and Kahl reported that *closo*-carboranes **1** (Scheme 1), which carry strongly electron-withdrawing carbonyl groups at C-1, are degraded in wet DMSO to *nido*-carboranes **2**.[19] Since then, it has been noted[20] that di-(*closo*-carboranyl)sulfoxide **3** is similarly deboronated to *nido*-derivative **4** and that 1-(2,4,5-triazin-2-yl)-*closo*-carboranes **5** are converted into *nido*-carboranes **6** in wet DMSO;[21] in these examples, the carborane is attached directly to a specialist electron-withdrawing group (sulfoxide and a very electron-deficient heterocycle, respectively). We now report that this deboronation can be extended to simpler carboranes, which carry substituted phenyl groups, and that the rate of deboronation depends on the electron-withdrawing character of the substituted phenyl.

1-Phenyl-*closo*-carborane **8** was synthesised in the usual way from decaborane(14) and phenylethyne **7** in

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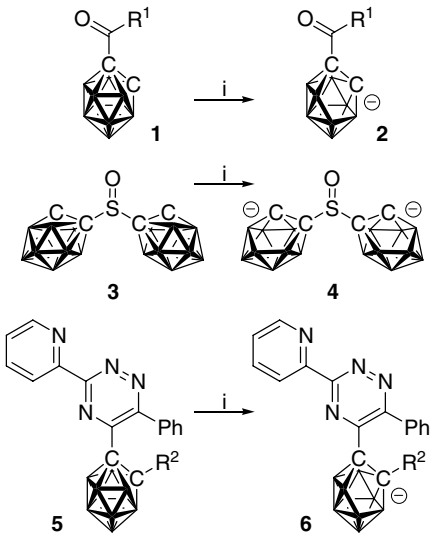


Scheme 1. Degradation of *closo*-carboranes **1**, **3**, **5** carrying strongly electron-withdrawing groups to the corresponding *nido*-carboranes **2**, **4**, **6** in wet DMSO. R^1 = H, OMe; R^2 = Me, Ph. Reagent: wet DMSO.

acetonitrile. Nitration of **8** in dichloromethane with mixed concentrated nitric and sulfuric acids gave a 67% overall yield of a mixture of *para*-, *meta*- and *ortho*-1-(nitrophenyl)-*closo*-carboranes **9a**–**c**, respectively, which was separable by careful silica gel chromatography to afford the pure samples of the individual isomers. The ratios of isolated yields of the mononitrophenylcarboranes formed (**9a**: 49%, **9b**: 16%, **9c**: 2%) corresponded to those observed by GC by Hawthorne et al.[22] in their early studies.

The ^{1}H NMR spectra of **9a**–**c** in $CDCl_3$ were mostly unremarkable (Table 1). The signal for the carborane 2-H in **9c** was at δ 4.30, some 0.3 ppm moved downfield from the corresponding signals in the spectra of **9a**,**b**. This may indicate some O···H–C hydrogen bonding from the adjacent nitro group. Intermolecular hydrogen bonding from the relatively acidic carborane C–H is known but intramolecular hydrogen bonding has only been described for 1-(2-pyridyl)-1,2-dicarba-*closo*-dodecaborane(12) and analogues.[23,24] As expected, when **9a**–**c** were dissolved in $(CD_3)_2SO$ and the spectra recorded immediately, the signals for the Ar–H protons moved downfield somewhat and those for the carborane C–H protons moved to δ 5.9–6.0, consistent with the extensive H-bonding to the solvent.

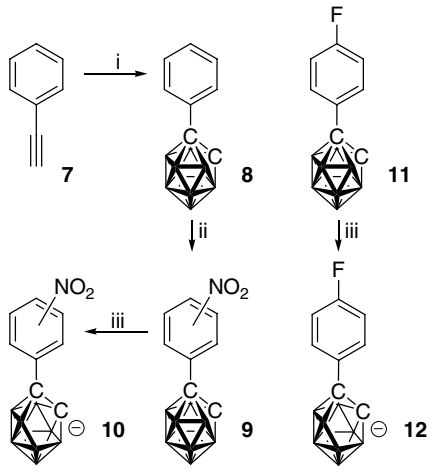
However, after the sample of **9a** in $(CD_3)_2SO$ (containing ca. 4 mol equiv of water) was allowed to stand at ambient temperature for 1 h the spectrum indicated the formation of a single new species in the solution. In this species, the signals for the aromatic protons had moved upfield by 0.26 ppm for 3,5-H_2 and by 0.50 ppm for 2,6-H_2 (Table 1), indicating that the aromatic ring had become more electron-rich. The apparent *para*-benzene substitution pattern was unchanged. Most remarkably, the signal for the carborane C–H had moved upfield by 3.52 ppm. These chemical shifts were shown to be inconsistent with the formation of 1-(4-aminophenyl)-*closo*-carborane by comparison with a spectrum of an authentic sample[25] in $(CD_3)_2SO$. The data suggested the formation of an anionic carborane species. The solution was allowed to stand for 3 d, after which the ^{1}H NMR spectrum showed that the conversion was complete and essentially stoichiometric. Formation of *nido*-carborane **10a** was confirmed by the ^{11}B NMR spectrum (showing nine discrete ^{11}B resonances from the asymmetric *nido*-structure at δ −35.9, −33.2, −23.6, −20.2, −18.6, −17.1, −13.0, −10.6, −9.0 and one for boric acid at δ +19.8) and by the observation of a molecular ion cluster (centred at *m*/*z* 254) in the negative ion FAB MS, with ^{10}B/^{11}B isotope distribution corresponding to a B_9 species. Removal of one of the borons linked to both carbons in the icosahedra of **9a**–**c** was shown by the close similarity of the chemical shifts of the signals in the ^{11}B NMR spectra with those reported for an analogous 4-fluorophenyl *nido*-carborane[18] (Scheme 2).

Similar treatment of isomers **9b**,**c** with DMSO caused complete conversion to the corresponding *nido*-carboranes **10b**,**c**, as confirmed by analogous sets of spectra. Noting that cage degradation of the three isomers by DMSO required different reaction times for completion,

Table 1. ^{1}H NMR chemical shifts for C–H protons in **9a**–**c** and **10a**–**c**

Compound no.	Solvent	Ar–H (δ)	Carborane 2-H (δ)
9a	$CDCl_3$	7.59 (2H, d, J = 9.0 Hz), 8.11 (2H, d, J = 9.0 Hz)	3.95
9a	$(CD_3)_2SO$	7.83 (2H, d, J = 9.0 Hz), 8.21 (2H, d, J = 9.0 Hz)	5.93
9b	$CDCl_3$	7.58 (1H, br t, J = 8.0 Hz), 7.85 (1H, ddd, J = 8.0, 2.0, 1.0 Hz), 8.26 (1H, ddd, J = 8.0, 2.0, 1.0 Hz), 8.32 (1H, t, J = 2.0 Hz)	4.06
9b	$(CD_3)_2SO$	7.72 (1H, dd, J = 9.0, 8.2 Hz), 8.03 (1H, ddd, J = 8.2, 2.3, 1.2 Hz), 7.86 (1H, ddd, J = 8.0, 2.3, 1.2 Hz), 7.87 (1H, t, J = 2.1 Hz)	6.00
9c	$CDCl_3$	7.37 (1H, m), 7.54 (2H, m), 7.89 (1H, m)[a]	4.30
9c	$(CD_3)_2SO$	7.66 (1H, dt, J = 2, 8 Hz), 7.70 (1H, dt, J = 2, 8 Hz), 7.78 (1H, dd, J = 8, 2 Hz), 7.83 (1H, dd, J = 8, 2 Hz)	5.83
10a	$(CD_3)_2SO$	7.33 (2H, d, J = 9.0 Hz), 7.95 (2H, d, J = 9.0 Hz)	2.41
10b	$(CD_3)_2SO$	7.38 (1H, br t, J = 8.0 Hz), 7.54 (1H, br d, J = 8.0 Hz), 7.86 (1H, br d, J = 8.0 Hz), 7.87 (1H, t, J = 2.0 Hz)	2.48
10c	$(CD_3)_2SO$	7.30 (1H, t, J = 8 Hz), 7.33 (1H, d, J = 8 Hz), 7.43 (1H, t, J = 8 Hz), 7.60 (1H, d, J = 8 Hz)	2.45

[a] Nonfirst-order coupling system.



Scheme 2. Synthesis of 1-(nitrophenyl)-*closo*-carborane isomers **9a**–**c** and cage degradation of **9a**–**c** and 1-(4-fluorophenyl)-*closo*-carborane **11** with wet DMSO to *nido*-carboranes **10a**–**c** and **12**, respectively. **a**: 4-nitrophenyl; **b**: 3-nitrophenyl; **c**: 2-nitrophenyl. Reagents: (i) $B_{10}H_{14}$, MeCN; (ii) HNO_3, H_2SO_4; (iii) wet $(CH_3)_2SO$ or $(CD_3)_2SO$.

a kinetic study was carried out. The samples (5.0 mg) of **9a**–**c** in $(CD_3)_2SO$ (0.6 mL) containing H_2O (ca. 4 mol equiv) in 5 mm NMR tubes were kept in the spectrometer at 20 °C. ^1H spectra (400 MHz) were recorded every 4 h for **9a**,**b** and every 1 h for **9c**. The progress of each reaction was monitored by integrating the signals (Ar–H, carborane C–H) for **9a**–**c** and **10a**–**c**. Figure 1 shows the graphs of consumption of **9a**–**c** with time. Each curve fits well with *pseudo*-first order kinetics at short time periods, as reported[26] for deboronation of 1-phenyl-*closo*-carborane with hydroxide, with slight deviations as the reactions near completion. The rank order of reaction rates (**9c** > **9a** > **9b**) is consistent with a mechanism in which the negative charge is built up strongly in the rate-determining step (Hammett $\sigma_{para} = 0.78$ and $\sigma_{meta} = 0.71$ for nitro). The evolution of a colourless gas (presumably H_2)[26] was noted during the reactions. In each experiment, the chemical shift of the residual water signal moved downfield as the reaction progressed, indicating an increasing acidity in the mixture owing to the formation of boric acid (H_3BO_3) from the excised boron atom. A similar cage degradation of 1-(4-fluorophenyl)-*closo*-carborane **11**[18] was much slower (as monitored by ^1H and ^{19}F NMR), only reaching an 84% conversion to **12**[18] after 88 days (Hammett $\sigma_{para} = 0.06$ for fluoro). As expected, raising the temperature increased the reaction rate, with the conversion of **11** to **12** being essentially complete after 24 h at 100 °C.

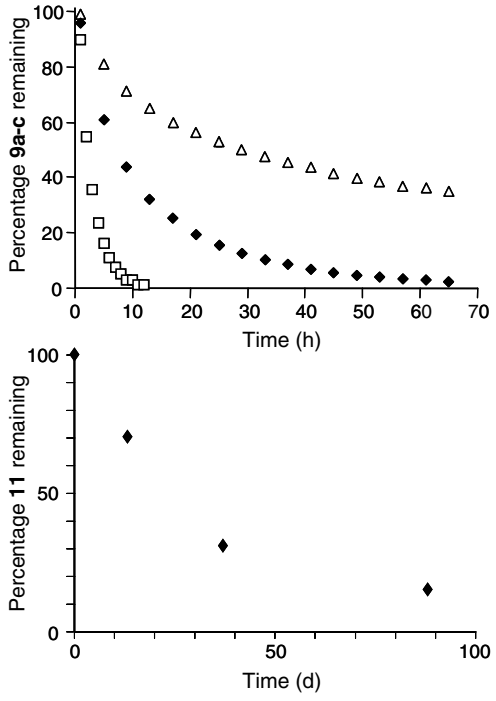


Figure 1. Upper: Graph showing rates of *closo* → *nido* carborane cage degradation of nitrophenylcarboranes in wet $(CD_3)_2SO$ at 20 °C. ◆, **9a**; △, **9b**; □, **9c**. Lower: Graph showing rate of *closo* → *nido* carborane cage degradation of fluorophenylcarborane **11** in wet $(CD_3)_2SO$ at ambient temperature.

In this Letter, we report a very mild and convenient *closo*- to *nido*- transformation in C-(substituted phenyl)carboranes with wet DMSO. This extension of the reaction into simpler carboranes points to the generality of this method with potential applications in the synthesis of *nido*-carboranes carrying a wide variety of sensitive substituents. Such *nido*-carboranes are of use in BNCT and other applications as themselves but also for further chemical reactions. For example, a boron atom can be 'stitched in' to the vacant icosahedral vertex of *nido*-carboranes with dichloroboranes ($RBCl_2$),[27] giving *closo*-carboranes with substituents at carbon and at the adjacent boron; such icosahedra have a great potential in the stereocontrolled display of reactive functional groups or bioactive ligands.

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References and notes

1. Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515–1562.
2. Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173–230.
3. Chen, W.; Mehta, S. C.; Lu, D. R. *Adv. Drug Del. Rev.* **1997**, *26*, 231–247.
4. Wood, P. J.; Scobie, M.; Threadgill, M. D. *Int. J. Radiat. Biol.* **1996**, *70*, 587–592.
5. Scobie, M.; Threadgill, M. D. *J. Org. Chem.* **1994**, *59*, 7008–7013.
6. Swenson, D. H.; Laster, B. H.; Metzger, R. L. *J. Med. Chem.* **1996**, *39*, 1540–1544.
7. Gottumukkala, V.; Ongayi, O.; Baker, D. G.; Lomax, L. G.; Vicente, M. G. H. *Bioorg. Med. Chem.* **2006**, *14*, 1871–1879.
8. Frixa, C.; Mahon, M. F.; Thompson, A. S.; Threadgill, M. D. *Org. Biomol. Chem.* **2003**, *1*, 306–317.

9. Hill, J. S.; Kahl, S. B.; Kaye, A. H.; Stylli, S. S.; Koo, M.-S.; Gonzales, M. F.; Vardaxis, N. J.; Johnson, C. I. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 1785–1789.
10. Barth, R. F.; Adams, D. M.; Soloway, A. H.; Alam, F.; Darby, M. V. *Bioconj. Chem.* **1994**, *5*, 58–66.
11. Soloway, A. H.; Zhuo, J.-C.; Rong, F.-G.; Lunato, A. J.; Ives, D. H.; Barth, R. F.; Anisuzzaman, A. K. M.; Barth, C. D.; Barnum, B. A. *J. Organomet. Chem.* **1999**, *581*, 150–155.
12. Yamamoto, Y.; Sadayori, N. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 9–12.
13. Vicente, M. G. H.; Edwards, B. F.; Shetty, S. J.; Hou, Y.; Boggan, J. E. *Bioorg. Med. Chem.* **2002**, *10*, 481–492.
14. Vicente, M. G. H.; Wickramasinghe, A.; Nurco, D. J.; Wang, H. J. H.; Nawrocky, M. M.; Makar, M. S.; Miura, M. *Bioorg. Med. Chem.* **2003**, *11*, 3101–3108.
15. 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*, 862–868.
16. Vaillant, J. F.; Schaffer, P.; Stephenson, K. A.; Britten, J. F. *J. Org. Chem.* **2002**, *67*, 383–387.
17. Fox, M. H.; Gill, W. R.; Herbertson, P. L.; MacBride, J. A. H.; Wade, K.; Colquhoun, H. M. *Polyhedron* **1996**, *15*, 565–571.
18. Fox, M. A.; MacBride, J. A. H.; Wade, K. *Polyhedron* **1997**, *16*, 2499–2507.
19. Schaeck, J. J.; Kahl, S. B. *Inorg. Chem.* **1999**, *38*, 204–206.
20. Batsanov, A. S.; Clegg, W.; Copley, R. C. B.; Fox, M. A.; Gill, W. R.; Grimditch, R. S.; Hibbert, T. G.; Howard, J. A. K.; McBride, J. A. H.; Wade, K. *Polyhedron* **2006**, *25*, 300–306.
21. Prokhorov, A. M.; Kozhevnikov, D. N.; Rusinov, V. L.; Chupakhin, O. N.; Glukhov, I. V.; Antipin, M. Y.; Kazheva, O. N.; Chekhlov, A. N.; Dyachenko, O. A. *Organometallics* **2006**, *25*, 2972–2977.
22. Hawthorne, M. F.; Berry, T. E.; Wegner, P. A. *J. Am. Chem. Soc.* **1965**, *87*, 4746–4750.
23. Frixa, C.; Scobie, M.; Black, S. J.; Thompson, A. S.; Threadgill, M. D. *Chem. Commun.* **2002**, 2876–2877.
24. 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. *Dalton Trans.* **2003**, 475–482.
25. Scobie, M.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2059–2063.
26. Wiesboeck, R. A.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1964**, *86*, 1642–1643.
27. Hawthorne, M. F.; Wegner, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 896–901.