Synthesis of a Porphyrin Having Eight Carborane Cages

Jongho Lee, Yil Sung Park,* Yong Il Kim, and Han Chyul Kang†

Central Research Center, Oriental Chemical Industries, Hakik-dong 587-102, Inchon 402-040, Korea
†Oxy Research Center, Hakik-dong 587-102, Inchon 402-040, Korea
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It has long been known that some macrocyclic nitrogen heterocycles such as porphyrin phthalocyanine show a propensity for localization in malignant tumors, remaining there in the long term.[1]

The use of boronated porphyrins as boron carriers in BNCT (Boron-10 Neutron Capture Therapy) has been explored since the early 1980s.[2-5] Representative derivatives synthesized for this purpose are based on tetraphenylporphyrin (BTTP[3]) and hematoporphyrin (VCDP[4] and BOPP[5]). As boron sources, carborane cluster compounds have been preferred due to not only their ability to move many boron atoms at a time but also their chemical stability and metabolic inertness. The carborane cluster BOPP (2,4-bis-[α,β-bis(1,2-dicarbacloso-dodecaboranecarboxy)ethyl]Deutero-porphyrin **IX** disodium salt (Figure 1), which contains four closo carborane cages, shows very high selective localization in tumors and is a leading compound for the clinical test of BNCT.[6] Representative examples of boron clusters are shown in Figure 2.

In this paper we report the synthesis of a novel boronated porphyrin where eight closocarborane cages are appended to the porphyrin macrocycle through four ester bonds between four OHs of bisglycol of deuteroporphyrin and four carboxyic acid chlorides of bis-*p*-carboranyl acid chlorides. This product is expected to be a potential BNCT agent having many boron atoms. As shown in Scheme 1 and 2, the synthesis of 2,4-bis-[α,β-bis(1,1'-bis-1,12-dicarbaclosododecaboranecarboxy)ethyl]deuteroporphyrin **IX** dimethyl ester (**6**) comprises four steps. The bis-*p*-carborane **2** can be obtained by the dimerization of the mono lithiated closo *para*-carborane through the carbon-carbon coupling with anhydrous cupric chloride followed by the acidic workup.[7]

The removal of salts and then column chromatography on alumina with hexanes as eluents lead to a moderate yield of pure bis-*p*-carborane **2**. The preparation of bis-*p*-carborane carboxylic acid **3** is based on the literature methods.[8] The carboxylation of **2** was accomplished by stepwise lithiation and CO_2 carboxylation followed by acidification.[9] The limited use of *n*-BuLi can prevent the formation of undesirable dicarboxylated bis-*p*-carborane. The conversion of the carborane carboxylic acid to the carborane acid chloride is usually achieved by treating the acid with phosphorous pentachloride.[10] However, the separation of the formed bis-*p*-carboranyl acid chloride has been hampered by its high boiling point. Therefore we studied other chlorination methods. Phos-

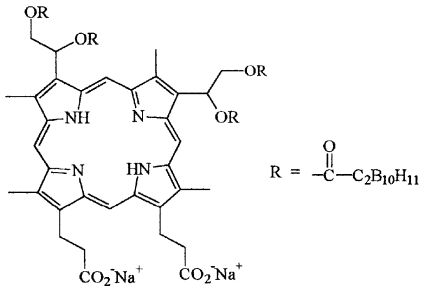


Figure 1. BOPP.

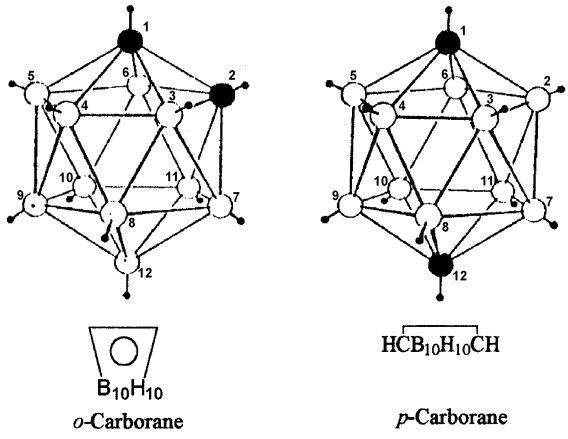
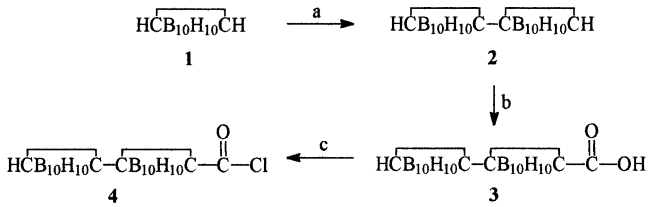
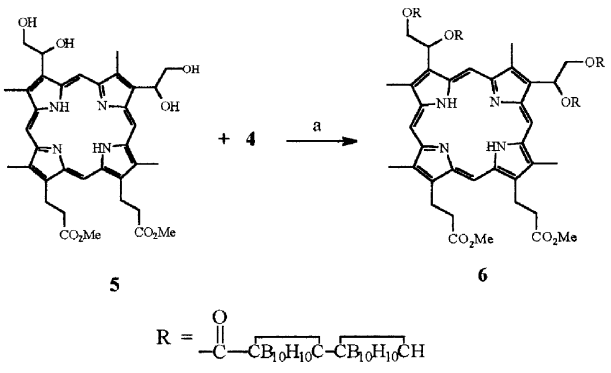


Figure 2. Boron Clusters.



Scheme 1. (a) 1.2 eq of *n*-BuLi, 1.4 eq of anhydrous $CuCl_2$, ether, 25 °C, 3 days, yield 40%. (b) 1 eq of *n*-BuLi, CO_2, ether, 0-10 °C, 2h, yield 41%. (c) excess $COCl_2$, Et_3N, 90-100 °C, ortho-dichlorobenzene (o-DCB).



Scheme 2. (a) 4 eq of DMAP, CH_2Cl_2, 25 °C, 24h, yield 50%.

Table 1. 300 MHz ^{1}H FT-NMR Data of **6** ($CDCl_3$)

Chemical Shift (δ)	Multiplicity	Assignment
10.03, 10.04, 10.06, 10.09	s, 4H	meso *H*
7.17	m, 2H	α-C*H*$_2$
5.27, 4.57	m, 4H	β-C*H*$_2$
4.38	m, 4H	C*H*$_2$CH$_2$CO$_2$CH$_3$
3.60, 3.63	s, 6H	CO$_2$C*H*$_3$
3.62, 3.65	m, 12H	Porphyrin C*H*$_3$
3.25	m, 4H	C*H*$_2$CO$_2$CH$_3$
1.55	s, 4H	carborane-C*H*
-0.7~3.3	broad, 80H	B*H*
-3.8	s, 2H	N*H*

gene has been safely used in our lab., and excess phosgene was effectively employed in the chlorinaiton of **3** and bis-*p*-carborane acid chloride **4** was formed quantitatively.

The end product compound **6** was obtained by the reaction of the deuteroporphyrin bisglycol **5** with the bis-*p*-carboranyl acid chloride. To take the reaction to full substitution, an excess amount of acid chloride was used in the presence of excess DMAP. Without DMAP in excess quantity, the reaction will not go to completion even over extended period of time, yielding only di or tri-substituted compounds.

The end product **6** was purified with a single washing of the prodcut mixture with 0.5 N HCl solution followed by a double washing with the saturated sodium bicarbonate solution, and the drying of the organic layer over the anhydrous sodium sulfate, and finally stripping the solvent. The flash column chromatography afforded analytically pure product in 50% yield by weight. The structural evidence of **6** was confirmed by proton NMR spectroscopy and fast atom bombardment mass spectrometry.

The FAB MS spectra showed molecular ion peak at m/e 1910, which corresponds to the mass calculated for the molecular ion, $[^{12}C_{56}{}^{1}H_{123}{}^{11}B_{67}{}^{10}B_{13}{}^{14}N_4{}^{16}O_{12}]^+$. Successive loss of the bis-*p*-carboranyl carboxylated fragments from the molecular ion was also clearly observed. Since the compound should be water soluble for BNCT because of blood injection, **6** would go to further treatments, which include the acidification with strong HCl for the conversion of **6** to the free acid and cation exchange through the cation exchange resin to produce the boronated deuteroporphyrin disodium or dipotassium salt.

Experimental Section

Synthesis of bis-*p*-carboranyl acid chloride (4). 475 mg (1.45 mmol) of bis-*p*-carboranyl acid (**3**) was placed in a three necked flask fitted with dry ice-acetone condenser containing both 50 mL of o-DCB and a catalytic amount of triethylamine. An excess amount of the 40% prepared phosgene solution in o-DCB was introduced into the reaction flask and the mixture stand for 1 hour to allow phosgene reflux. After the reaction, excess phosgene and solvent were stripped *in vacuo*, resulting in a crude bis-*p*-carborane acid chloride. **4**. The crude product was used for the next step without further purification.

Synthesis of 2,4-bis-[α,β-bis(1,1-bis-1,12-dicarbaclosododecaborane)carboxyethyl] deuteropo-rphyrin IX dimethyl ester (6). 220 mg (0.33 mmol) of 2,4-bis(α,β-dihydroxyethyl)deuteroporphy-rin **IX** dimethyl ester (**5**) and 179 mg (1.46 mmol) of DMAP were dissolved in 40 mL CH_2Cl_2. After bubbling the solution with argon, the bis-*p*-carborane acid chloride obtained from the above procedure was added to the reaction mixture. The solution was stirred over night at room temperature and poured into water. The organic layer was separated, washed with 0.5 M HCl solution, saturated sodium bicarbonate solution and water, and then dried over anhydrous sodium sulfate. The solution was filtered and evaporated *in vacuo* to give dark violet powder that was purified by flash chromatography on silica (MC eluent) to give **6** (315 mg, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03, 10.34, 10.06, 0.9 (s, 4H, meso *H*), 7.17 (m, 1H, α-C*H*), 5.27, 4.57 (m, 4H, β-C*H*$_2$), 4.38 (m, 4H, C*H*$_2$ CH$_2$CO$_2$CH$_3$), 3.60, 3.63 (s, 6H, CO$_2$C*H*$_3$), 3.62, 3.65 (m, 12H, Porphyrin C*H*$_3$), 3.25 (m, 4H, C*H*$_2$CO$_2$CH$_3$), 1.55 (s, 4H, carborane-C*H*), -0.7-3.3 (broad, 80H, B*H*), -3.8 (s, 2H, N*H*); FAB MS *m/z* 1910 (M^+)

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