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LETTERS

Direct Cu(I)-catalysed coupling of a carborane to a *meso*-tetraphenylporphyrin

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Abstract—The copper-catalysed coupling of 1,2-dicarba*closo*dodecaborane(12) with a *meso*-iodophenylporphyrinatozinc has been investigated. Optimisation of the reaction conditions gave 5-(4-(1,2-dicarba*closo*dodecaboran(12)yl)phenyl)-10,15,20-triphenylporphyrin as its Zn complex. The crystal structure of 5-(4-chlorophenyl)-10,15,20-triphenylporphyrinatocopper(II), a side product, has been determined. © 2002 Elsevier Science Ltd. All rights reserved.

Boron neutron capture therapy (BNCT) is a binary therapeutic technique used for the treatment of cancer, which relies on the efficient capture of low-energy neutrons by ^{10}B and subsequent emission of an α-particle and a recoiling ^{7}Li nucleus.[1,2] The α-particle has a range of 5–10 μm in tissue. Thus, if sufficient ^{10}B is located within a tumour cell, these particles will cause extensive DNA damage and be lethal to that cell. Selective delivery of sufficient ^{10}B to tumours remains one of the major outstanding problems in this promising therapy.[3] We have previously reported strategies for selective delivery of boron to hypoxic regions of solid tumours.[4,5] Accumulation of porphyrins in tumours has been known for many years but it is only more recently that attachment of clusters of boron atoms to porphyrins has been explored as a strategy for selective delivery.[6–9] In many of the porphyrin–carborane constructs under investigation, the carboranes (1,2-dicarba*closo*dodecaborane(12) or a corresponding *nido*-carborane) are linked to the porphyrin core through heteroatoms (O or N). These links are potentially metabolically labile and carbon-linked carboranylporphyrins are being sought as more physiologically robust agents.[9] Indeed, Lauceri et al.[10] have very recently indicated that there may be an attractive interaction between *nido*-carboranylporphyrins and DNA. In this letter, we report the first direct coupling of a carborane to a *meso*-tetraphenylporphyrin through a C–C link; previous syntheses[9] of carbon-linked carboranyl-*meso*-tetraphenylporphyrins have relied on carrying the carboranylphenyl unit through the assembly of the porphyrin ring.

Copper(I)-catalysed coupling of 1,2-dicarba*closo*dodecaborane(12) ('carborane') to simple iodoarenes has been reported by Coult et al.[11] but the reaction is highly sensitive to steric hindrance. We reasoned that the optimum position for coupling of the carborane to a *meso*-tetraphenylporphyrin was to place the iodine *para* to the point of attachment of a phenyl to the porphyrin core. Using our modification[12] of the method of Kruper et al.,[13] *meso*-tetraphenylporphyrin **1** was selectively mononitrated using 90% nitric acid in chloroform (Scheme 1). Reduction of **2** to the aminophenylporphyrin **3** was achieved in high yield by treatment with tin(II) chloride. Subsequent diazotisation and Sandmeyer reaction afforded the iodophenylporphyrin **4**. Since the coupling of carboranyl-copper(I) with iodoarenes normally requires highly basic conditions,[11] the centre of the porphyrin **4** was protected by formation of the zinc complex **5**.[14,15] Carborane was monolithiated (*n*-BuLi or *sec*-BuLi) and transmetallated with excess copper(I) chloride. Coupling of the carboranylcopper with **5** was investigated under a variety of conditions in dry 1,2-dimethoxyethane in the presence of pyridine. The maximum yield of **6** obtained was 0.7%, after 6 days at reflux, with much iodophenylporphyrinatozinc **5** recovered. Rationalising that higher temperatures were required and that a more co-ordinating solvent may aid the reaction,[16] the coupling was investigated under a variety of conditions with the triether bis(2-methoxyethyl)ether ('diglyme') as solvent. This procedure afforded an 8% yield of **6** after 12 days at reflux.[17]

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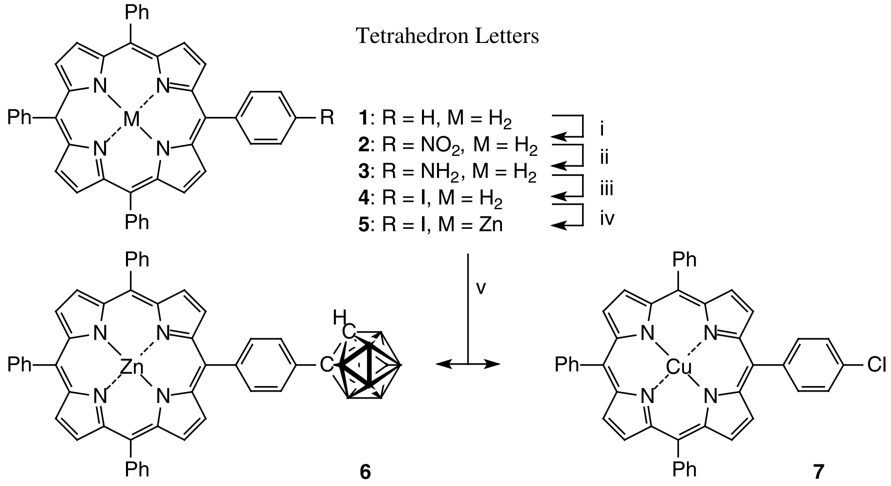

Scheme 1. Coupling of 1,2-dicarba*closo*dodecaborane(12) with iodophenylporphyrin **5** and formation of 5-(4-chlorophenyl)-10,15,20-triphenylporphyrinatocopper(II) **7**. *Reagents*: (i) HNO_3, $CHCl_3$; (ii) $SnCl_2$; (iii) $NaNO_2$, H_2SO_4, KI; (iv) $Zn(OAc)_2$; (v) 1,2-dicarba*closo*dodecaborane(12), BuLi, CuCl, various ether solvents, Δ.

An additional metalloporphyrin was also isolated in significant yields from these reactions. ^1H NMR analysis showed that it was paramagnetic, suggesting that it was a Cu(II) complex, rather than Zn(II); it also demonstrated that it did not contain the carborane cage. X-Ray crystallography showed it to be the novel 5-(chlorophenyl)-10,15,20-triphenylporphyrinatocopper(II) complex **7**. Details of the crystal structure are given below.[18,22] The asymmetric unit consisted of one-half of a molecule of the porphyrinatocopper(II) complex **7**, with the central Cu located on 2-fold rotation axis in the space group. The chlorine attached to C13 was seen to be disordered equally on *para* positions of all phenyl rings in **7** and was hence refined at 25% occupancy (only one chlorine is illustrated in Fig. 1, for clarity). A suggestion of tetragonal symmetry based on metric calculations was not borne out in reality for this structure, as higher symmetry would have mandated an extra uncharacteristic absence condition in the data. Bond lengths and angles in **7** are unremarkable.

The extensive formation of the chlorophenylporphyrinatocopper(II) complex **7** from **5** may explain the relatively low maximum yield of the coupled product **6**, as the coupling of the carboranyl-copper is known[11] to

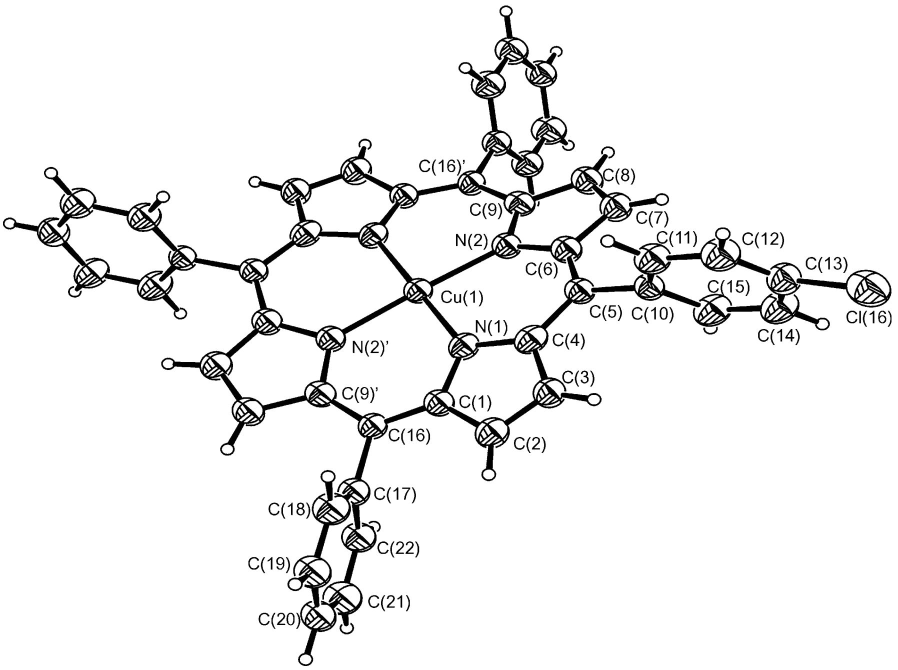

Figure 1. Crystal structure of 5-(4-chlorophenyl)-10,15,20-triphenylporphyrinatocopper(II) **7**.

require the iodoarene which, in this case, is consumed in a side-reaction. Direct replacement of iodine with chlorine on a benzene ring with CuCl at high temperatures has been reported previously[23,24] but it is interesting to note that such replacement only takes place on the copper complex whereas **6** contains only zinc.

Although this process requires further optimisation, it represents the first direct coupling of a carborane with a porphyrin via a carbon–carbon bond. As such, it provides an opportunity for access to tumour-targeted carboranylporphyrins for therapeutic applications.

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15. **Selected spectroscopic data for 5**: δ_H ($CDCl_3$) 7.76 (9H, m, 3×Ph 3,4,5-H_3), 7.96 (2H, d, $J=8.2$ Hz, Ar 2,6-H_2), 8.09 (2H, d, $J=8.2$ Hz, Ar 3,5-H_2), 8.22 (6H, d, $J=7.5$ Hz, 3×Ph 2,6-H_2), 8.93 (2H, d, $J=4.8$ Hz) and 8.96 (2H, d, $J=4.8$ Hz) (2,3,7,8-H_4), 8.95 (4H, s, 12,13,17,18-H_4); MS (FAB) m/z 807.0559 (M+H) ($C_{44}H_{28}N_4I^{68}Zn$ requires 807.0607), 805.0579 (M+H) ($C_{44}H_{28}N_4I^{66}Zn$ requires 805.0619), 803.0610 (M+H) ($C_{44}H_{28}N_4I^{64}Zn$ requires 803.0650).
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17. **Coupling reaction**: *sec*-BuLi (780 μmol) was stirred with 1,2-dicarba*closo*dodecaborane(12) (750 μmol) in bis(2-methoxyethyl)ether (3 mL) at −78°C for 5 min. The mixture was warmed to 20°C for 40 min before CuCl (1.0 mmol) was added. After 2 h, pyridine (450 μL) was added. After a further 2 h, **5** (250 mg, 310 μmol) was added; the mixture was boiled under reflux for 12 days. Evaporation and chromatography (hexane/$CHCl_3$, 2:1→3:4) gave **7** (65%) (purple crystals); mp >350°C. Further elution gave **6** (8%) as a purple solid; mp >350°C; δ_H ($CDCl_3$) 2.4 (10H, brq, $J_{B-H}=145$ Hz, $B_{10}H_{10}$), 4.29 (1H, brs, carborane 2-H), 7.75 (9H, m, 3×Ph 3,4,5-H_3), 7.86 (2H, d, $J=8.5$ Hz, Ar 2,6-H_2), 8.17 (2H, d, $J=8.5$ Hz, Ar 3,5-H_2), 8.21 (6H, m, 3×Ph 2,6-H_2), 8.83 (2H, d, $J=4.4$ Hz) and 8.94 (6H, m) (2,3,7,8,12,13,17,18-H_8); MS (FAB) m/z (all M+H) 824.3387 ($C_{46}H_{39}N_4{}^{10}B^{11}B_9{}^{68}Zn$ requires 824.3390), 823.3359 ($C_{46}H_{39}N_4B_{10}{}^{66}Zn$ requires 823.3366), 822.3384 ($C_{46}H_{39}N_4{}^{10}B^{11}B_9{}^{66}Zn$ requires 822.3402), 821.3382 ($C_{46}H_{39}N_4B_{10}{}^{65}Zn$ requires 821.3397), 820.3408 ($C_{46}H_{39}N_4{}^{10}B^{11}B_9{}^{65}Zn$ requires 820.3433).
18. **Crystal data**: $C_{44}H_{24}ClCuN_4$, $M=707.66$, wavelength = 0.71073 Å, orthorhombic, space group $F2dd$, $a=14.1650(9)$, $b=21.3960(13)$, $c=21.600(2)$ Å, $U=6546.4(8)$ Å^3, $Z=8$, $D_{calcd}=1.436$ mg m^{-3}, $\mu=0.789$ mm^{-1}, $F(000)=2896$, crystal size 0.20×0.08×0.08 mm, unique reflections = 2220 [R(int) = 0.0833], observed $I>2\sigma(I)=1863$, $R_1=0.0608$, $wR_2=0.1046$ (observed data), max. peak/hole 0.211 and −0.341 e Å^{-3}. Structural solution and refinement completed using SHELXS-86,[19] SHELXL-97.[20] Plot produced from ORTEX.[21]
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22. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 173872. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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