Synthesis of Zwitter-Ionic Conjugate of Nido-Carborane with Cholesterol

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Abstract: 9-HC≡CCH2Me2N-nido-7,8-C2B11H11, a previously described carboranyl terminal alkyne, was used for the copper(I)-catalyzed azide-alkyne cycloaddition with azido-3β-cholesterol to form a novel zwitter-ionic conjugate of nido-carborane with cholesterol, bearing a 1,2,3-triazol fragment. The conjugate of nido-carborane with cholesterol, containing a charge-compensated group in the linker, can be used as a precursor for the preparation of liposomes for BNCT (Boron Neutron Capture Therapy). The solid-state molecular structure of a nido-carborane derivative with the 9-Me2N(CH2)3Me2N-nido-7,8-C2B11H11 terminal dimethylamino group was determined by single-crystal X-ray diffraction.

Keywords: nido-carborane; “click” reaction; cholesterol; X-ray diffraction

1. Introduction

Due to their unique structure and chemical properties, as well their wide range of applications, polyhedral boron hydrides attract the continued interest of researchers working in various fields [1–3]. Nido-Carborane or 7,8-dicarba-nido-undecaborane anion and its derivatives have highly polarizable spherical aromaticity as a result of their σ-delocalized electron density [4,5]. Therefore, they display characteristic electronic properties [6], and thermal [7], chemical and photochemical stability [8]. All these features make them interesting systems for use in such fields as materials science [9,10] and medicinal chemistry [11–14]. Boron neutron capture therapy (BNCT) for cancer is one of the most significant applications of nido-carborane derivatives in medicine [15].

The basic concept of BNCT for cancer, proposed for the first time by Gordon L. Locher in 1936, is based on the selective accumulation of the non-radioactive isotope 10B in tumor cells, and their subsequent treatment with a flux of thermal neutrons [16]. On absorption of a thermal neutron by a 10B atom, an excited 11B atom is formed, which almost immediately undergoes a fission reaction, producing two high-energy heavy ions (4He2+ and 7Li3+) that selectively destroy tumor cells, while not causing serious damage to the surrounding normal cells [17]. To ensure the successful development of BNCT, the selective delivery and high accumulation of boron in the tumor tissue, at a therapeutic concentration (20–35 µg 10B/g), are required for subsequent irradiation with thermal neutrons [17]. For this purpose, the development of efficient 10B delivery carriers to tumors is important in BNCT.
The promising trend towards the achievement of the necessary therapeutic concentrations of boron in the tumor is enabled by the use of nido-carborane derivatives containing high contents of boron atoms in their molecules \[15,18,19\]. Another promising trend is the development of various nanomaterials, such as liposomes, that could be used as both boron host molecules and for the targeted delivery of boron to cancer cells \[20,21\].

Liposomes are artificially constructed spherical vesicles consisting of a phospholipid bilayer \[22\]. First discovered in 1961 by Alec Bangham, liposomes are now being studied for their ability to overcome cell membranes and transport boron clusters into a cancerous tumor. There are examples of the production of liposomes based on polyhedral boron hydrides containing borane and carborane derivatives both in the aqueous core and in the composition of the lipid bilayer \[23–25\]. The main difference between tumor and normal cells is the presence of a phospholipid/cholesterol shell with a diameter of approximately 15–20 nm, which is filled with cholesterol and glyceryl esters of long-chain alkyl carboxylic acids. This difference is based on an increase in the cholesterol requirement of tumor cells to promote the formation of new membranes. Therefore, the design of stable biocompatible boron-containing cholesterol nanostructures for the further creation of liposomal agents that contain derivatives of polyhedral boron hydrides is an effective approach that can solve the problem of the selective delivery of boron into tumor cells required to carry out BNCT. It was also recently shown that the inclusion of lipophilic boron-containing species in the bilayer of liposomes provides an attractive means of increasing the total boron content in liposomes contained within the formulation \[26,27\]. In addition, it was found that the encapsulation of nido-carborane with PEGylated liposome via the hydration of thin lipid films significantly suppresses tumors in BNCT \[28\].

It should be noted that the penetration of boronated liposomes through biological membranes, and their accumulation and retention in cells, largely depend on their charge. It is known that positively charged liposomes have better penetration through biological membranes than negatively charged ones. Positively charged liposomes containing carborane derivatives were found to be the most efficient delivery system for rat colon carcinoma and murine melanoma cell lines, as compared with negatively charged liposomes \[29–31\]. The high accumulation of such liposomes was probably due to favorable electrostatic interactions with the negatively charged outer leaflets of mammalian plasma membranes. This inspired us to synthesize positively charged nido-carborane derivatives with cholesterol for further use in the form of liposomes. The design of such compounds is based on the introduction of two ammonium centers, the first of which compensates for the negative charge of the nido-carborane cluster, and the second one provides the overall positive charge of the molecule.

There are only a few examples of lipids with polyhedral boron hydrides that contain molecules with zwitter-ionic characteristics \[32,33\]. Here, we use the “click” methodology to approach the synthesis of a novel zwitter-ionic nido-carboryl-cholesterol conjugate. The hydrophilic part of such lipids contains a nido-carboryl cluster, while the lipophilic part contains cholesterol. The resulting conjugate can be used to produce boron-containing liposomes as potential drugs for BNCT.

2. Results and Discussion
2.1. Synthesis of Nido-Carboryl Cholesterol Bearing a 1,2,3-Triazole Fragment

The synthesis of biologically active molecules is a very important area of bioorganic chemistry. Among the methods for obtaining bioconjugates, the Cu(I)-catalyzed 1,3-dipolar \[3+2\] cycloaddition reaction of alkynes to azides is widely used, leading to the formation of 1,2,3 triazoles; this is known as the "click" reaction" \[34–36\]. Earlier, the "click" reaction was successfully used to obtain a wide range of conjugates of polyhedral boron hydrides with various biologically active molecules, such as nucleosides \[37\] and chlorine \(e_6\) \[38\], as well as derivatives of cholesterol based on cobalt/iron bis(dicarbollide) \[26,27,33,39\], closo-dodecaborate dianion \[40\] and nido-carborane \[41\]. In this work, we used cholesterol.
derivatives, as well as 3β-(2-azido-ethoxy)cholest-5-ene and nido-carboranyl derivatives, that contained different spacers between the boron cage and the terminal acetylene group.

Thus, to obtain a target positively charged conjugate by means of the “click” reaction, a previously described terminal alkyne based on nido-carborane derivative, with two ammonium centers in its spacer [9-HC≡CCH₂Me₂N(CH₂)₂Me₂N-nido-7,8-C₂B₉H₁₁]Br (1) [42], was used. However, it was found that the reaction of acetylene 1 with azido-3β-chololesterol 2 in the refluxing of ethanol in the presence of diisopropylethylamine (DIPEA) and a catalytic amount of Cul did not lead to the desired conjugate 3. During this reaction, we observed the elimination of the propargyl fragment of compound 1 and the formation of the nido-carborane derivative with the terminal dimethylamino group 9-Me₂N(CH₂)₂Me₂N-nido-7,8-C₂B₉H₁₁ (4). This can be explained by the acetylene-allen rearrangement under the action of DIPEA. The structure of compound 4 was confirmed by ¹H, ¹³B and ¹³C NMR spectra. The spectral characteristics of 4 are in good agreement with the data given in the literature [42]. The structure of 9-Me₂N(CH₂)₂Me₂N-nido-7,8-C₂B₉H₁₁ 4 was additionally confirmed via single-crystal X-ray diffraction study (Figure 1).

**Figure 1.** Molecular view of 9-Me₂N(CH₂)₂Me₂N-nido-7,8-C₂B₉H₁₁ 4 presented by thermal ellipsoids at 50% probability level. Shortened H4A . . . H12 and H4 . . . H1A contacts are shown by dashed lines.

Further, we decided to use a more stable terminal nido-carboranyl alkyne with one ammonium center, 9-HC≡CCH₂Me₂N-nido-7,8-C₂B₉H₁₁ (5) [42]. The usage of this alkyne excluded the elimination of the propargyl fragment in compound 5. Indeed, the reaction of acetylene 5 with azido-3β-chololesterol 2, under the same conditions as for compound 1, produced the novel conjugate of nido-carboranyl cholesterol 6 with a zwitter-ionic character of its target molecule (Scheme 1).
The structure of the obtained conjugate 6 was confirmed by $^1$H, $^{11}$B, $^{13}$C NMR, IR and high-resolution mass-spectrometry. The $^1$H and $^{13}$C NMR spectra of compound 6, along with the signals for the heteroaliphatic chain, contained signals that were characteristic of the triazole ring. In the $^1$H NMR spectrum, the signals for the protons of the CH group of triazole appeared at 8.37 ppm for conjugate 6. For 1,2,3-triazole 6, the $^{13}$C NMR spectrum showed signals for two carbon atoms of the triazole fragment at 140.6 ppm (the “nodal” atom) and at 123.3 ppm. In the $^1$H NMR spectrum, the signal of the methylene group next to the triazole cycle was observed at 4.63 ppm and the characteristic signals of the $\text{Me}_2\text{N}$ hydrogens appeared at 3.02 and 3.08 ppm. The characteristic signal for the proton at the double bond of the steroid core (CHst) of the conjugate was observed in the region of 5.33 ppm. The $^{11}$B NMR spectrum of 6 contained a pattern of eight signals (one singlet at 5.8 ppm and seven doublets at $-5.7$, $-17.4$, $-19.4$, $-24.7$, $-26.9$, $-38.2$ and $-38.8$ ppm), which demonstrates the absence of a plane of symmetry and unambiguously confirms the nido form. In the $^1$H-NMR spectra, the signal of the extra-hydrogen, as expected, was observed at approx. $-3.2$ ppm. In addition, the signals of the $\text{CH}$ groups in the $^1$H NMR spectra of 6 appeared as broad singlets at 2.81 and 2.06 ppm; in the $^{13}$C NMR spectra, the signals of $\text{CH}$ groups appeared at 33.6 and 39.7 ppm. The IR spectrum of compound 5 exhibited absorption band characteristic of the BH group at 2549 cm$^{-1}$ and of the triazole ring at 1421 cm$^{-1}$.

Based on synthesized zwitter-ionic compound, the preparation of the boronated liposomes was planned in order to deliver boron clusters into a cancer cell for the BNCT experiment.

2.2. Single-Crystal X-ray Diffraction Studies

The molecular and crystal structure of charge-compensating nido-carborane derivative with terminal dimethylamino group 9-$\text{Me}_2\text{N}($CH$_2$)$_2$Me$_2$N-nido-7,8-C$_2$B$_9$H$_{11}$ (4) was determined by means of a single-crystal X-ray diffraction study (Figure 1). Crystals of 4 that were suitable for single-crystal X-ray analysis were obtained from the CDCl$_3$ solution in the NMR tube.

The side substituent was relatively flexible and had the potential to form shortened C-H…H-B contacts with carborane cages, which would have influenced its orientation.
relative to the cage. On the other hand, relative orientation could have been affected by the crystal packing. Torsion angles and shortened H…H contacts, which defined the relative orientation, are provided in Table 1. In Table 1, we also included two recently studied compounds (Figure 2) [42], with similar substituents, at the same position in the carborane cage, as well as the calculated molecular geometry results obtained in an isolated state for all three compounds. Calculations were carried out in terms of density functional theory using the PBE0 function, which is widely used for the geometric optimization of a variety of classes of compounds [43–46].

![Figure 2. Molecular view of 9-NC≡CCH₂Me₂N-nido-7,8-C₂B₉H₁₁ (a) and 9-PhCH₂Me₂N-nido-7,8-C₂B₉H₁₁ (b). Only necessary numbering is provided. Shortened H₄…H₁A contacts are shown by dashed lines.](image)

| Torsion Angle or H…H Contact | 9-Me₂N(CH₂)₂Me₂N-Nido-7,8-C₂B₉H₁₁ | 9-NC≡CCH₂Me₂N-Nido-7,8-C₂B₉H₁₁ | 9-PhCH₂Me₂N-Nido-7,8-C₂B₉H₁₁ |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
|                               | X-ray | DFT     | X-ray | DFT     | X-ray | DFT     |
| C₈-B₉-N₁-C₁                   | 19.4(2) | 28.3     | 50.4(2) | 36.0     | 35.3(2) | 41.9     |
| C₈-B₉-N₁-C₂                   | 138.4(2) | 148.0     | 172.4(2) | 157.8     | 155.8(2) | 162.2     |
| C₈-B₉-N₁-C₃                   | –103.6(2) | –94.7     | –69.2(2) | –84.1     | –84.8(2) | –78.8     |
| B₉-N₁-C₃-C₄                   | 64.0(2) | 63.9     | 177.4(2) | 179.6     | 171.9(2) | –179.7    |
| N₁-C₃-C₄-N₂                   | 178.3(2) | –170.6     | –       | –       | –       | –       |
| C₃-C₄-N₂-C₅                   | 74.1(2) | 81.5     | –       | –       | –       | –       |
| C₃-C₄-N₂-C₆                   | –163.1(2) | –152.8     | –       | –       | –       | –       |
| H₄…H₁A                        | 2.33     | 2.29     | 2.26     | 2.24     | 2.33     | 2.27     |
| H₄A…H₁₂                       | 2.38     | 2.39     | –       | –       | –       | –       |

Crystal packing analysis of the recently studied 9-NC≡CCH₂Me₂N-nido-7,8-C₂B₉H₁₁ and 9-PhCH₂Me₂N-nido-7,8-C₂B₉H₁₁ [42] revealed that the crystal packing of 9-PhCH₂Me₂N-nido-7,8-C₂B₉H₁₁ is mostly stabilized by numerous weak van-der-Waals intermolecular interactions, while, in 9-NC≡CCH₂Me₂N-nido-7,8-C₂B₉H₁₁, relatively strong π…π interactions between cyano groups were observed. In the case of 9-Me₂N(CH₂)₂Me₂N-nido-7,8-C₂B₉H₁₁ 4, we found that the side substituent formed one slightly shortened C-H…H-B
contact (2.31Å) while all the other intermolecular interactions were of the van-der-Waals type. Those observations agree well with the results shown in Table 1.

It can be seen that, in all three compounds, the crystal packing influenced the molecular structure. This influence was relatively small (at least, all shortened H . . . H contacts were preserved upon the transferring of a molecule from an isolated state to a crystal) and appeared to be more pronounced for 9-NC≡CCH2Me2N-nido-7,8-C2B9H11, for which π . . . π intermolecular interactions were observed.

3. Materials and Methods

3.1. General Methods

[9-HC≡CCH2Me2N(CH2)3Me2N-nido-7,8-C2B9H11]Br 1 [42], azido-3β-cholesterol 2 [39,47] and 9-HC≡CCH2Me2N-nido-7,8-C2B9H11 5 [42] were prepared according to the literature. Cholesterol (Fisher Scientific, Loughborough, UK), diisopropylethylamine (Carl Roth GmbH, Karlsruhe, Germany) and CuI (PANREAC QUIMICA SA, Barcelona, Spain) were used without further purification. Ethanol, CH31 and CH23 were commercial reagents of analytical grade. The reaction progress was monitored by thin-layer chromatography (Merck F245 silica gel on aluminum plates) and visualized using 0.1% PdCl2 in 3 M HCl. Acros Organics silica gel (0.060–0.200 mm) was used for column chromatography. The NMR spectra at 400.1 MHz (1H), 128.4 MHz (13B) and 100.0 MHz (13C) were recorded with a Bruker Avance-400 spectrometer (Bruker, Karlsruhe-Zurich, Switzerland-Germany). The residual signal of the NMR solvent relative to Me4Si was taken as the internal reference for the 1H- and 13C-NMR spectra. 13B-NMR spectra were referenced using BF3*Et2O as external standard. Infrared spectra were recorded on an IR Prestige-21 (SHIMADZU) instrument. High resolution mass spectra (HRMS) were measured on a micrOTOF II (Bruker Daltonic, Bremen, Germany) instrument using electrospray ionization (ESI). The measurements were conducted in a positive ion mode (interface capillary voltage –4500 V), with a mass range from m/z 50 to m/z 3000; external or internal calibration was performed with the ESI Tuning Mix, produced by Agilent. A syringe injection was used for the addition of the solutions to acetonitrile (flow rate 3 µL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C.

The X-ray experiment for 4 was carried out using the SMART APEX2 CCD diffractometer (λ(Mo-Kα) = 0.71073 Å, graphite monochromator, ω-scans) at 120K. The collected data were processed using the SAINT and SADABS programs that were incorporated into the APEX2 program package [48]. The structure was solved using direct methods and was refined by the full-matrix least-squares procedure against F2 via an anisotropic approximation. The refinement was carried out with the SHELXTL program [49]. The CCDC number 2113014 contains the supplementary crystallographic data (Supplementary Materials) for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (accessed on 14 July 2021).

3.2. General Procedure for the Synthesis of the Compounds 4 and 6

A mixture of azido-3β-cholesterol 2, alkyne, diisopropylethylamine and CuI in ethanol was heated under reflux for 3 h. Then, the reaction mixture was cooled to room temperature and was passed through ca. 2–3 cm of silica on a Schott filter. Then, the solvent was removed in vacuo. The crude product was purified on a silica column using CH2Cl2–CH3CN as an eluent to provide the desired products 4 or 6.

3.3. Synthesis of 9-Me2N(CH2)3Me2N-Nido-7,8-C2B9H11 (4)

9-Me2N(CH2)3Me2N-nido-7,8-C2B9H11 was prepared from azido-3β-cholesterol 2 (0.21 g, 0.45 mmol), boronated alkyne 1 (0.20 g, 0.45 mmol), diisopropylethylamine (1 mL, 0.74 g, 5.73 mmol) and CuI (0.009 g, 0.05 mmol) in 15 mL of ethanol. The product was purified on a silica column using CH2Cl2–CH3CN (1:1) as an eluent to give the white solid of 4 (0.07 g, yield 63%). The NMR data of 4 are in good agreement with the data in the literature [39]. Crystallographic data: crystals of 4, C9H27B3N2 are monoclinic, space group
C2c: a = 32.1867(12)Å, b = 6.6299(3)Å, c = 16.1995(6)Å, β = 116.1480(10)°, V = 3103.1(2) Å³, Z = 8, M = 248.60, d_{cryst} = 1.064 g·cm⁻³, ρ_{calc} = 0.1369 calculated on F² for all 4947 independent reflections with 2θ < 62.0°, (GOF = 1.117, R = 0.0546 calculated on F² for 3942 reflections with I > 2σ(I)).

3.4. Synthesis of 9-3β-Chol-O(CH₂)₃N₃-CH-C-(CH₂)Me₂N-nido-7,8-C₂B₉H₁₁ (6)

9-3β-Chol-O(CH₂)₃N₃-CH-C-(CH₂)Me₂N-nido-7,8-C₂B₉H₁₁ was prepared from azido-3β-cholesterol 2 (0.09 g, 0.21 mmol), boronated alkyne 5 (0.06 g, 0.21 mmol), disopropyl-ethylamine (0.5 mL, 0.40 g, 2.87 mmol) and CuI (0.004 g, 0.02 mmol) in 7 mL of ethanol.

The product was purified on a silica column using CH₂Cl₂-CH₃CN (7:1) as an eluent to give the white solid of 6 (0.10 g, yield 72%). ¹H NMR (400 MHz, acetone-d₆) δ 8.37 (1H, s, CCH₃), 5.34 (1H, m, C₆t(6)H), 4.69 (4H, s, -OCH₂CH₂N₃), 3.96 (2H, s, CH₂NMe₂), 3.17 (1H, m, C₆t(3)H), 3.08 (3H, s, NMe₂), 3.02 (3H, s, NMe₂), 2.81 (1H, br. s, CH₂(aryl)), 2.31 (1H, m, C₆t(H)), 2.40 (1H, m, C₆t(H)), 2.06 (1H, br. s, CH₂(aryl)), 1.86 (6H, m, C₆t(H)), 1.57–1.03 (22H, m, C₆t(H)), 1.00–0.96 (3H, d, J = 6.3 Hz, C₆t(21)H₃), 0.89 (3H, s, C₆t(26)H₃), 0.88 (3H, s, C₆t(27)H₃), 0.73 (3H, s, C₆t(18)H₃), −3.16 (1H, br. s, Hextra) ppm; ¹³C NMR (101 MHz, acetone-d₆) δ 140.5 (CCH₃), 137.3 (C₆t(5)), 123.3 (CCH₃), 121.5 (C₆t(6)), 79.1 (C₆t(3)), 66.0 (CCH₃CH₂), 61.2 (O-CH₂), 56.7 (C₆t(14)), 56.1 (C₆t(17)), 51.9 (NMe₂), 50.9 (NMe₂), 50.7 (C₆t(9)), 50.3 (CH₂NMe₂), 42.2 (C₂), 39.7 (C₆t(12)), 39.4 (C₆t(13)), 37.0 (C₆t(24)), 36.6 (C₆t(1)), 36.1 (C₆t(10)), 35.7 (C₆t(22)), 33.6 (C₆t(23)), 31.8 (C₆t(20)), 31.7 (C₆t(8)), 28.2 (C₆t(2)), 28.0 (C₆t(7)), 27.8 (C₆t(16)), 24.0 (C₂t(25)), 23.6 (C₆t(15)), 22.2 (C₆t(23)), 22.0 (C₆t(26), C₆t(27)), 20.9 (C₆t(11)), 18.8 (C₆t(19)), 18.2 (C₂t(21)), 11.3 (C₆t(18)) ppm. IR (solid): ν = 2549 cm⁻¹ (BH), 1421 cm⁻¹ (triazole). HRMS-ESI+ m/z for [C₆H₄B₉N₄+OH]+ calc 642.6016, found: 642.6028.

4. Conclusions

In this work, the “click” reaction of 9-HC≡CCH₂Me₂N-nido-7,8-C₂B₉H₁₁ with azido-3β-cholesterol, in a good yield, was conducted to prepare a novel zwitterionic conjugate of nido-carborane with cholesterol. We also studied the behavior of the nido-carborane derivative [9-HC≡CCH₂Me₂N(CH₂)₃Me₂N-nido-7,8-C₂B₉H₁₁]Br in the copper(I)-catalyzed azide-alkyne cycloaddition reaction with azido-3β-cholesterol, and revealed that during this process, in the presence of a strong base, acetylene-allen rearrangement occurred, resulting in the elimination of the propargyl fragment in carboxyl acetylene and the formation of 9-Me₂N(CH₂)₃Me₂N-nido-7,8-C₂B₉H₁₁. The solid-state molecular structure of this previously described compound was determined by means of single-crystal X-ray diffraction studies. Comparing the structure of 9-Me₂N(CH₂)₃Me₂N-nido-7,8-C₂B₉H₁₁ with the previously described analogs shows that the flexibility of side substituent does not significantly affect the crystal packing. Based on synthesized zwitter-ionic conjugate, the preparation of the boronated liposomes was planned in order to deliver boron clusters into a cancer cell for BNCT experiments.

Supplementary Materials: The following are available online. Figures S1–S6 NMR, IR and high-resolution mass spectra of compound 6.

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Sample Availability: Samples of compound 6 are available from the authors.

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