Synthesis of triazolyl methyl-substituted amino- and oxy-undecahydrododecaborates for potential application in boron neutron capture therapy†‡

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A general approach to the synthesis of triazole conjugates containing undecahydro-*closo*-dodecaborate anions based on Huisgen 1,3-dipolar cycloaddition is presented. Undecahydro-*closo*-dodecaborate anions bearing terminal alkyne groups were synthesized by the reaction of $H_3N–B_{12}H_{11}^-$ or $HO–B_{12}H_{11}^{2-}$ with alkyne halides in *N*,*N*-dimethylformamide using KOH as a base. Variation of reaction time, alkyne halide concentration and steric demands of the alkyne halide resulted in the stepwise introduction of one to three alkyne groups into $H_3N–B_{12}H_{11}^-$. Two compounds {$(CH{\equiv}CCH_2)_3N–B_{12}H_{11}^-$ and $(CH{\equiv}CCH_2)O–B_{12}H_{11}^{2-}$} were crystallized for single-crystal X-ray diffraction studies. *N*- and *O*-alkyne undecahydro-*closo*-dodecaborate anions reacted with various functionalized azides including lipid, carborane, aryl and hydroxyalkyl groups. The current study provides various synthetic applications not only for BNCT but also for boron cluster materials.

Introduction

Boron neutron capture therapy (BNCT) focuses on the treatment of patients with malignant neoplasms, especially high-grade gliomas, melanomas and their metastatic manifestations.[1–3] The goal of this therapy is to destroy tumour cells by combining two methods: enrichment of boron-10 in cancer cells and subsequent irradiation of the tissue with neutrons. After capturing thermal neutrons, the boron nucleus disintegrates into ionizing particles, destroying the cell. To improve this therapeutic model, non-toxic and water-soluble boron compounds, which accumulate in cancer cells, are required.[4–6] Icosahedron ($B_{12}H_{12}^{2-}$) is an interesting compound for BNCT. Its main advantages are its hydrophilic properties, simple methods of parent anion synthesis from ^{10}B-enriched raw material and its safety to man. Sodium borocaptate ($Na_2B_{12}H_{11}SH$) accumulates in tumour tissue and is successfully used in BNCT. The $B_{12}H_{12}^{2-}$ cluster can be connected to organic tumour-seeking moieties through links with exoskeletal substituents (S, O, N).[7–12]

Various *S*-, *N*- and *O*-alkylated $B_{12}H_{12}^{2-}$ derivatives have already been described.[13–19] Utilizing the *S*-substituted icosahedron as a nucleophile, it was found that direct or indirect alkylation by primary alkyl halides leads to surprisingly stable sulfonium or thioether salts ($R_2S–B_{12}H_{11}^-$ or $RS–B_{12}H_{11}^{2-}$, respectively).[13] The reaction with acid halides gave stable *S*-acyl derivatives ($RCOS–B_{12}H_{11}^{2-}$).[13] *N*-Alkylated $B_{12}H_{12}^{2-}$ clusters were obtained by the reactions of amines with diborane at higher temperatures.[14] The potassium salt of $[(CH_3CH_2)_3N–B_{12}H_{11}]^-$ was also isolated from the reaction of decaborane(14) with triethylamine in triethylamine–borane.[15] Different degrees of alkylation ($RH_2N–B_{12}H_{11}^-$, $R_2HN–B_{12}H_{11}^-$ and $R_3N–B_{12}H_{11}^-$) of amine-undecahydro-*closo*-dodecaborate(1−) ($H_3N–B_{12}H_{11}^-$)[20] under strong basic conditions were observed, depending on the type of halide used.[16] Another possibility for alkylation of $H_3N–B_{12}H_{11}^-$ is derived from the reduction of $B_{12}H_{11}^-$ Schiff bases $[RCH{=}HN–B_{12}H_{11}]^-$ to their monosubstituted amines $[RCH_2H_2N–B_{12}H_{11}]^-$.[18] The study of hydroxo-undecahydro-*closo*-dodecaborate(2−) ($HO–B_{12}H_{11}^{2-}$)[21] chemistry showed that $HO–B_{12}H_{11}^{2-}$ is a very weak nucleophile, and its alkylation resulted in monoalkyated derivatives ($RO–B_{12}H_{11}^-$).[18] Sivaev *et al.* presented another strategy to obtain alkylated $HO–B_{12}H_{11}^{2-}$ derivatives *via* ring opening reactions of the tetramethylene oxonium derivative $[B_{12}H_{11}O(CH_2)_4]^-$ with different nucleophiles.[19]

The emergence of the copper-catalyzed azide–alkyne cycloaddition reaction as an entry point to 1,4-disubstituted triazoles raises a challenge for the discovery of new chemical approaches with equal or even greater fidelity.[22–24] The click cycloaddition reactions were suggested as an increasingly popular method for the rapid synthesis of novel biologically active boronated compounds (*e.g.* chlorins,[25] hyaluronans[26] and nucleotides[27,28]). Recently, we reported the first example for click reaction of $HS–B_{12}H_{11}^{2-}$ with different organic azides.[8] This reaction constitutes a good entry for the synthesis of various $HS–B_{12}H_{11}^{2-}$-containing compounds and can be

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† Electronic supplementary information (ESI) available: X-ray crystallographic files for the structure determinations of **2** and **6**. ^1H, ^{13}C and ^{13}C dept 135° NMR spectra of compounds **2–4** and **6–20**. CCDC reference numbers 763111 and 763112. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0nj00046a

‡ This article is dedicated to the memory of Professor Pascal Le Floch, who made a significant contribution to this thematic issue before he passed away on March 17, 2010. This article is part of a themed issue on Main Group chemistry.

used to clarify the biological mechanism of boron clusters in BNCT.[8]

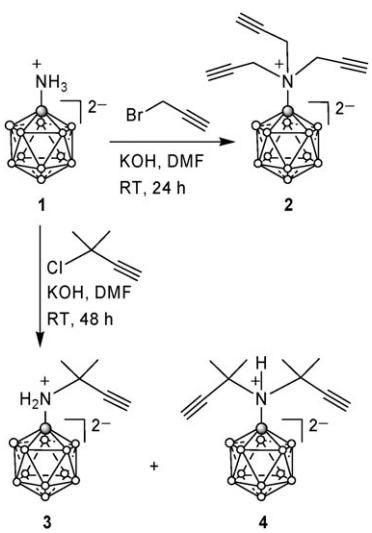
In our course of synthesizing new undecahydrododecaborate derivatives, we report here that the reaction of $H_3N–B_{12}H_{11}^-$ and $HO–B_{12}H_{11}^{2-}$ with alkyne halides (propargyl bromide or 3-chloro-3-methyl-1-butyne) leads to the formation of *N*- and *O*-terminal alkyne groups, respectively. The broad substrate tolerance of $B_{12}H_{11}^{2-}$-containing alkynes including mono-, di- and tri-alkyne groups demonstrates the versatility of this protocol. Meanwhile, the terminal azides could carry substituents such as lipid, carborane and aryl or hydroxyalkyl groups. These derivatives enable a convenient preparation of BNCT agents on the basis of click chemistry reactions.

Results and discussion

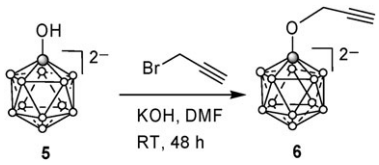
Reactions of undecahydro-*closo*-dodecaborate anions with terminal alkynes

The formation of stable undecahydro-*closo*-dodecaborate anions containing terminal alkynes seems to be one of the characteristic features of the chemistry of polyhedral boron hydrides. In our synthetic strategy, two types of undecahydro-*closo*-dodecaborate anion building blocks were constructed: one is the *N*-alkylation of **1** with alkyl halides, which afforded mono-, di- and tri-alkylated derivatives equipped with terminal alkyne groups (Scheme 1). The alkylation products contained positively charged nitrogen, as expected because **1** is itself isolated in its protonated form.[20] The second is the *O*-alkylation of **5** bearing two negative charges, similarly furnished with a terminal ethynyl function (Scheme 2). The combination of these four compounds with different azides provides high versatility for the proposed methodology.

N-Alkylation of **1** with propargyl bromide or 3-chloro-3-methyl-1-butyne is shown in Scheme 1. Following Gabel's seminal studies on alkylation of undecahydro-*closo*-dodecaborate anions,[16,17] an analogous approach was described but using *N*,*N*-dimethylformamide (DMF) instead of dimethyl sulfoxide as a reaction medium. The reaction of **1** with propargyl



Scheme 1



Scheme 2

bromide yielded *N*,*N*,*N*-tris-(prop-2-ynyl)amino-undecahydro-*closo*-dodecaborate(1−) (**2**) in 97% yield. The ^{1}H NMR spectrum of compound **2** in CD_3CN contains signals of the CH and CH_2 hydrogens of the propyne groups at 2.87 and 4.25 ppm, respectively, with disappearance of the NH_3 protons. No vibrational frequency ν(N–H) was found in the IR spectrum of **2**, in which a band for ν(B–H) dominated at 2492 cm^{-1}. Furthermore, the trialkylated anion (**2**) is confirmed by ESI mass spectrum. Its ^{13}C NMR spectrum displayed three signals for propyne groups, at 80.3, 76.0 and 53.3 ppm. The X-ray crystal structure of **2** was obtained from its tetramethylammonium salt as shown in Fig. 1.

The reaction of **1** with 3-chloro-3-methyl-1-butyne afforded mono- and di-alkylated anions **3** and **4**, respectively. It was observed that the ratio of the products **3** and **4** depends upon the reaction time and concentration of 3-chloro-3-methyl-1-butyne. Two sharp peaks at 3220 and 3210 cm^{-1} in the IR spectra of **3** and **4** are assigned to the NH_2 and NH bond vibrations, respectively. In the ^{1}H NMR spectra, two broad singlets at 5.42 and 6.55 ppm are assigned to NH_2 and NH of **3** and **4**, respectively. However, the singlets at 2.83 and 1.82 ppm, respectively, are attributed to CH and CH_3 protons of the 3-methyl-1-butyne group. The ^{13}C NMR spectra of the anions **3** and **4** showed four signals at approximately 80, 75, 52 and 22 ppm. The *N*-alkylation reaction of **1** with propargyl bromide gave solely the trialkylated derivative **2** even with an equimolar ratio of the reactants. However, the reaction of **1** with an excess of 3-chloro-3-methyl-1-butyne afforded only **3** after 24 h. The extension of the reaction time to two days gave a statistical mixture of **3** and **4**. The rate of alkylation of **1**

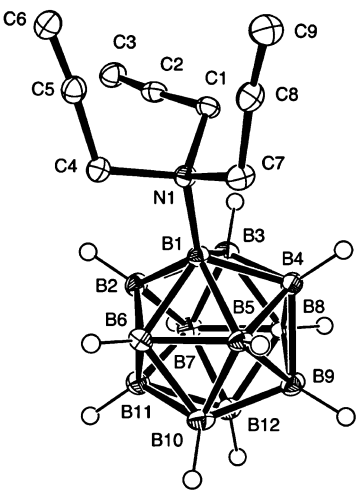


Fig. 1 ORTEP representation of anion **2**, showing 50% probability thermal ellipsoids (hydrogen atoms of the propyne groups are omitted for clarity).

depends on the structure and the nature of the halogen atom (Br or Cl) of the alkyl halides. Accordingly, the steric hindrance and the leaving group ability are important factors to control the reaction rate.

Similarly, alkylation of the hydroxyl group on the boron cluster **5** was achieved as indicated in Scheme 2. Alkylation of **5** with propargyl bromide yielded 92% of **6**. Conversely to **1**, alkylation of **5** generally afforded monoalkylated derivatives.[17] This is probably due to the lower nucleophilicity of oxygen and instability of the resulting oxonium cation. The colourless crystal of **6** was obtained from slow evaporation of dichloromethane-layered ethanol at room temperature. The molecular structure of **6** was determined by single-crystal X-ray diffraction (Fig. 2). The ^{11}B NMR data (see experimental section) of compounds **1–4** and **6** exhibit deshielding for B1, but the chemical shifts of vertices B2–12 are the same in the cases of **2–4**. In contrast to **6**, the B12 vertex is shifted to a higher field. Only the spectra of **6** shows the typical 1 : 5 : 5 : 1 pattern usually observed for **1** and **5**. Compared to $B_{12}H_{12}^{2-}$, the B1 atom is strongly affected by substitution because of the *–I* effect of nitrogen and oxygen atoms.[29]

Crystal structures of the anions 2 and 6

The solid-state structure of the anion **2**, determined by X-ray diffraction, is depicted in Fig. 1. The anion **2** consists of an icosahedral boron cluster with tripropynylamine molecules co-ordinated through the nitrogen atom to the boron cluster. Slight distortion of the icosahedral geometry is found for the boron cluster of **2** (Table 1). Selected bond lengths and angles of **2** are given in Table 2. The B–B bond distances span a narrow range of 1.77(2)–1.795(2) Å (Table 2). The B(1)–N(1) bond length is 1.6275(18) Å. These results are similar to the B–B {(1.742(7)–1.806(7) Å} and the B(1)–N(1) {1.63(1) Å} bond lengths reported for $[(CH_2CH_3)_3N–B_{12}H_{11}]^-$.[16] Table 3 lists the bond lengths and selected bond angles of the anion **6**. A view of the solid-state structure is shown in Fig. 2. The molecule consists of an icosahedral boron cluster with a propynoxyl substituent. The pseudoicosahedral geometry of the cluster is distorted (Table 1). The B–B bond lengths lie in the range of 1.772(5) to 1.798(5) Å. The B(1)–O(1) distance is 1.451(4) Å. Similar results were obtained for the B–B {1.752(7) to 1.809(6) Å} and B(1)–O(1) {1.442(5) Å} bond distances of $[CH_3CH_2O–B_{12}H_{11}]^{2-}$.[17] Significant difference from the sp^3 geometry is found for the B(1)–O(1)–C(1) angle {117.3(2)°}. Similar deviation is observed for $[CH_3CH_2O–B_{12}H_{11}]^{2-}$ {115.9(3)°}.[1]

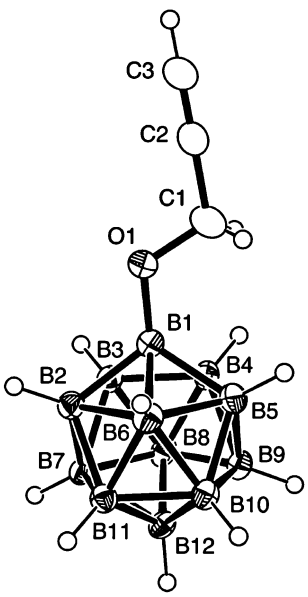


Fig. 2 ORTEP representation of anion **6**, showing 50% probability thermal ellipsoids.

Table 1 Details of crystallographic data collection for anions **2** and **6**

	2	**6**
Formula	$C_{15}H_{35}B_{12}N_3$	$C_{35}H_{86}B_{12}NO$
FW	387.18	666.77
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/n$	*Pbca*
a/Å	9.6724(11)	16.5356(12)
b/Å	8.4355(10)	18.6466(14)
c/Å	29.307(3)	29.656(2)
α/°	90	90
β/°	96.981(2)	90
γ/°	90	90
V/nm^3	2.3735(5)	9.1439(12)
Z	4	8
D_c/g cm^{-3}	1.084	0.969
F(000)	824	2968
μ/mm^{-1}	0.056	0.051
λ/Å	0.71073	0.71073
Range (2θ) for data collection/°	2.15–27.54	2.46–26.91
GOF	1.027	1.049
T/K	173	123
R_1 [a] ($I > 2\sigma(I)$)	0.0494	0.0927
$_wR_2$ [b] ($I > 2\sigma(I)$)	0.1134	0.1717
R_1 [a] (all data)	0.0727	0.1322
$_wR_2$ [b] (all data)	0.1233	0.1905

[a] $R_1 = \sum F_o F_c \sum F_o$. [b] $wR_2 = [\sum w(F_o^2 - F_c^2)^2\alpha/\sum w(F_o^2)^2)]^{1/2}$.

Table 2 Selected bond lengths (Å) and angles (°) for anion **2**

N(1)–C(1)	1.5196(18)	C(1)–C(2)	1.463(2)
B(1)–N(1)	1.6275(18)	C(2)–C(3)	1.180(2)
B(1)–B(2)	1.770(2)	B(1)–B(3)	1.775(2)
B(1)–B(4)	1.774(2)	B(1)–B(5)	1.781(2)
B(2)–B(7)	1.779(2)	B(1)–B(6)	1.782(2)
B(2)–B(11)	1.784(2)	B(2)–B(6)	1.789(3)
B(3)–B(7)	1.773(2)	B(2)–B(3)	1.790(2)
B(3)–B(8)	1.777(2)	B(3)–B(4)	1.786(2)
B(4)–B(9)	1.776(2)	B(4)–B(8)	1.789(2)
B(5)–B(10)	1.776(2)	B(4)–B(5)	1.795(2)
B(5)–B(9)	1.779(2)	B(5)–B(6)	1.790(2)
B(6)–B(10)	1.785(2)	B(6)–B(11)	1.786(2)
B(7)–B(12)	1.783(2)	B(7)–B(8)	1.788(2)
B(8)–B(9)	1.779(3)	B(7)–B(11)	1.783(2)
B(9)–B(12)	1.778(2)	B(8)–B(12)	1.783(2)
B(10)–B(12)	1.779(2)	B(9)–B(10)	1.782(2)
B(10)–B(11)	1.786(2)	B(11)–B(12)	1.787(2)
N(1)–C(1)–C(2)	114.00(12)	C(1)–C(2)–C(3)	175.31(15)
N(1)–B(1)–B(2)	122.33(11)	C(1)–N(1)–B(1)	111.60(10)
N(1)–B(1)–B(4)	119.27(11)	N(1)–B(1)–B(3)	120.79(11)
N(1)–B(1)–B(5)	120.52(11)	N(1)–B(1)–B(6)	122.12(11)
N(1)–C(1)	1.5196(18)	C(1)–C(2)	1.463(2)
B(1)–N(1)	1.6275(18)	C(2)–C(3)	1.180(2)

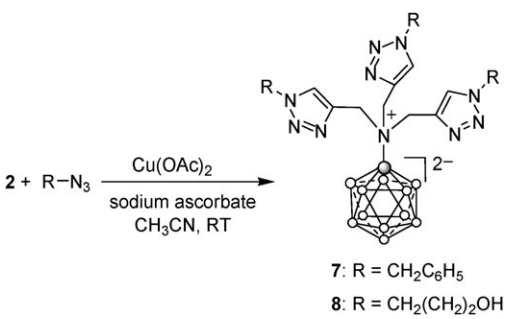
Table 3 Selected bond lengths (Å) and angles (°) for anion **6**

O(1)–C(1)	1.370(4)	C(1)–C(2)	1.483(5)
B(1)–O(1)	1.451(4)	C(2)–C(3)	1.154(5)
B(1)–B(3)	1.785(4)	B(1)–B(5)	1.788(4)
B(1)–B(2)	1.787(4)	B(1)–B(6)	1.797(5)
B(2)–B(7)	1.776(4)	B(1)–B(4)	1.798(5)
B(2)–B(11)	1.782(4)	B(2)–B(3)	1.782(4)
B(3)–B(8)	1.775(4)	B(2)–B(6)	1.788(4)
B(3)–B(4)	1.782(4)	B(3)–B(7)	1.783(4)
B(4)–B(8)	1.775(5)	B(4)–B(5)	1.788(4)
B(5)–B(9)	1.772(5)	B(4)–B(9)	1.780(4)
B(5)–B(10)	1.781(4)	B(5)–B(6)	1.786(5)
B(6)–B(10)	1.781(4)	B(6)–B(11)	1.783(4)
B(7)–B(8)	1.772(4)	B(7)–B(12)	1.779(4)
B(8)–B(12)	1.774(4)	B(7)–B(11)	1.781(4)
B(9)–B(12)	1.773(4)	B(8)–B(9)	1.790(4)
B(10)–B(11)	1.785(4)	B(9)–B(10)	1.782(4)
B(10)–B(12)	1.786(4)	B(11)–B(12)	1.791(4)
O(1)–C(1)–C(2)	112.4(3)	C(1)–C(2)–C(3)	179.5(4)
O(1)–B(1)–B(3)	121.8(2)	C(1)–O(1)–B(1)	117.3(2)
O(1)–B(1)–B(5)	123.4(2)	O(1)–B(1)–B(2)	120.2(2)
O(1)–B(1)–B(4)	123.9(2)	O(1)–B(1)–B(6)	120.8(2)

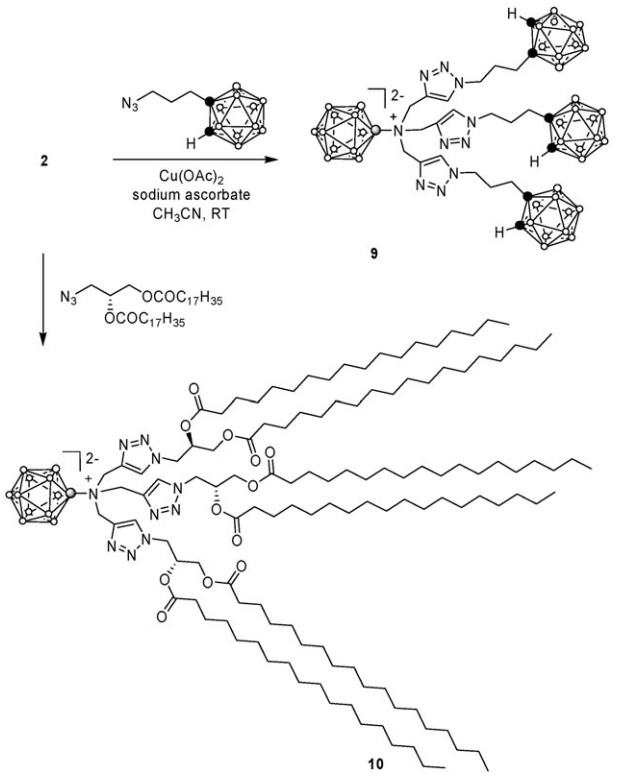
Click chemistry of undecahydro-*closo*-dodecaborane anions 2–4 and 6

The advantageous properties of Huisgen cycloaddition, together with the most useful modular nature of the click chemistry approach, make it well-suited for use in the synthesis of new molecules, especially conjugates composed of two quite different subunits. Examples are bioorganic–inorganic conjugates such as the organic azides and the boron clusters presented here.

The synthesis of undecahydro-*closo*-dodecaborate anions conjugated to triazoles **7–10** based on the click reaction is shown in Scheme 3 and 4. Catalytic amounts of $Cu(OAc)_2$ and sodium ascorbate were added to a solution of the corresponding undecahydro-*closo*-dodecaborate anion in acetonitrile. A suitable amount of azide of a different terminal type (lipid, carborane and aryl and hydroxyalkyl groups) was added. With the exception of the lipid azide reaction, which was carried out at 70 °C because of the insolubility of lipid azide in CH_3CN at room temperature, the reaction was performed at room temperature for 6 h; the reaction progress was monitored by TLC. After reaction completion, the products were purified by recrystallization from a co-solvent of acetonitrile and diethyl ether to generate the desired tris-triazoles in quantitative high yields. During the course of our studies, as previously reported by Sharpless,[30] the use of Cu^{II} [$Cu(OAc)_2$] reduced by sodium ascorbate gave generally higher yields than a direct source of



Scheme 3

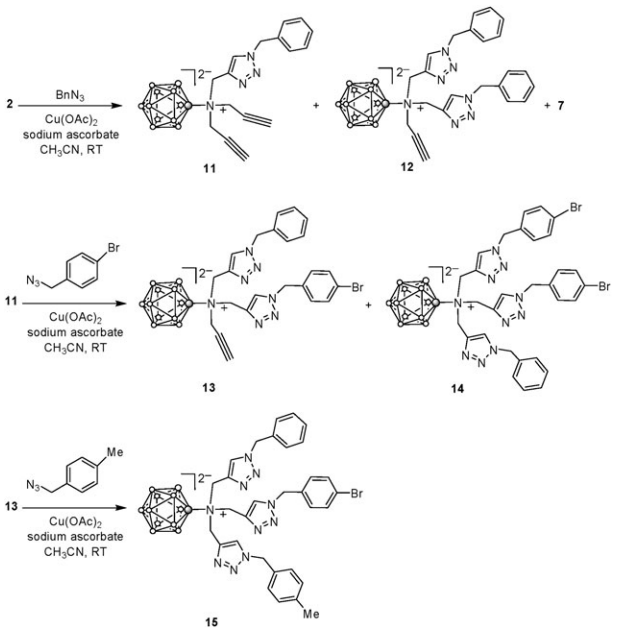


Scheme 4

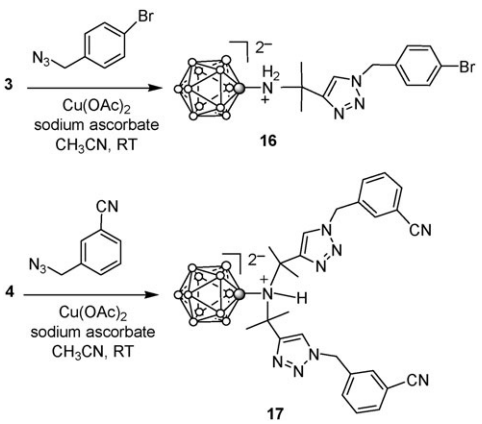
Cu^{I} (CuBr). Trace amounts of copper salts in the products were easily removed by adding a small amount of diethyl ether (**7–15**) or by washing with CH_2Cl_2 water (**16–20**). Owing to the high degree of efficiency, the reaction could be conducted with a stoichiometric amount (4.5 equiv.) of azides. Purification was greatly simplified by the absence of side products. Triazolo dodecaborates (**7–10**) were designed as a symmetrical trifunctional dodecaborate with triazoles functioning as a rigid linker unit (Schemes 3 and 4). It is also possible to functionalize the surface of the resulting compounds using azide-terminated hydroxyl and aryl groups as building blocks for further chemical reactions. Under controlled reaction conditions, unsymmetrical trifunctional dodecaborate (**15**) was synthesized as shown in Scheme 5. This was prepared in a three-step process: firstly, the reaction of equimolar amounts of **2** with benzyl azide afforded a mixture of **7**, **11** and **12**. Secondly, treatment of **11** with *p*-bromobenzyl azide yielded two products **13** and **14**. Thirdly, tris-triazolyl dodecaborate anion (**15**) was obtained by reaction of **13** with 1.5 equivalents of *p*-methylbenzyl azide.

Compounds **11–15** were purified by preparative TLC using MeOH–CH_2Cl_2 (1 : 8) as a mobile phase. A synthetic protocol for unsymmetric dodecaborates (**11–15**) was constructed to provide a wide variety of triazole-based dodecaborate anions. Mono- and ditriazole conjugates (**16** and **17**, respectively) were obtained from the corresponding mono- and dipropargylic aminododecaborates, respectively (Scheme 6).

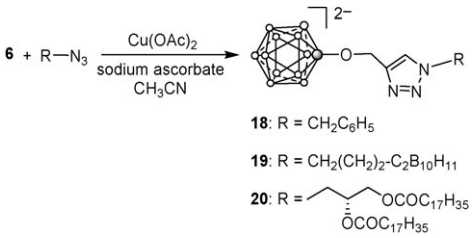
Following the same procedure, hydroxydodecaborates conjugated with a triazole unit (**18–20**) were also prepared in excellent yields (Scheme 7). The advantages of the presented compounds (**7–20**) stem from the attractive properties of the



Scheme 5



Scheme 6



Scheme 7

triazole linker formed as a result of azide and dodecaborate alkynes fusion. Due to the high dipole moment (actually higher than an amide bond), the triazole linker can participate in hydrogen bond formation as both hydrogen bond donor and acceptor, which help the triazole unit fit well into the diverse environments of biological molecules.[27]

Compounds **9** and **19** have a high percentage of boron by weight (up to approximately 44%), enabling them to deliver high therapeutic amounts of boron to the target tumour with tolerable toxicity. Each compound contains two different units of boron clusters carrying one or two negative charges. These compounds may be used to optimize BNCT treatment through a cocktail of different boron clusters in one BNCT agent. Finally, lipids are a class of biomolecules that serve critical roles in cellular function and can also modulate the activities of other biomolecules such as proteins and glycans. From this viewpoint, we designed the first dodecaborate lipid **10** containing six tail moieties with only one negative charge. Thus, dodecaborate cluster lipids with reduced net charge (up to a neutral molecule) might be desirable with regards to therapeutic efficacy.[12] Therefore compounds **10** and **20** are presented as useful examples in liposomal boron delivery systems in neutron capture therapy.

In the ^{1}H NMR spectra of compounds **7–20**, we found a low-field shift of CH of the former ethyne groups in compounds **2–4** and **6**, from 2.85 ppm to approximately 7.95 ppm, indicating the formation of a triazole moiety. Moreover, the chemical shift of the CH_2 group of the former propyl groups (compounds **2** and **6**) changed from approximately 4.25 to approximately 4.75 ppm. Similarly, the CH_2 group of the free azide was downfield-shifted from approximately 4.35 to approximately 5.35 ppm in compounds **7–20** upon click reaction with dodecaborate-terminated alkynes. The ^{13}C NMR spectra showed new signals at approximately 136 and 128 ppm for the C=CH triazole carbons of compounds **7–20**. ^{11}B NMR spectra of undecahydro-*closo*-dodecaborates presented a characteristic shielding pattern over a remarkable range of approximately −20 to +3 ppm, showing only minor differences in the overall ^{11}B cluster shielding patterns. The ESI-MS spectra of the compounds **7–17** and **18–20** in CH_3CN showed molecular ion peaks at M^- and $M^-/2$, respectively, attributed to the typical pattern of boron isotopes (^{10}B and ^{11}B). The IR spectra of compounds **7–20** contain a strong band of B–H stretching at approximately 2495 cm^{-1} and bands of the C=C and N=N at approximately 1651 and 1562 cm^{-1}, respectively. This can be explained by the existence of the dodecaborate anion conjugate's triazole moiety.

Conclusions

We have conveniently synthesised a series of novel mono-, bi- and tri-alkynyl undecahydro-*closo*-dodecaborate anions for Huisgen cycloaddition reactions. The degree of alkylation of **1** was dependent upon the structure of alkyl halides used. X-ray structural analyses of anions **2** and **6** indicate that no change in cluster bonding takes place upon alkylation. Reaction of **2–4** and **6** with compounds of clinical interest *via* a click reaction were also investigated. The click reaction is experimentally simple, proceeding well in acetonitrile solutions without protection from oxygen, requiring only stoichiometric amounts of starting materials and generating virtually no by-products. The wide scope is equally important, high selectivity and nearly quantitative yields of this transformation. In our procedure for the best click reaction to date,[31] the components and catalysts are simply mixed and stirred, whereupon pure products are isolated by filtration or simple extraction. All dodecaborate-conjugated triazoles were isolated

directly as pure solids (*i.e.* without chromatographic separations), meeting the requirements for large-scale applications. Chromatographic purification is required for compounds **11–14**. A variety of functional groups are compatible with each process. The current study provides guidance for ongoing efforts in our laboratories to develop new BNCT delivery agents.

Experimental section

Materials and instruments

Most chemicals were of analytical grade and used without further purification. Azides {$C_6H_5CH_2N_3$, *p*-Br-$C_6H_4CH_2N_3$, *p*-Me-$C_6H_4CH_2N_3$, *m*-CN-$C_6H_4CH_2N_3$, 3-azido-1-propanol, 3-azidopropyl-*o*-carborane, and (*R*)-3-azidopropane-1,2-diyl distearate}, $[(CH_3)_4N]$ H_3N–$B_{12}H_{11}$ (**1**) and $(MePh_3P)_2HO$–$B_{12}H_{11}$ (**5**) were prepared as described in the literature.[8,20,21,32,33] Moisture was removed from $[(CH_3)_4N]$ H_3N–$B_{12}H_{11}$ by heating for 3 h at 100 °C under vacuum. ^{1}H NMR and ^{13}C NMR spectra were measured on a JEOL JNM-AL 300 (300 MHz) and VARIAN UNITY-INOVA 400 (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR and ^{13}C NMR are expressed in parts per million (ppm, δ units), and coupling constant (J) values are expressed in units of hertz (Hz). ^{11}B NMR spectra were recorded on a JEOL JNM-AL 300 spectrometer (96.3 MHz) and the chemical shifts were reported in δ units relative to external $BF_3{\cdot}Et_2O$ in $CDCl_3$. IR (cm^{-1}) spectra were determined using a KBr disc on a Shimadzu FTIR-8600PC spectrometer. Electron spray ionization (ESI) mass spectra were recorded on a Shimadzu LCMS-2010 eV spectrometer or Bruker Daltonics micro TOF-15 focus. Elemental analyses were performed using a Perkin-Elmer 2400 automatic elemental analyzer. All compounds gave elemental analysis within ±0.3% of the theoretical values. Analytical thin layer chromatography (TLC) was performed on a glass plates of silica gel 60 GF_{254} (Merck). Visualization was accompanied by UV light (254 nm), I_2, $KMnO_4$, or $PdCl_2$. Preparative TLC was carried out using 0.75 mm layers of silica gel 60 GF_{254} (Merck) made from water slurries on glass plates of dimensions 20 × 20 cm^2, followed by drying in air at 100 °C. Column chromatography was conducted on silica gel (Merck Kieselgel 70–230 mesh).

N,*N*,*N*-Tris-(prop-2-ynyl)amino-undecahydro-*closo*-dodecaborate(1−) tetramethylammonium salt (2)

A solution of **1** (600 mg, 2.6 mmol) and KOH (726 mg, 13 mmol) in dry DMF (25 ml) was stirred at room temperature under an argon atmosphere. To this solution, 1.95 ml (26 mmol) of propargyl bromide was added. After stirring for 24 h the solvent was evaporated *in vacuo* and the brown residue dissolved in 20 ml acetonitrile. The insoluble material was filtered off and the filtrate was added dropwise through a dropping funnel over a period of 10 min to a stirred solution of diethyl ether (750 ml). A yellow precipitate was formed, which was collected by filtration and recrystallized from water to yield white needles of **2** (870 mg, 97%). Crystals suitable for X-ray structure analysis were grown from an acetonitrile solution layered with diethyl ether at 4 °C. mp > 300 °C. IR (KBr, cm^{-1}) 3263, 3031 (ν_{CH}), 2492 (ν_{BH}), 2125 ($\nu_{C\equiv C}$), 1438 (ν_{BN}), 1485, 1405, 1342 (ν_{CH}), 1150 (ν_{CN}), 1057 (ν_{B-B}), 995, 949, 852, 721, 678 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 4.28 (s, 6H, N–CH_2), 3.07 (s, 12H, $N(CH_3)_4$), 2.87 (m, 3H, C≡CH), 1.7–0.42 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 80.32 (3C, C≡CH), 75.99 (3C, C≡CH), 56.14 (4C, $N(CH_3)_4$), 53.32 (3C, N–CH_2). ^{11}B NMR (96.3 MHz; CD_3CN): δ −3.11 (s, 1B, B1), −20.81 (bs, 11B, B2-12). MS (ESI): m/z 272.3 [100, M^-]. Anal. Calcd. for $C_{13}H_{32}B_{12}N_2$: C, 45.11; H, 9.32; N, 8.09%. Found: C, 44.92; H, 9.2; N, 8.01%.

N-(1,1-Dimethylprop-2-ynyl)amino-undecahydro-*closo*-dodecaborate(1−) tetrabutylammonium salt (3) and *N*,*N*-bis(1,1-dimethylpropynyl)amino-undecahydro-*closo*-dodecaborate(1−) tetrabutylammonium salt (4)

A solution of **1** (500 mg, 2.16 mmol) and KOH (607 mg, 10.9 mmol) in dry DMF (50 ml) was stirred at room temperature under an argon atmosphere. To this solution, 5.1 ml (45.1 mmol) of 3-chloro-3-methyl-1-butyne was added dropwise over 10 min. After stirring for two days, the solvent was evaporated *in vacuo* and the orange residue dissolved in 10 ml of acetonitrile. The insoluble material was filtered off and the filtrate was added dropwise through a dropping funnel over a period of 10 min to a stirred solution of diethyl ether (500 ml). A yellow precipitate was formed, which was collected by filtration and dissolved in 20 ml of water. This aqueous solution was filtered and 700 mg of tetrabutylammonium bromide (2.16 mmol) was added to the filtrate, resulting in a precipitate that was filtered off. Recrystalization from ethanol gave **3** as white needles (372 mg, 37%). The water-insoluble residue contained bisalkylated derivative **4**. This was recrystallized from water and dissolved in water–acetonitrile. A solid was precipitated by addition of 700 mg of tetrabutylammonium bromide (2.16 mmol) and recrystallized from ethanol to give **4** as white needles (322 mg, 28%).

3: mp 169–171 °C. IR (KBr, cm^{-1}) 3220 (ν_{NH}), 2962, 2935, 2873 (ν_{CH}), 2480 (ν_{BH}), 2120 ($\nu_{C\equiv C}$), 1442 (ν_{BN}), 1469, 1377, 1238 (ν_{CH}), 1153 (ν_{CN}), 1045 (ν_{B-B}), 1010, 895, 855, 740 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 6.55 (m, 2H, H_2N-), 3.08 (m, 8H, $N(CH_2)_4$), 2.87 (m, 1H, C≡CH), 1.83 (s, 6H, $(CH_3)_2$), 1.56 (m, 8H, $N(CH_2CH_2)_4$), 1.38 (m, 8H, $N(CH_2CH_2CH_2)_4$), 0.95 (t, J = 14.71 Hz, 12H, $N(CH_2CH_2CH_2CH_3)_4$), 1.85–0.37 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 80.31 (C, C≡CH), 75.99 (C, C≡CH), 59.23 (4C, $N(CH_2)_4$), 52.26 (C, H_2N-C), 24.2 (4C, $N(CH_2CH_2)_4$), 22.31 (2C, $(CH_3)_2$), 20.22 (4C, $N(CH_2CH_2CH_2)_4$), 13.68 (4C, $N(CH_2CH_2CH_2CH_3)_4$). ^{11}B NMR (96.3 MHz; CD_3CN): δ −3.11 (s, 1B, B1), −20.02 (s, 10B, J = 85.22 Hz, B2-11), −16.17 (s, 1B, B12). MS (ESI): m/z 223.6 [100, M^-]. Anal. Calcd. for $C_{21}H_{56}B_{12}N_2$: C, 54.08; H, 12.1; N, 6.01%. Found: C, 53.89; H, 11.92; N, 5.94%.

4: mp 139–141 °C. IR (KBr, cm^{-1}) 3263, 3031 (ν_{CH}), 3210 (ν_{NH}), 2495 (ν_{BH}), 2127 ($\nu_{C\equiv C}$), 1440 (ν_{BN}), 1485, 1407, 1340 (ν_{CH}), 1147 (ν_{CN}), 1055 (ν_{B-B}), 998, 952, 856, 725, 675 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 5.42 (bs, 1H, NH), 3.09 (m, 8H, $N(CH_2)_4$), 2.83 (m, 2H, C≡CH), 1.82 (s, 12H, $(CH_3)_2$), 1.55 (m, 8H, $N(CH_2CH_2)_4$), 1.35 (m, 8H, $N(CH_2CH_2CH_2)_4$), 0.95 (t, J = 14.71 Hz, 12H, $N(CH_2CH_2CH_2CH_3)_4$), 1.7–0.41 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 81.34 (2C, C≡CH), 75.96, 75.23 (2C, C≡CH), 59.35 (4C, $N(CH_2)_4$),

53.56 (2C, NH-C), 24.35 (4C, $N(CH_2CH_2)_4$), 22.24, 21.92 (4C, $(CH_3)_2$), 20.18 (4C, $N(CH_2CH_2CH_2)_4$), 13.75 (4C, $N(CH_2CH_2CH_2CH_3)_4$). ^{11}B NMR (96.3 MHz; CD_3CN): δ −3.08 (s, 1B, B1), −20.84 (bs, 11B, B2-12). MS (ESI): m/z 290.6 [100, M^-]. Anal. Calcd. for $C_{26}H_{62}B_{12}N_2$: C, 58.64; H, 11.74; N, 5.26%. Found: C, 58.39; H, 11.57; N, 5.02%.

O-(Prop-2-ynyl)hydroxo-undecahydro-*closo*-dodecaborate(2−) ditetrabutylammonium salt (6)

Propargyl bromide (1.05 ml, 14 mmol) was added to a stirred solution of **5** (1.0 g, 1.4 mmol) and KOH (396 mg, 7.1 mmol) in 50 ml dry DMF under an argon atmosphere. The solution was stirred for two days at room temperature. The solvent was evaporated *in vacuo* and the residue was washed with diethyl ether and dissolved in 25 ml of water. Addition of 4.51 g (14 mmol) of tetrabutylammonium bromide gave a white precipitate of **6** (877 mg, 92%). To obtain crystals suitable for X-ray analysis, **6** was dissolved in dichloromethane. Ethanol was added. Crystals were grown by slowly evaporating the volatile constituents at room temperature to yield colourless needles. mp 208–210 °C. IR (KBr, cm^{-1}) 3263, 3030, 2960 (ν_{CH}), 2495 (ν_{BH}), 2123 ($\nu_{C\equiv C}$), 1701 (ν_{BO}), 1485, 1404, 1286 (ν_{CH}), 1150 (ν_{CN}), 1045 (ν_{B-B}), 995, 948, 821, 719, 673 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 3.95 (s, 2H, O–CH_2), 3.12 (m, 16H, $N(CH_2)_4$), 3.06 (m, 1H, C≡CH), 1.57 (m, 16H, $N(CH_2CH_2)_4$), 1.38 (m, 16H, $N(CH_2CH_2CH_2)_4$), 0.95 (t, J = 14.41 Hz, 24H, $N(CH_2CH_2CH_2CH_3)_4$), 1.85–0.16 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 71.25 (2C, C≡CH), 59.34 (8C, $N(CH_2)_4$), 56.79 (C, O–CH_2), 24.31 (8C, $N(CH_2CH_2)_4$), 20.26 (8C, $N(CH_2CH_2CH_2)_4$), 13.75 (8C, $N(CH_2CH_2CH_2CH_3)_4$). ^{11}B NMR (96.3 MHz; CD_3CN): δ 8.44 (s, 1B, B1), −12.07 (d, J = 266.17 Hz, 10B, B2-11), −21.03 (s, 1B, B12). MS (ESI): m/z 97.8 [100, $M^-/2$]. Anal. Calcd. for $C_{35}H_{86}B_{12}N_2O$: C, 61.75; H, 12.73; N, 4.11%. Found: C, 61.67; H, 12.69; N, 4.07%.

N,*N*,*N*-Tris[1-benzyl-(1,2,3-triazol-4-yl)methyl]amino-undecahydro-*closo*-dodecaborate(1−) tetramethylammonium salt (7)

To a solution of **2** (345 mg, 1 mmol) in acetonitrile (20 ml), were added $Cu(OAc)_2$ (75 mg, 0.41 mmol) and sodium ascorbate (150 mg, 0.75 mmol) at room temperature and benzyl azide (599 mg, 4.5 mmol) was added dropwise with stirring. The reaction mixture was stirred for 6 h until complete consumption of **2** monitored by TLC (MeOH–CH_2Cl_2 1 : 4). The mixture was filtered through a pad of celite and diethyl ether (10 ml) was added until a precipitate (inorganic salts) formed. This precipitate was removed by filtration and another 200 ml of diethyl ether was added to the filtrate, whereupon a crystalline solid was precipitated. The finely crystalline product was filtered to give **7** (722 mg, 97%) as a white solid. For analysis a sample recrystallized again from acetonitrile–ether was obtained as colourless needles. mp 205–207 °C. IR (KBr, cm^{-1}) 3265, 3032 (ν_{CH}), 2499 (ν_{BH}), 1651 ($\nu_{C=C}$), 1562 ($\nu_{N=N}$), 1454 (ν_{BN}), 1485, 1405, 1361 (ν_{CH}), 1130 (ν_{CN}), 1053 (ν_{B-B}), 1029, 948, 852, 721, 680 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 7.95 (s, 3H, CH-triazole), 7.31–7.23 (m, 15H, CH-phenyl), 5.36 (s, 6H, CH_2-benzyl), 4.76 (s, 6H, N–CH_2), 3.05 (s, 12H, $N(CH_3)_4$), 1.85–0.59 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 140.3, 136.01 (3C, C-triazole), 129.64, 129.18, 129.1, 128.75 (18C, CH and C-phenyl), 128.75 (3C, CH-triazole), 57.42 (3C, N–CH_2), 56.95 (4C, $N(CH_3)_4$), 54.19 (2C, CH_2-benzyl). ^{11}B NMR (96.3 MHz; CD_3CN): δ −2.39 (s, 1B, B1), −20.79 (bs, 11B, B2-12). MS (ESI): m/z 671.6 [100, M^-]. Anal. Calcd. for $C_{34}H_{53}B_{12}N_{11}$: C, 54.77; H, 7.16; N, 20.66%. Found: C, 54.49; H, 6.89; N, 20.29%.

N,*N*,*N*-Tris[1-(3-hydroxypropyl)-(1,2,3-triazol-4-yl)methyl]amino-undecahydro-*closo*-dodecaborate(1−) tetramethylammonium salt (8)

This compound was prepared from **2** (173 mg, 0.5 mmol) and 3-azido-1-propanol (0.51 g, 2.25 mmol), using the procedure described for **7** to give **10** (493 mg, 96%) as a white solid. mp 158–160 °C. IR (KBr, cm^{-1}) 3455 (ν_{OH}), 3267, 3030 (ν_{CH}), 2502 (ν_{BH}), 1655 ($\nu_{C=C}$), 1565 ($\nu_{N=N}$), 1455 (ν_{BN}), 1485, 1405, 1365 (ν_{CH}), 1132 (ν_{CN}), 1055 (ν_{B-B}), 1030, 952, 855, 725, 685 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 7.97 (s, 3H, CH-triazole), 4.76 (s, 6H, N–CH_2), 4.35 (m, 6H, N–CH_2-), 3.95 (m, 6H, –CH_2–OH), 3.07 (s, 12H, $N(CH_3)_4$), 2.25 (m, 6H, –CH_2–), 1.85–0.59 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 136.25 (3C, C-triazole), 128.39 (3C, CH-triazole), 59.62 (3C, –CH_2–OH), 57.43 (3C, N–CH_2), 56.92 (4C, $N(CH_3)_4$), 35.42 (3C, –CH_2–). ^{11}B NMR (96.3 MHz; CD_3CN): δ −2.79 (s, 1B, B1), −20.19 (bs, 11B, B2-12). MS (ESI): m/z 574.6 [100, M^-]. Anal. Calcd. for $C_{22}H_{53}B_{12}N_{11}O_3$: C, 40.69; H, 8.23; N, 23.72%. Found: C, 40.59; H, 8.03; N, 23.38%.

N,*N*,*N*-Tris[1-(3-*o*-carboranylpropyl)-(1,2,3-triazol-4-yl)methyl]amino-undecahydro-*closo*-dodecaborate(1−) tetramethylammonium salt (9)

This compound was prepared from **2** (173 mg, 0.5 mmol) and 3-azidopropyl-*o*-carborane (0.51 g, 2.3 mmol), using the procedure described for **7** to give **8** (493 mg, 96%) as a white solid. mp 179–181 °C. IR (KBr, cm^{-1}) 3460, 3043 (ν_{CH}), 2595, 2503 (ν_{BH}), 1624 ($\nu_{C=C}$), 1558 ($\nu_{N=N}$), 1439 (ν_{BN}), 1485, 1405, 1384 (ν_{CH}), 1141 (ν_{CN}), 1053 (ν_{B-B}), 1022, 949, 848, 725, 675 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 8.06 (s, 2H, CH-triazole), 4.75 (m, 6H, N–CH_2-), 4.33 (m, 6H, N–CH_2), 4.13 (m, 3H, CH-carborane), 3.84 (m, 6H, –CH_2–), 3.42 (m, 6H, CH_2-carborane), 3.08 (s, 12H, $N(CH_3)_4$), 1.85–0.35 (m, 41H, $B_{12}H_{11}$ and $C_2B_{10}H_{10}$). ^{13}C NMR (75 MHz, CD_3CN): δ 147.54 (3C, CH-triazole), 126.21 (3C, C-triazole), 76.16 (3C, C-carborane), 65.37 (3CH, CH-carborane), 57.55 (3C, N–CH_2), 56.34 (4C, $N(CH_3)_4$), 50.12 (3C, CH_2-N), 35.21 (3C, –CH_2–) 30.76 (3C, CH_2-carborane). ^{11}B NMR (96.3 MHz; CD_3CN): δ −3.12 (bs, 1B, B1), −8.03, −15.04, −16.8, −20.14, −20.57, −21.31 (bs, 41B, $B_{12}H_{11}$ and $C_2B_{10}H_{10}$). MS (ESI): m/z 954.12 [100, M^-]. Anal. Calcd. for $C_{28}H_{83}B_{42}N_{11}$: C, 32.71; H, 8.14; N, 14.99%. Found: C, 32.52; H, 7.83; N, 14.71%.

N,*N*,*N*-Tris[1-(1,2-*O*-distearoyl-*sn*-3-glycerol)-(1′,2′,3′-triazol-4-yl)methyl]amino-undecahydro-*closo*-dodecaborate(1−) tetramethylammonium salt (10)

A solution of **2** (173 mg, 0.5 mmol), $Cu(OAc)_2$ (37.5 mg, 0.2 mmol), and sodium ascorbate (75 mg, 0.37 mmol) in

acetonitrile (10 ml) was stirred at 50 °C for 5 min. While stirring, (*R*)-3-azidopropane-1,2-diyl distearate (511 mg, 0.75 mmol) was added dropwise. The reaction mixture was stirred at 60 °C for 6 h until complete consumption of **2** monitored by TLC (MeOH–CH_2Cl_2 1 : 4). The reaction mixture evaporated to dryness. The residue was redissolved in 10 ml dry CH_2Cl_2 and filtered off and evaporated again to dryness. The resulting substance was recrystallized from acetonitrile. The finely crystalline product was collected by filtration to give a white solid of **9** (1.12 g, 94%). mp 183–185 °C. IR (KBr, cm^{-1}) 2975, 2920, 2850 (ν_{CH}), 2503 (ν_{BH}), 1743 ($\nu_{C=O}$), 1620 ($\nu_{C=C}$), 1542 ($\nu_{N=N}$), 1469 (ν_{BN}), 1485, 1405, 1377 (ν_{CH}), 1172 (ν_{CN}), 1103 (ν_{B-B}), 1050, 1014, 950, 852, 721, 675 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 7.98 (s, 3H, CH-triazole), 5.25 (m, 6H, N–CH_2–), 5.16 (m, 3H, CH–), 4.85 (m, 6H, N–CH_2), 4.27 (m, 6H, –$CHCH_2C$═O), 4.14 (m, 6H, $CHCH_2C$═O), 3.05 (s, 12H, $N(CH_3)_4$), 2.32 (m, 12H, –CH_2CH_2C═O), 1.85–0.55 (m, 11H, $B_{12}H_{11}$), 1.61 (m, 12H, CH_2), 1.25 (s, 120H, CH_2), 0.88 (t, 18H, J_{CH} = 12.61 Hz, CH_3). ^{13}C NMR (75 MHz, CD_3CN): δ 173.36, 172.95 (6C, CO), 137.05 (3C, CH-triazole), 129.1 (3C, C-triazole), 58.12 (3C, N–CH_2), 56.41 (4C, 4C, $N(CH_3)_4$), 51.08 (3C, N–CH_2), 70.42, 62.47, 35.63, 35.03, 32.19, 29.65, 29.42, 29.37, 29.33, 29.22, 29.05, 29.02, 28.95, 25.17, 25.05, 22.23, 14.05 (lipid-carbons). ^{11}B NMR (96.3 MHz; CD_3CN): δ −3.08 (bs, 1B, B1), −20.57 (bs, 11B, B2-12). Anal. Calcd. for $C_{133}H_{263}B_{12}N_{11}O_{15}$: C, 66.94; H, 11.11; N, 6.46%. Found: C, 66.69; H, 10.94; N, 6.25%.

N,*N*-Bis(Prop-2-ynyl)-*N*-[1-benzyl-(1,2,3-triazol-4-yl)methyl]-amino-undecahydro-*closo*-dodecaborate(1−) (11) and *N*-(prop-2-ynyl)-*N*,*N*-bis[1-benzyl-(1,2,3-triazol-4-yl)methyl]amino-undecahydro-*closo*-dodecaborate(1−) (12)

This compound was prepared from **2** (345 mg, 1 mmol) and benzyl azide (159 mg, 1.2 mmol), using the procedure described for **7** to give a mixture of **11** and **12** as a white solid. This mixture was purified by column chromatography with MeOH–CH_2Cl_2 (1 : 4) as the mobile phase to give a white solid of **11** (R_f = 0.25, 105 mg, 22%) and **12** (R_f = 0.47, 43 mg, 7%).

11: mp 265–267 °C. IR (KBr, cm^{-1}) 3260, 3032 (ν_{CH}), 2503 (ν_{BH}), 2123 ($\nu_{C\equiv C}$), 1651 ($\nu_{C=C}$), 1565 ($\nu_{N=N}$), 1455 (ν_{BN}), 1485, 1405, 1362 (ν_{CH}), 1135 (ν_{CN}), 1057 (ν_{B-B}), 1030, 955, 848, 725, 685 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 7.95 (s, 1H, CH-triazole), 7.3–7.25 (m, 5H, CH-phenyl), 5.34 (s, 2H, CH_2-benzyl), 4.72 (s, 2H, N–CH_2), 4.32 (s, 4H, N–CH_2), 2.85 (m, 2H, C≡CH), 1.85–0.55 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 136.01 (1C, C-triazole), 129.55, 129.05, 128.52 (6C, CH and C-phenyl), 128.52 (1C, CH-triazole), 57.53 (1C, N–CH_2), 54.25 (1C, CH_2-benzyl), 79.98 (2C, C≡CH), 76.02 (2C, C≡CH), 53.56 (2C, N–CH_2). ^{11}B NMR (96.3 MHz; CD_3CN): δ −2.78 (s, 1B, B1), −20.35 (bs, 11B, B2-12). MS (ESI): *m*/*z* 405.6 [100, M^-]. Anal. Calcd. for $C_{20}H_{39}B_{12}N_5$: C, 50.12; H, 8.2; N, 14.61%. Found: C, 49.93; H, 8.01; N, 14.47%.

12: mp 173–175 °C. IR (KBr, cm^{-1}) 3262, 3030 (ν_{CH}), 2499 (ν_{BH}), 2125 ($\nu_{C\equiv C}$), 1648 ($\nu_{C=C}$), 1563 ($\nu_{N=N}$), 1455 (ν_{BN}), 1485, 1405, 1365 (ν_{CH}), 1138 (ν_{CN}), 1055 (ν_{B-B}), 1022, 958, 852, 725, 686 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 8.05 (s, 2H, CH-triazole), 7.33–7.26 (m, 10H, CH-phenyl), 5.37 (s, 4H, CH_2-benzyl), 4.75 (s, 4H, N–CH_2), 4.33 (s, 2H, N–CH_2), 2.87 (m, 1H, C≡CH), 1.85–0.55 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 137.23 (2C, C-triazole), 129.55, 129.11, 128.64 (12C, CH and C-phenyl), 128.64 (2C, CH-triazole), 57.55 (2C, N–CH_2), 54.28 (2C, CH_2-benzyl), 80.03 (1C, C≡CH), 75.89 (1C, C≡CH), 53.55 (1C, N–CH_2). ^{11}B NMR (96.3 MHz; CD_3CN): δ −3.05 (s, 1B, B1), −20.25 (bs, 11B, B2-12). MS (ESI): *m*/*z* 537.6 [100, M^-]. Anal. Calcd. for $C_{47}H_{46}B_{12}N_8$: C, 52.95; H, 7.57; N, 18.3%. Found: C, 52.79; H, 7.29; N, 17.98%.

N-(Prop-2-ynyl)-*N*-[1-benzyl-(1,2,3-triazol-4-yl)methyl]-*N*-[1-(*p*-bromobenzyl-1,2,3-triazol-4-yl)methyl]amino-undecahydro-*closo*-dodecaborate(1−) (13) and *N*,*N*-bis[1-(*p*-bromobenzyl-1,2,3-triazol-4-yl)methyl]-*N*-[1-benzyl-(1,2,3-triazol-4-yl)methyl]amino-undecahydro-*closo*-dodecaborate(1−) (14)

This compound was prepared from **11** (500 mg, 1.04 mmol) and *p*-bromobenzyl azide (265 mg, 1.2 mmol), using the procedure described for **7** to give a mixture of **13** and **14** as a white solid. This mixture was purified by column chromatography with MeOH–CH_2Cl_2 (1 : 8) as the mobile phase to give a white solid of **13** (R_f = 0.27, 145 mg, 20%) and **14** (R_f = 0.53, 424 mg, 45%).

13: mp 187–189 °C. IR (KBr, cm^{-1}) 3263, 3036 (ν_{CH}), 2502 (ν_{BH}), 2123 ($\nu_{C\equiv C}$), 1647 ($\nu_{C=C}$), 1562 ($\nu_{N=N}$), 1457 (ν_{BN}), 1485, 1407, 1364 (ν_{CH}), 1136 (ν_{CN}), 1055 (ν_{B-B}), 998, 948, 852, 721, 682 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 8.03, 7.99 (s, 2H, CH-triazole), 7.53 (d, J_{CH} = 7.84 Hz, 2H, CH-phenyl), 7.32–7.27 (m, 5H, CH-phenyl), 7.22 (d, J_{CH} = 7.84 Hz, 2H, CH-phenyl), 5.42, 5.35 (s, 4H, CH_2-benzyl), 4.77, 4.69 (s, 4H, N–CH_2), 4.31 (s, 2H, N–CH_2), 2.85 (m, 1H, C≡CH), 1.85–0.55 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 136.05, 135.98 (2C, C-triazole), 132.83, 130.86, 129.55, 129.05, 128.52 (12C, CH and C-phenyl), 128.52, 127.03 (2C, CH-triazole), 57.63 (2C, N–CH_2), 54.22, 53.35 (2C, CH_2-benzyl), 79.94 (1C, C≡CH), 75.68 (1C, C≡CH), 53.41 (1C, N–CH_2). ^{11}B NMR (96.3 MHz; CD_3CN): δ −2.75 (s, 1B, B1), −20.19 (bs, 11B, B2-12). MS (ESI): *m*/*z* 615.6 [100, M^-]. Anal. Calc. for $C_{27}H_{45}B_{12}BrN_8$: C, 46.91; H, 6.56; N, 16.21%. found: C, 46.83; H, 6.42; N, 16.09%.

14: mp 192–194 °C. IR (KBr, cm^{-1}) 3265, 3031 (ν_{CH}), 2492 (ν_{BH}), 1645 ($\nu_{C=C}$), 1562 ($\nu_{N=N}$), 1452 (ν_{BN}), 1485, 1405, 1365 (ν_{CH}), 1132 (ν_{CN}), 1052 (ν_{B-B}), 995, 945, 842, 725, 680 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 8.05, 7.96 (s, 3H, CH-triazole), 7.55 (d, J_{CH} = 7.85 Hz, 4H, CH-phenyl), 7.31–7.27 (m, 5H, CH-phenyl), 7.21 (d, J_{CH} = 7.84 Hz, 4H, CH-phenyl), 5.42, 5.35 (s, 6H, CH_2-benzyl), 4.75, 4.68 (s, 6H, N–CH_2), 1.85–0.55 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 136.01, 135.76 (3C, C-triazole), 132.85, 130.82, 129.52, 129.12, 128.73 (18C, CH and C-phenyl), 128.73, 127.05 (3C, CH-triazole), 57.49 (3C, N–CH_2), 54.31, 53.32 (3C, CH_2-benzyl). ^{11}B NMR (96.3 MHz; CD_3CN): δ −2.86 (s, 1B, B1), −19.97 (bs, 11B, B2-12). MS (ESI): *m*/*z* 828.2 [100, M^-]. Anal. Calc. for $C_{34}H_{51}B_{12}Br_2N_{11}$: C, 45.2; H, 5.69; N, 17.06%. Found: C, 44.93; H, 6.51; N, 16.84%.

_N_-[1-Benzyl-(1,2,3-triazol-4-yl)methyl]-_N_-[1-(_p_-bromobenzyl-1,2,3-triazol-4-yl)methyl]-_N_-[1-(_p_-methylbenzyl-1,2,3-triazol-4-yl)methyl]amino-undecahydro-_closo_-dodecaborate(1−) (15)

This compound was prepared from **13** (100 mg, 0.14 mmol) and _p_-methylbenzyl azide (32 mg, 0.21 mmol), using the procedure described for **7** to give **15** (120 mg, 99%) as a white solid. mp 173–175 °C. IR (KBr, cm^{-1}) 3265, 3032 (ν_{CH}), 2495 (ν_{BH}), 1651 ($\nu_{C=C}$), 1565 ($\nu_{N=N}$), 1455 (ν_{BN}), 1485, 1405, 1365 (ν_{CH}), 1126 (ν_{CN}), 1055 (ν_{B-B}), 1010, 949, 852, 721, 685 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 8.03–7.78 (m, 3H, CH-triazole), 7.56 (d, J_{CH} = 7.85 Hz, 2H, CH-phenyl), 7.32–7.25 (m, 5H, CH-phenyl), 7.22 (d, J_{CH} = 7.85 Hz, 2H, CH-phenyl), 7.14 (bs, 4H, CH-phenyl), 5.42–5.37 (m, 6H, CH_2-benzyl), 4.75–4.69 (m, 6H, N–CH_2), 1.85–0.55 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 136.01, 135.76, 134.02 (3C, C-triazole), 132.85, 130.82, 129.52, 129.12, 128.73, 126.02 (18C, CH and C-phenyl), 128.73, 127.05 (3C, CH-triazole), 57.49 (3C, N–CH_2), 54.31, 54.21, 53.32 (3C, CH_2-benzyl). ^{11}B NMR (96.3 MHz; CD_3CN): δ −2.75 (s, 1B, B1), −20.17 (bs, 11B, B2-12). MS (ESI): m/z 765.5 [100, M^-]. Anal. Calcd. for $C_{35}H_{54}B_{12}BrN_{11}$: C, 50.13; H, 6.49; N, 18.37%. Found: C, 49.88; H, 6.29; N, 18.06%.

_N_-[1-(_p_-Bromobenzyl-1,2,3-triazol-4-yl)isopropyl]amino-undecahydro-_closo_-dodecaborate(1−) tetrabutylammonium salt (16)

This compound was prepared from **3** (232 mg, 0.5 mmol) and _p_-bromobenzyl azide (159 mg, 0.75 mmol), using the procedure described for **7** to give **16** (327 mg, 97%) as a white solid. mp 181–183 °C. IR (KBr, cm^{-1}) 3225 (ν_{NH}), 3031 (ν_{CH}), 2488 (ν_{BH}), 1685 ($\nu_{C=C}$), 1565 ($\nu_{N=N}$), 1454 (ν_{BN}), 1473, 1434, 1380 (ν_{CH}), 1135 (ν_{C-N}), 1053 (ν_{B-B}), 1010, 955, 802, 740, 685 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 7.96 (s, 1H, CH-triazole), 7.49 (d, J_{CH} = 8.11 Hz, 2H, CH-phenyl), 7.16 (d, J_{CH} = 7.51 Hz, 2H, CH-phenyl), 5.52 (bs, 2H, NH_2), 5.36 (s, 2H, CH_2-benzyl), 3.07 (m, 8H, $N(CH_2)_4$), 1.85 (s, 6H, $(CH_3)_2$), 1.56 (m, 8H, $N(CH_2CH_2)_4$), 1.32 (m, 8H, $N(CH_2CH_2CH_2)_4$), 0.94 (t, J = 14.11 Hz, 12H, $N(CH_2CH_2CH_2CH_3)_4$), 1.75–0.35 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 135.67 (1C, C-triazole), 132.75, 130.88, 129.24 (6C, CH and C-phenyl), 122.67 (1C, CH-triazole), 59.3 (4C, $N(CH_2)_4$), 54.75 (1C, CH_2-benzyl), 51.96 (1C, H_2N–C), 24.28 (4C, $N(CH_2CH_2)_4$), 22.37 (2C, $(CH_3)_2$), 20.22 (4C, $N(CH_2CH_2CH_2)_4$), 13.72 (4C, $N(CH_2CH_2CH_2CH_3)_4$). ^{11}B NMR (96.3 MHz; CD_3CN): δ −3.11 (s, 1B, B1), −20.81 (bs, 11B, B2-12). MS (ESI): m/z 435.6 [100, M^-]. Anal. Calcd. for $C_{26}H_{58}B_{12}BrN_5$: C, 48.01; H, 8.99; N, 10.77%. Found: C, 47.69; H, 8.63; N, 10.59%.

_N_,_N_-Bis[1-(_m_-cyanobenzyl-1,2,3-triazol-4-yl)isopropyl]amino-undecahydro-_closo_-dodecaborate(1−) tetrabutyl-ammonium salt (17)

This compound was prepared from **4** (266 mg, 0.5 mmol) and _m_-cyanobenzyl azide (119 mg, 0.75 mmol), using the procedure described for **7** to give **17** (350 mg, 98%) as a white solid. mp 223–225 °C. IR (KBr, cm^{-1}) 3205 (ν_{NH}), 3030 (ν_{CH}), 2503 (ν_{BH}), 2233 ($\nu_{C\equiv N}$), 1651 ($\nu_{C=C}$), 1565 ($\nu_{N=N}$), 1454 (ν_{BN}), 1485, 1434, 1365 (ν_{CH}), 1135 (ν_{C-N}), 1053 (ν_{B-B}), 1010, 955, 852, 725, 686 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 8.09, 8.03 (s, 2H, CH-triazole), 7.62–7.49 (m, 10H, CH-phenyl), 6.59 (s, 1H, NH), 5.47 (s, 4H, CH_2-benzyl), 3.1 (m, 8H, $N(CH_2)_4$), 1.83 (s, 12H, $(CH_3)_2$), 1.55 (m, 8H, $N(CH_2CH_2)_4$), 1.35 (m, 8H, $N(CH_2CH_2CH_2)_4$), 0.95 (t, J = 14.11 Hz, 12H, $N(CH_2CH_2CH_2CH_3)_4$), 1.85–0.59 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 140.6, 137.69 (2C, C-triazole), 133.59, 133.53, 132.99, 130.83, 113.34 (12C, CH and C-phenyl), 129.72, 129.34 (2C, CH-triazole), 119.14 (2C, CN), 59.32 (4C, $N(CH_2)_4$), 53.42 (2C, CH_2-benzyl), 52.65 (2C, HN-C), 24.17 (4C, $N(CH_2CH_2)_4$), 22.28 (4C, $(CH_3)_2$), 20.25 (4C, $N(CH_2CH_2CH_2)_4$), 13.72 (4C, $N(CH_2CH_2CH_2CH_3)_4$). ^{11}B NMR (96.3 MHz; CD_3CN): δ −2.19 (s, 1B, B1), −20.86 (bs, 11B, B2-12). MS (ESI): m/z 471.6 [100, M^-]. Anal. Calcd. for $C_{38}H_{66}B_{12}N_{10}$: C, 57.57; H, 8.39; N, 17.67%. Found: C, 57.26; H, 8.19; N, 17.58%.

_O_-[1-Benzyl-(1,2,3-triazol-4-yl)methyl]hydroxo-undecahydro-_closo_-dodecaborate(2−) ditetrabutylammonium salt (18)

This compound was prepared from **6** (340 mg, 0.5 mmol) and benzyl azide (100 mg, 0.75 mmol), using the procedure described for **7** to give **18** (400 mg, 98%) as a colourless oil. IR (KBr, cm^{-1}) 3263, 3031 (ν_{CH}), 2472 (ν_{BH}), 1651 ($\nu_{C=C}$), 1565 ($\nu_{N=N}$), 1454 (ν_{BN}), 1485, 1434, 1361 (ν_{CH}), 1338 (ν_{B-O}), 1056 (ν_{B-B}), 1005, 948, 852, 745, 685 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 7.37 (s, 1H, CH-triazole), 7.37–7.27 (m, 5H, CH-phenyl), 5.5 (s, 2H, CH_2-benzyl), 4.55 (s, 2H, O-CH_2), 3.07 (m, 16H, $N(CH_2)_4$), 1.56 (m, 16H, $N(CH_2CH_2)_4$), 1.35 (m, 16H, $N(CH_2CH_2CH_2)_4$), 0.95 (t, J = 14.71 Hz, 24H, $N(CH_2CH_2CH_2CH_3)_4$), 1.65–0.28 (m, 11H, $B_{12}H_{11}$). ^{13}C NMR (75 MHz, CD_3CN): δ 136.77 (1C, C-triazole), 129.72, 129.14, 128.81 (6C, CH and C-phenyl), 128.81 (1C, CH-triazole), 59.23 (8C, $N(CH_2)_4$), 54.34 (1C, O–CH_2), 54.29 (1C, CH_2-benzyl), 24.2 (8C, $N(CH_2CH_2)_4$), 20.19 (8C, $N(CH_2CH_2CH_2)_4$), 13.67 (8C, $N(CH_2CH_2CH_2CH_3)_4$). ^{11}B NMR (96.3 MHz; CD_3CN): δ 1.96 (s, 1B, B1), −22.52 (d, J = 110.45 Hz, 10B, B2-11), −27.48 (s, 1B, B12). MS (ESI): m/z 164.5 [100, $M^-/2$]. Anal. Calcd. for $C_{42}H_{93}B_{12}N_5O$: C, 61.98; H, 11.52; N, 8.6%. Found: C, 61.77; H, 11.23; N, 8.28%.

_O_-[1-(3-_o_-Carboranylpropyl)-(1,2,3-triazol-4-yl)methyl]hydroxo-undecahydro-_closo_-dodecaborate(2−) ditetrabutylammonium salt (19)

This compound was prepared from **6** (170 mg, 0.25 mmol) and 3-azidopropyl-_o_-carborane (85 mg, 0.375 mmol), using the procedure described for **7** to give 19 (225 mg, 99%) as a colorless oil. IR (KBr, cm^{-1}) 3444, 3024 (ν_{CH}), 2572, 2476 (ν_{BH}), 1689 ($\nu_{C=C}$), 1558 ($\nu_{N=N}$), 1469, 1380 (ν_{CH}), 1141 (ν_{CN}), 1049 (ν_{B-B}), 1022, 950, 883, 725, 680 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 7.66 (s, 1H, CH-triazole), 4.48 (s, 2H, O–CH_2), 4.27 (s, 2H, N–CH_2), 4.15 (m, 1H, CH-carborane), 3.85 (m, 2H, –CH_2-), 3.41 (m, 2H, CH_2-carborane), 3.06 (m, 16H, $N(CH_2)_4$), 1.53 (m, 16H, $N(CH_2CH_2)_4$), 1.33 (m, 16H, $N(CH_2CH_2CH_2)_4$), 0.95 (t, J = 14.65 Hz, 24H, $N(CH_2CH_2CH_2CH_3)_4$), 1.85–0.52 (m, 21H, $B_{12}H_{11}$ and $C_2B_{10}H_{10}$). ^{13}C NMR (75 MHz, CD_3CN): δ 136.55 (3C, CH-triazole), (1C, C-triazole), 76.45 (1C, C-carborane),

65.35 (1CH, CH-carborane), 59.24 (8C, $N(CH_2)_4$), 50.21 (1C, CH_2-N), 35.24 (1C, $-CH_2-$) 30.75 (1C, CH_2-carborane), 24.22 (8C, $N(CH_2CH_2)_4$), 20.2 (8C, $N(CH_2CH_2CH_2)_4$), 13.65 (8C, $N(CH_2CH_2CH_2CH_3)_4$). ^{11}B NMR (96.3 MHz; CD_3CN): δ 1.99 (bs, 1B, B1), −8.05, −15.12, −16.76, −20.15,-20.42, −27.35 (bs, 21B, $B_{12}H_{11}$ and $C_2B_{10}H_{10}$). MS (ESI): m/z 211.6 [100, $M^-/2$]. Anal. Calcd. for $C_{40}H_{103}B_{22}N_5O$: C, 52.9; H, 11.43; N, 7.71%. Found: C, 52.82; H, 11.36; N, 7.49%.

O-[1-(1,2-*O*-Distearoyl-*sn*-3-glycerol)-(1′,2′,3′-triazol-4-yl)methyl]hydroxo-undecahydro-*closo*-dodecaborate(2−) ditetrabutylammonium salt (20)

This compound was prepared from **6** (170 mg, 0.25 mmol) and (*R*)-3-azidopropane-1,2-diyl distearate (255 mg, 0.375 mmol), using the procedure described for **9** to give **20** (333 mg, 98%) as a white solid. mp 101–103 °C. IR (KBr, cm^{-1}) 2958, 2920, 2850 (ν_{CH}), 2476 (ν_{BH}), 1743 ($\nu_{C=O}$), 1685 ($\nu_{C=C}$), 1558 ($\nu_{N=N}$), 1469, 1405, 1380 (ν_{CH}), 1161 (ν_{CN}), 1107, 1049 (ν_{B-B}), 1014, 883, 721, 675 (ν_{CH}). ^{1}H NMR (300 MHz, CD_3CN): δ 7.96 (s, 1H, CH-triazole), 5.15 (m, 1H, CH–), 4.52 (m, 2H, O–CH_2-), 4.35 (s, 2H, N–CH_2), 4.22 (m, 2H, –$CHCH_2C$═O), 4.15 (m, 2H, $CHCH_2C$═O), 3.07 (s, 16H, $N(CH_2)_4$), 2.35 (m, 4H, –CH_2CH_2C═O), 1.85–0.55 (m, 11H, $B_{12}H_{11}$), 1.61 (m, 4H, CH_2), 1.55 (m, 16H, $N(CH_2CH_2)_4$), 1.35 (m, 16H, $N(CH_2CH_2CH_2)_4$), 1.25 (s, 40H, $-CH_2-$), 0.95 (m, 24H, $N(CH_2CH_2CH_2CH_3)_4$), 0.88 (m, 6H, CH_3). ^{13}C NMR (75 MHz, CD_3CN): δ 173.35, 172.75 (2C, CO), 136.95 (1C, CH-triazole), 128.79 (1C, C-triazole), 59.11 (8C, $N(CH_2)_4$), 52.15 (1C, O–CH_2), 51.08 (1C, N–CH_2), 70.52, 62.47, 35.65, 35.11, 32.22, 29.67, 29.43, 29.42, 29.35, 29.25, 29.07, 29.02, 28.97, 25.22, 25.06, 22.21, 14.02 (lipid-carbons), 24.23 (8C, $N(CH_2CH_2)_4$), 20.26 (8C, $N(CH_2CH_2CH_2)_4$), 13.67 (8C, $N(CH_2CH_2CH_2CH_3)_4$). ^{11}B NMR (96.3 MHz; CD_3CN): δ 1.97 (s, 1B, B1), −22.43 (d, J = 110.35 Hz, 10B, B2-11), − −27.52 (s, 1B, B12). MS (ESI): m/z 422.9 [100, $M^-/2$]. Anal. Calcd. for $C_{75}H_{163}B_{12}N_5O_6$: C, 66.19; H,12.07; N, 5.15%. Found: C, 65.97; H, 11.92; N, 5.02%.

Crystal structure determination of 2 and 6

Colourless single crystals of **2** and **6** suitable for XRD analyses were obtained from CH_3CN–diethyl ether at 4 °C and slow evaporation of CH_2Cl_2–EtOH at room temperature, respectively. Each crystal was mounted on a glass fiber, and the diffraction data of all the complexes were collected on a Bruker-AXS APEX II CCD detector using graphite-monochromated Mo Kα radiation at 123 K. The crystal data and experimental details are listed in Table 1.

All the structures were solved by the combination of the direct method and Fourier techniques, and all the non-hydrogen atoms were isotropically refined by full-matrix least-squares calculations. The atomic scattering factors and anomalous dispersion terms were obtained from the International Tables for X-ray Crystallography IV,[34] since the number of reflections data for the above-mentioned crystals were insufficient for refining all the parameters of the hydrogen atoms, except for the hydrogen atoms of the boron cluster, which were obtained from difference Fourier maps.

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