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Dodeca(carboranyl)-substituted closomers: toward unimolecular nanoparticles as delivery vehicles for BNCT

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The syntheses of the dodeca(carboranyl)-substituted closomers, dodeca[7-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)heptanoate]-*closo*-dodecaborate(2−) and dodeca[7-(8-methyl-7,8-dicarba-*nido*-dodecaboran-7-yl)-heptanoate]-*closo*-dodecaborate(14−) are reported. These boron-rich, unimolecular nanospheres possess great potential for future use as drug-delivery platforms for boron neutron capture therapy (BNCT).

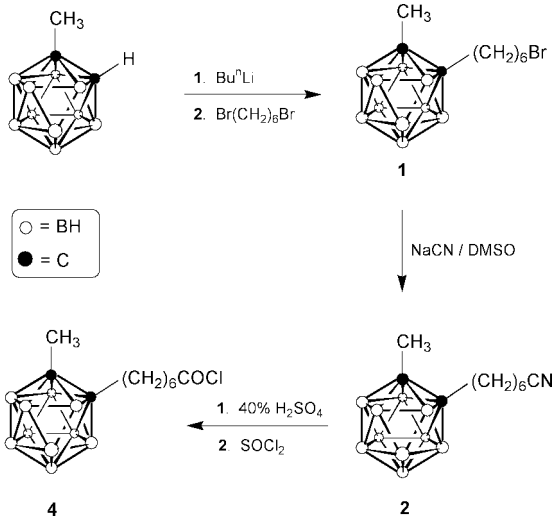
The selective delivery of therapeutic quantities of boron to tumor tissue is the most crucial requirement for effective use of boron neutron capture therapy BNCT.[1–3] Liposomes have demonstrated the ability to accumulate in tumors in high concentration relative to normal tissues, including blood[4–7] if they are sufficiently small (30–150 nm diameter). This selective uptake has been attributed to the ability of these small vesicles to pass through the porous, immature vasculature of tumor tissue. Liposomes may deliver therapeutic quantities of boron to tumor tissue,[8,9] but they are an extremely inefficient system with approximately 90% of the total liposome mass consisting of the therapeutically inactive phospholipid and cholesterol normally used in construction of the vesicle.

Closomers are a new class of polyhedral borane derivatives[10,11] which have the potential to provide a new BNCT drug-delivery system. The closomers employed here are dodeca-substituted organic derivatives of the icosahedral $B_{12}H_{12}^{2-}$ parent ion and may be viewed as cousins of dendrimers. Properly functionalized closomers would result in small, boron-rich unimolecular nanoparticles of high sphericity which, in principle, may be constructed with sizes ranging from that of micelles (3–4 nm) to that of liposomes (30–100 nm). In this manner, the inefficiency of liposomes could be abated while still retaining their size-dependent tumor specificity.[8,9] Reported here is the synthesis of a closomer equipped with twelve side chains, each carrying a *closo*-2-methyl-1,2-carboran-1-yl substituent and having the properties of a nearly spherical unimolecular nanoparticle containing approximately 40% boron by weight. This species was subsequently deboronated[12] to the corresponding highly charged (14−) dodeca-*nido*-carborane analogue.

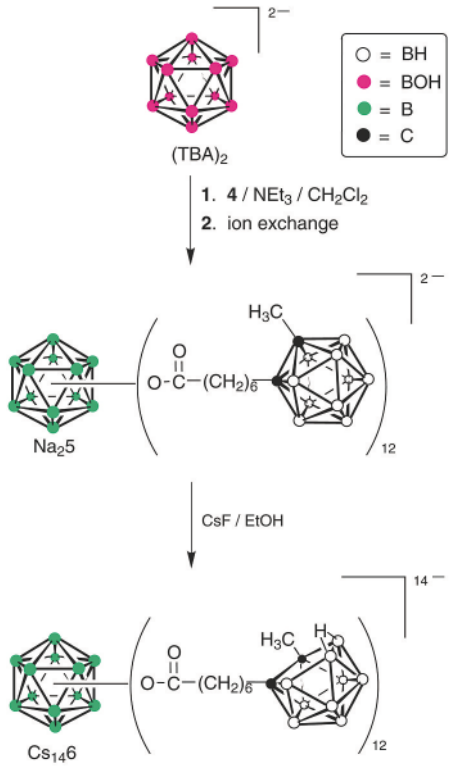
The synthesis of a closomer requires the conjugation of the polyfunctional core with reactive species providing pendant moieties. The preparation of the icosahedral *closo*-$B_{12}(OH)_{12}^{2-}$ core was performed with slight modification to published methods[13] and isolated from ion-exchange as the bis(tetra-*n*-butylammonium) salt.

The synthesis of the reactive carborane-containing pendant moieties is shown in Scheme 1. A solution of *closo*-1-methyl-1,2-carborane was treated with *n*-butyllithium at 0 °C and warmed to room temperature to afford the intermediate lithiated species. This was added to a vigorously stirred solution of 1,6-dibromohexane in THF at the reflux temperature to give 1-bromo-6-(*closo*-2-methyl-1,2-carboran-1-yl)hexane **1**. A solution of **1** in DMSO was treated with sodium cyanide and heated for 24 h at 65 °C to give 1-cyano-6-(*closo*-2-methyl-1,2-carboran-1-yl)hexane **2**. Compound **2** was subsequently hydrolyzed to the carboxylic acid **3** by heating in a 40% H_2SO_4 solution for 18 h at reflux. The generation of the acid chloride **4**, was accomplished by treatment of 3 with an excess of $SOCl_2$ in methylene chloride at reflux.

Subsequent conjugation of the acid chloride **4** with the dodecahydroxy dodecaborate(2−) closomer core afforded **5**, as



Scheme 1



Scheme 2

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shown in Scheme 2. This conjugation was accomplished in methylene chloride with a three-fold excess of **4** and triethylamine. Purification was accomplished by silica gel chromatography to give disodium **5** in an isolated yield of 95%. The salt **5** was characterized by ^{1}H, ^{13}C and ^{11}B NMR spectroscopy as well as by MALDI-MS.†

The closomer **5** possesses twelve pendant groups containing *closo*-1,2-carborane units. These may all be degraded to anionic *nido*-7,8-carborane cages by the action of fluoride ion.[12] Compound **5** was treated with a large excess of CsF in absolute ethanol and heated for 4 days at reflux. The quantitative conversion of the pendant groups was documented by its ^{11}B NMR spectrum. The modified closomer **6** was isolated in a 98% yield and further characterized by ES–MS.‡

While these macromolecular compounds possess great potential as delivery platforms for BNCT, they are interesting as materials in their own right. The organic functionalization of this platform gives a novel 'inverse molecular micelle' salt with a dinegative core which is soluble in organic solvents. The structure of this globular species is presented in Fig. 1. Deboronation of the pendant carborane units[12] imparts hydrophilicity to the system, which attains solubility in hot water as the Cs^{+} salt while maintaining solubility in polar organics. The twelve-fold functional icosahedral dodecaborate(2−) core provides a scaffold which is apparently free of serious steric encumbrance. Substitution with twelve bulky carborane units is easily attained, promising significant flexibility in the future design of species having novel applications.

In summary, a closomer species with an icosahedral dodecaborate(2−) core and twelve pendant anionic *nido*-7,8-carborane groups has been synthesized. This boron-rich amphiphilic ion represents the first example of a new class of unimolecular nanoparticles for evaluation as drug delivery devices for BNCT.

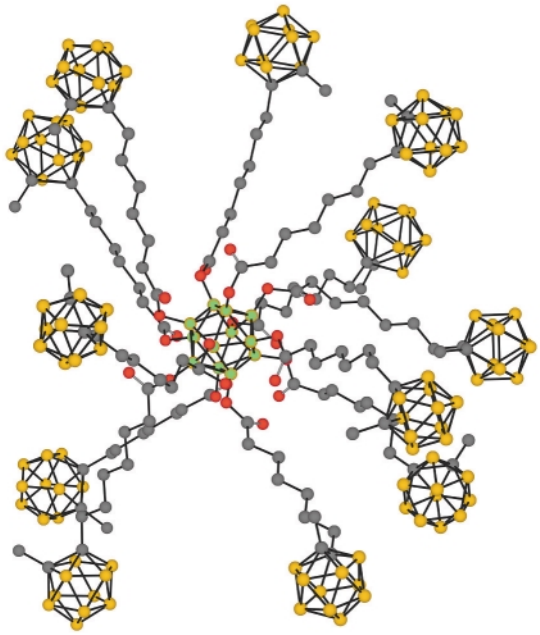

Fig. 1 Representation of the boron-rich closomer dodeca[7-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)heptanoate]-*closo*-dodecaborate(2−). The boron atoms of the icosahedral core are shown in green. The carborane boron atoms are yellow, oxygen is red and all carbon atoms are depicted in black. Hydrogen atoms have been omitted.

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Notes and references

† *Experimental details* for **5**: to a solution of 7-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)heptanoyl chloride (5.10 g, 16.7 mmol) in CH_2Cl_2 (20 mL) was added a solution of $(NBu^{n}_{4})_2B_{12}(OH)_{12}$ in CH_2Cl_2 (5 mL). Triethylamine (3.8 mL, 2.7 g, 27.3 mmol) was added with the formation of an immediate precipitate. The resulting mixture was heated at the reflux temperature for one week, resulting in a brown solution. The reaction flask was cooled to room temperature and the reaction mixture extracted with $NaHCO_3$ solution (3 × 20 mL). The organic portion was collected and the solvent removed under vacuum. The remaining residue was added to a silica gel column, flushed with diethyl ether, and eluted with acetone. Elution through silica gel resulted in an *in situ* ion exchange to produce the sodium salt. The acetone was removed *in vacuo* to give an off-white solid in 95% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.22 (br, CH_2, 24H); 2.11 (br, CH_2, 24H); 1.97 (s, $C_{cb}CH_3$, 36H); 1.50 (br, CH_2, 48H); 1.23 (br, CH_2, 48H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz): δ 180.0 (CO); 78.12, 74.92 (C_{cb}); 35.62 ($C(O)CH_2$); 35.22 ($C_{cb}CH_2$); 29.67, 29.13, 28.78, 24.80 (CH_2); 23.74 ($C_{cb}CH_3$). $^{11}B\{^{1}H\}$ NMR ($CDCl_3$, 160 MHz): δ −5.79 (24B); −10.50 (96B); −18.01 (12B). LRMS (MALDI): *m*/*z* 3576 $[M + Na]^{-}$.

‡ *Experimental details* for **6**: to a solution of disodium dodeca[7-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)heptanoate]-*closo*-dodecaborate (0.10 g, 2.8 × 10^{-2} mmol) in absolute ethanol (25 mL) was added caesium fluoride (0.10 g, 0.66 mmol) and the resulting solution was heated at the reflux temperature for 5 days. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo* to give a white residue. This residue was dissolved in acetone and filtered. The solvent was removed *in vacuo* to give the product as an off-white solid in 98% yield. $^{11}B\{^{1}H\}$ NMR ($CDCl_3$, 160 MHz): δ −8.326 (12B); −9.783 (12B); −17.23 (60B + 12B); −33.73 (12B); −36.17 (12B). LRMS (ES): *m*/*z* 244.84 $[M]^{14-}$.

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