Dicarba-closo-dodecaborane(12) derivatives of phosphonium salts: easy formation of nido-carborane phosphonium zwitterions†

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Received 16th January 2007, Accepted 20th February 2007

First published as an Advance Article on the web 14th March 2007
DOI: 10.1039/b700689f

The first examples of arylphosphonium salts containing a dicarba-closo-dodecaborane(12) (closo-carborane) are reported; in contrast to the 1,12-carborane derivative, the 1,2- and 1,7-isomers undergo a facile deboronation reaction in polar solvents to afford the corresponding nido-carborane phosphonium zwitterions.

Delocalised lipophilic cations (DLCs) can readily traverse the lipophilic mitochondrial membrane and accumulate in mitochondria.1−4 The selection of DLCs for use as tumour imaging and anti-cancer agents has been based solely on their advantageous physical properties, lipophilicity and delocalised positive charge.5−8 A high negative electrical potential that exists across the mitochondrial membrane enhances the uptake of DLCs into the mitochondria.9 The potential difference across the membrane in normal, healthy cells has been determined to be −104 mV.9 Mitochondria from human colon carcinoma cells, for example, have been shown to consistently exhibit elevated membrane potentials of −163 mV, sufficient to account for a ten-fold increase of DLC concentration in cancerous cells over healthy cells.2

Phosphonium salts represent a promising class of DLCs for use in tumour targeting and imaging. Tetraphenylphosphonium (TPP) salts, triphenylmethylphosphonium (TPMP) salts and related compounds based on these structures have demonstrated highly cancer-selective accumulation and cytotoxicity.10−12 TPMP iodide, radio-labelled with the 11C isotope, has been investigated for in vitro uptake and retention in canine brain tumour in the interest of imaging tumours using PET.12 Not only was this compound rapidly taken up and retained in the tumour, but it was retained for a significant time (ca. 95 min) and achieved a tumour : healthy tissue ratio of 48 : 1. This ratio is also one order of magnitude greater than for other available glioma PET tracers and for clinical agents currently used in boron neutron capture therapy (BNCT).14−16 TPMP is also known to suppress tumour growth.15 Furthermore, animal studies have demonstrated that the expected toxic effects of TPMP may not prevent its use in humans.13 In the context of BNCT, incorporation of boron into this compound would potentially result in the selective delivery of boron to the tumour site.

Compounds that are selective toward certain cancers by targeting the mitochondria represent a new class of BNCT agents. To our knowledge, the only example of a carborane-containing DLC reported to date is the 1,12-carborane analogue of dequalinium, which was found to accumulate selectively in human epidermoid carcinoma of the oral cavity and rat glioma in vitro.1 It also exhibited similar uptake and retention properties to Rhodamine 123, MKT-077 and TPP chloride, suggesting this and other boron-containing DLCs such as the phosphonium salts are worthy of investigation as potential BNCT agents. Herein we describe the synthesis and characterisation of novel carborane-containing phosphonium derivatives. The present study describes TPMP analogues that have one phenyl group replaced by either a closo-1,2-, 1,7- or 1,12-carborane. In two out of three cases, a deboronation reaction occurs in polar solvents to afford the corresponding nido-carborane phosphonium zwitterions.

Syntheses of trisubstituted phosphines from the parent closo-carboranes were based upon the known preparation of the closo-1,2-carborane derivative 1.18 One equivalent of n-BuLi was treated with closo-1,2-, 1,7- or 1,12-carborane in DME at low temperatures to minimise disproportionation and hence dissubstitution at the carbon atoms,19 and chlorodiphenylphosphine was then added to afford the desired phosphine compounds 1−3,16,18,20−22 Small amounts of the disubstituted carborane derivative were also obtained in all three cases and could be separated readily from the monosubstituted species by means of flash column chromatography.

The synthesis of the phosphonium salts was achieved in all cases by a facile methylation reaction between 1−3 and MeI to afford the corresponding phosphonium iodides 4−6 (Schemes 1−3). An excess of MeI was used in the reaction as this step was generally not high-yielding, possibly because the carborane cage is somewhat electron-withdrawing thereby deactivated the phosphorus centre toward electrophiles. The characterisation of 4−6 was primarily achieved by means of mass spectrometry and NMR spectroscopy.‡ The Me group exhibited a downfield-shifted doublet in the 1H NMR spectra, with 𝑗�Me = 13−14 Hz. A single peak in the 31P{1H} NMR spectra at δ 24−30 was located downfield from the peak of the corresponding tertiary phosphine precursor.

Compounds 5 and 6 were found to readily deboronate to afford the corresponding nido-carborane zwitterions 7 and 8, respectively, in polar solvents such as DMSO and DMF. Alternatively, treatment of 5, for example, with fluoride ion in EtOH solution resulted in the rapid formation of the zwitterionic product 7 with an optimised yield (Scheme 1).‡ The deboronation reaction was not observed for 4, which contains closo-1,12-carborane and is therefore highly resistant to the deboronation reaction because

† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b700689f
no boron atoms within the cluster are bonded to two adjacent and electronegative carbon atoms. In contrast, the deboronation of closo-1,2-carborane under mild, non-basic conditions is known with alcohols, water and acids and has also been observed when functional groups located a to the cage are electron-withdrawing and the compounds are exposed to polar solvents containing small amounts of H2O or MeOH. In our case, the deboronation reactions occur in polar solutions such as dry DMF and thus most likely proceed by nucleophilic attack of the iodide counter-ion on the most electrophilic boron atoms in the cage, i.e. B3 (or B6) for 1,2-carborane and B2 (or B3) for 1,7-carborane. To our knowledge, no other halides except fluoride are known to deboronate closo-1,2- and 1,7-carborane.

Selective degradation of the closo-carborane cages in 5 and 6 to the corresponding nido derivatives was confirmed by the presence of an upfield broad peak at δ = 2 in the 1H{11B} NMR spectra of 7 and 8 which is attributed to the bridging H-atom, as well as the significant upfield shifts of resonances in the 11B{1H} NMR spectra. In addition to the NMR studies, the structure of 7 was confirmed by X-ray crystallography. An ORTEP representation of 7 is presented in Fig. 1. The bond angles and lengths fall in the range of typical alkyltriarylphosphonium salts, e.g. MePh3P+X− (X = ClO4, BF4), and are almost identical to those found in the phosphonium salt MePh3P+(7,8-Et2-7,8-nido-C2B9H10). The central phosphorus atom is close to an ideal tetrahedral geometry with bond angles ranging from 112.87(6)° (C(2)–P(1)–C(4)) to 106.88(6)° (C(2)–P(1)–C(10)). The C(2)–P(1) bond length of 7 (1.7867(14) Å) is only marginally shorter than the C(10)–P(1) and C(4)–P(1) bond lengths (1.7982(13) and 1.7981(13) Å, respectively) indicating there is very little double-bond character between the phosphorus centre and the cage carbon atom. Hence, a zwitterionic structure bearing separate but delocalised positive and negative charges at the MePh2 moiety and nido-carborane cage, respectively, is consistent with the X-ray data rather than a ylide-like structure in which there exists significant double-bond character and, consequently, a shortened phosphorus–carbon bond. Such bond shortening has been observed in simple phosphorus ylide compounds, e.g. PPh3CH2 (1.661 Å) and phosphorus–borane ylides such as endo-7-[Ph2(H)P]-8-R-hypho-7,8-C2B6H11, in which the P–C bond lengths were found to be 1.737(3) and 1.742(3) Å for R = H and Me, respectively.
In conclusion, we have reported the first examples of arylyphosphonium salts containing a closo-carborane. In contrast to the 1,12-carbaro derivative 4, the 1,2- and 1,7-isomers undergo a facile deboronation reaction in polar solvents to afford the corresponding zwitterionic nido-carborane phosphonium species. Preliminary in vitro cytotoxicity screening of 4 against the SF268 (human glioblastoma) cell line demonstrated a favourable GI50 > 40 μM compared with the control compound TPMP (GI50 = 12.5 μM). We are currently evaluating the detailed tumour cell uptake and biodistribution of 4 and the zwitterionic species 7 and 8, and the results of this study will be published in due course.

We thank Dr Ian Luck (The University of Sydney) for assistance with the NMR studies and Dr Carleen Cullinan (Peter MacCallum Cancer Institute, Melbourne) for the cytotoxicity studies. We also thank the Australian Research Council for financial support.

Notes and references

[1] NMR spectroscopic and ESI-MS data for 4: 1H NMR (d7-DMSO) δ 8.11 (m, 4H), 7.95 (m, 2H), 7.80 (m, 4H), 4.33 (br s, 1H, Cnsp-H). 3.04 (d, 2JHH = 13.42 Hz, 3H). 13C{1H} NMR (d7-DMSO) δ -12.5 (br, 10B). 31P{1H} NMR (d7-DMSO) δ 27.1 (s). 31P{1H} NMR (d7-DMSO) δ 0.157 mm, colourless prism, temperature range 15 to 15.

[2] Colourless prismatic crystals were grown from the slow diffusion of diethyl ether into a DMSO solution containing 7 over several days. X-Ray data: Formula C₉H₅BP,F,M = 322.60, monoclinic, space group P2₁/n (14, a = 11.4316(14), b = 9.4232(10), c = 17.5472(6), β = 102.805(6)°, V = 1834.2(4) Å³, Z = 4, crystal size = 0.316 × 0.290 × 0.157 mm, colourless prism, temperature 150(2) K, λ(MoKα) = 0.71073 Å, μ(MoKα) = 0.143 mm-1, T(SADABS)min,max = 0.750, 0.98, 2max = 61.28, hkl range = -16 to 16, -13 to 13, -25 to 25, N = 37976, Nhkl = 5637 (Rmerge = 0.0635), Nw = 4857 (I > 2σ(I)), Nw = 242, residual R1 = wΣ ||Fw(obs) - Fw(calc)|| / Σ Fw(obs) = 0.0444, wR2(F) = 0.1318, GoF(all) = 1.085, Dmax < 0.584, 0.499 Å⁻³. CCDRC reference number 629312. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b700669f.

[3] The X-ray structure of 7 reveals a number of ring-stacking interactions present throughout the crystal lattice. The zwitterionic molecules pack together forming infinite one-dimensional chains through offset face-to-face interactions which are illustrated by (C7)···(C7)12 [at x, 1/2 - y, 1/2 + z] = 3.446(2) Å. These chains pack closely together with adjacent chains forming a two-dimensional sheet-like motif, which propagates in the bc-plane and is held together by π-BH interactions between the delocalised carborane cages and the phenyl rings of adjacent molecules. Indicative BH···-ring centroid distances are the B(8)H···-ring centroid of the C(12)-containing ring = 3.35 Å and B(4)H···-ring centroid of the C(8)-containing ring = 3.41 Å.


