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Formation of a remarkably robust 2:1 complex between β-cyclodextrin and a phenyl-substituted icosahedral carborane†

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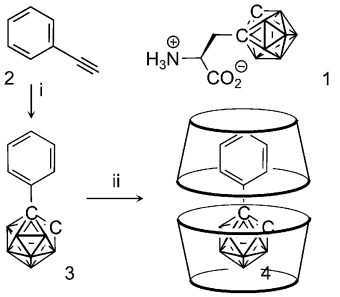
The structure of the 2:1 complex between β-cyclodextrin and 1-phenyl-1,2-dicarba-*closo*-dodecaborane(12) is demonstrated by NOE and NOESY spectroscopy; this complex is remarkably refractory.

A major challenge in designing boron-containing drugs for boron neutron capture therapy (BNCT) of cancer is selective delivery of ^{10}B to the tumour.[1] A biologically stable boron cluster, 1,2-dicarba-*closo*-dodecaborane(12) ('*o*-carborane') has been attached to tumour-targetting moieties.[2–4] This cluster is highly lipophilic; thus BNCT agents containing it must be adapted to allow sufficient aqueous solubility for formulation, administration and biodistribution.[3–5] Cyclodextrins (cyclic 1,4-α-linked oligomers of D-glucose) have often been used to solubilise lipophilic drugs by forming complexes in which aromatic groups are included in the cyclodextrin. However, when carboranylalanine **1** was solubilised by a β-cyclodextrin derivative, uptake into cells was actually inhibited by this complexation,[6] an observation consistent with formation of a very strong complex between the cyclodextrin and the carborane.

Complexes of *pseudo*-spherical C_{60} fullerene with γ-cyclodextrin have been extensively studied in terms of their structure, their water-solubility and other physicochemical properties.[7] However, there is only one structural study of inclusion complexes of icosahedral carboranes with cyclodextrins, in which complexes of α-, β- and γ-cyclodextrins with unsubstituted *o*-carborane were isolated;[8] the stoichiometries of the complexes (2:1 or 1:1 (depending on the preparative method), 1:1 and 1:1, respectively) were determined by elemental analysis and by integration of the ^1H NMR spectra but the proposed structures were based on computer modelling.

We present the first report of the preparation of a highly stable, isolable 2:1 β-cyclodextrin–phenylcarborane complex and the determination by its structure by ^1H NMR, NOE and NOESY spectroscopy. Heating phenylcarborane (1-phenyl-1,2-dicarba-*closo*-dodecaborane(12))[9] **3** in aqueous isopropanol with two equivalents of β-cyclodextrin gave the crude complex as a white powder (Scheme 1). Washing with hot water removed residual cyclodextrin and with hot toluene removed residual **3**; complex **4** is insoluble in these solvents. The tightness of binding in the complex was initially indicated by its resistance to dissociation under these conditions. Further evidence for the formation of a complex was given by its thermal stability; β-cyclodextrin is charred and caramelised by heating > 200 °C and **3** melts at 65–67 °C but **4** was recovered unmelted and unscathed at 350 °C.

An initial ^1H NMR spectrum of **4** in DMSO solution showed 2:1 β-cyclodextrin/phenylcarborane stoichiometry. This stoichiometry remains 2:1, even when the ratio of β-cyclodextrin to **3** is varied during the preparation of **4**. The IR spectrum of **4** was the sum of the spectra of β-cyclodextrin and **3**. Similarly, there are no significant changes in the ^1H NMR chemical shifts of the protons in either component caused by the complexation. The



Scheme 1 Structure of carboranylalanine **1** and synthesis of the β-cyclodextrin–phenylcarborane 2:1 complex **4**. Unlabelled atoms in the carborane are B; unlabelled atoms in the phenyl ring are C. Each B and the carborane C-2 carry one H. *Reagents and conditions*: i, $B_{10}H_{14}$, MeCN, reflux, 5 d, 59%; ii, β-cyclodextrin, aq. Pr^{i}OH, ambient temperature, 35 min, 79%.

structure of **4** was resolved by NOE and NOESY spectroscopy. A 1-D NOE spectrum (at 400 MHz) with irradiation of cyclodextrin 3-H gave enhancement of the signals for cyclodextrin 1,2,4-H) and for carborane 2-H. The cyclodextrin 3-H are located inside the cavity; thus the carborane is located within this cavity. A 2-D NOESY at 600 MHz (mixing time 900 ms), was more informative. Intermolecular NOE correlations were seen between the signals from the phenyl 2,6-H and cyclodextrin 3-H. Thus the phenyl is also located within a cyclodextrin cavity. The expected intramolecular NOE interaction between phenyl 2,6-H and carborane C–H was also observed. Other NOESY spectra showed NOE connectivities between the phenyl 3,4,5-H and the corresponding cyclodextrin inner protons (Fig. 1). No NOE was observed from the B–H signals, owing to their broadness. The involatility and refractory nature of **4** precluded any mass spectrometric study by EI, CI, FAB, ES and MALDI. In the light of these data, the structure shown in Fig. 1 is proposed for **4**.

Complexes of unsubstituted *o*-carborane with shallow cup- and bowl-shaped hosts, such as calix[5]arene[10] and cycloveratrylene (CTV),[11] are relatively weak and are observed in the crystalline state, whereas those with hosts with deeper cavities, such as cyclodextrins[4] and cucurbit[7]uril[12] are more robust. The cucurbit[7]uril–carborane complex is in slow equilibrium[12] with its components, whereas the simple cyclodextrin–carborane complexes apparently do not dissociate[4] in solution. The new 2:1 complex **4** appears to be very strong. It is completely undissociated by treatment with hot water and with hot toluene, solvents which extract the individual components. Similarly, complexation with the phenylcarborane protects the cyclodextrin from thermal degradation. The 2:1 stoichiometry is independent of the ratio of host:guest in the reaction mixture. Inclusion of the phenyl and the carborane units into different cyclodextrins would bring the wide aperture edges of the cyclodextrins into close contact, providing a series of strong H-bonds around the interface of the two host molecules; this has been observed in the crystal structures of several β-cyclodextrin complexes.[13,14] The stabilities of cyclodextrin inclusion complexes are often governed by 'goodness of fit'. The carborane icosahedron is an excellent fit in the cavity of β-cyclodextrin[8]

† Electronic supplementary information (ESI) available: formation of complex **4**. See http://www.rsc.org/suppdata/cc/b2/b209339a/

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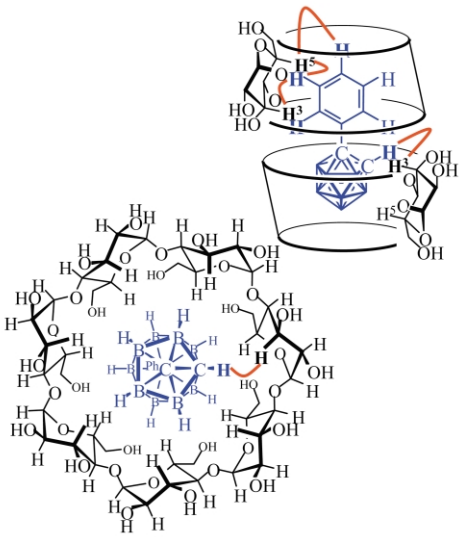

Fig. 1 Diagrams of the 2:1 complex **4** in elevation and plane views; the β-cyclodextrins are shown in black and the phenylcarborane is in blue. In the plane view, only the carborane and its β-cyclodextrin are shown, looking from the phenyl towards the carborane and into the wide end of the cyclodextrin. In the elevation, unlabelled atoms in the carborane are boron; unlabelled atoms in the phenyl ring are carbon. Host–guest NOE connectivities are shown in red.

and its hydrophobic nature complements the relative hydrophobicity of the cavity. A molecular modelling study[8]‡ confirmed that the shape of the carborane is an excellent fit for the pocket of its corresponding cyclodextrin, placing the phenyl ring in a good position for inclusion into the second cyclodextrin (Fig. 2). Additionally, the carborane C–H may be presented near to the interglycosidic oxygen to which it may H-bond.[15] All these factors may contribute to the remarkable stability of

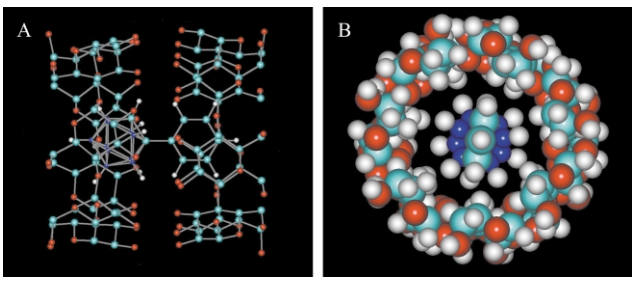

Fig. 2 Structure of the 2:1 complex **4** in side (A) and plane (B) views, derived from a molecular modelling study. In A, the hydrogen atoms are omitted from the cyclodextrins for clarity; in B, all hydrogens are shown. Colour code: hydrogen, white; boron, blue; carbon, cyan; oxygen, red.

complex **4**. We are studying the scope of this complex formation, with the aim of extending it to multicarborane arrays.

Notes and references

‡ Molecular modelling was performed using Tripos Sybyl software. The structure of the β-cyclodextrin dimer was taken from that of its complex with adamantane-1-carboxylic acid reported by Hamilton and Sabesan[13] and that of the phenylcarborane **3** was derived from an X-ray crystal structure of 5,15-di(3-nitrophenyl)-10,20-di(3-(1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethoxy)phenyl)-21*H*,23*H*-porphine.[16] The phenylcarborane structure was identified and modified from this carboranylphenylporphyrin structure and was then docked into the β-cyclodextrin dimer in the approximate location of the adamantane-1-carboxylic acid, to give a starting structure. The structure of the complex was then subjected to molecular mechanics calculations (1 ps and 300 K) and then minimised to give the final structure.

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