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Synthesis of ether- and carbon-linked polycarboranyl porphyrin dimers for cancer therapies

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Dedicated with gratitude and admiration to Professor M. Frederick Hawthorne on the occasion of his 75th birthday

Abstract

Porphyrin dimers bearing multiple carborane cages for potential use as sensitizers in boron neutron capture therapy (BNCT) and photodynamic therapy (PDT) were synthesized from protoporphyrin dimethyl ester and characterized. Diastereomeric ether-linked dimers bearing four *closo* carborane cages (40 boron atoms) were found to be unstable to the acidic conditions necessary for conversion into water-soluble salts. In contrast, the carbon–carbon-linked dimers bearing six icosahedral carboranes (60 boron atoms) were stable to acid and could be isolated as water-soluble sodium salts. In vitro and in vivo studies of these novel molecules are currently under investigation.

Keywords: Boron neutron capture therapy; Boronated porphyrin; Carborane; Photodynamic therapy; Porphyrin; Porphyrin dimer

1. Introduction

Boron neutron capture therapy (BNCT) and photodynamic therapy (PDT) are binary cancer therapies in which administration of a sensitizing drug is followed by local application of an activating agent. BNCT involves the administration of a non-toxic, tumor-seeking boron compound followed at an appropriate time by application of a low-energy neutron beam. This process yields metastable ^{11}B nuclei that promptly undergo fission, producing dense, highly cytotoxic trails of ionizing radiation [1]. PDT is a similar binary therapy in which light is used to activate a photophore with local production of cytotoxic singlet oxygen [2]. One of the distinctive hallmarks of binary therapies for cancer such as BNCT and PDT is the selectivity afforded by the treatment; only cells that take up the sensitizer will be killed when activated. The fission products resulting from thermal neutron absorption by ^{10}B have mean free paths of 5 and 9 μm, and the singlet oxygen produced on light absorption by the porphyrin chromophore has a mean free path of <1 μm, i.e. all less than the average cancer cell diameter. Both therapies can employ boron cluster compounds, in BNCT as a source of boron atoms and in PDT as determinants of physicochemical properties leading to selective tumor uptake of the photosensitizer. An example is a boronated porphyrin (BOPP) from our laboratory that has undergone Phase I/II human trials for PDT of glioma and has also been under consideration for BNCT treatment of glioma [3,4].

Porphyrins have been widely observed to accumulate in malignant cells more than in normal cells [2,5]. Photofrin®-II, a semi-purified form of hematoporphyrin derivative (HpD) manufactured and marketed by Axcan Pharma of Canada, is currently in Phase III clinical trials worldwide for PDT treatment of a variety of solid tumors. Chemical analyses of Photofrin®-II showed that it is a complex mixture of monomeric, dimeric and oligomeric porphyrins linked with ether [6–9], ester [10] and/or carbon–carbon linkages [11]. The monomeric fraction was found to be inactive in vivo while the higher molecular weight components containing dimers and higher oligomers were biologically active

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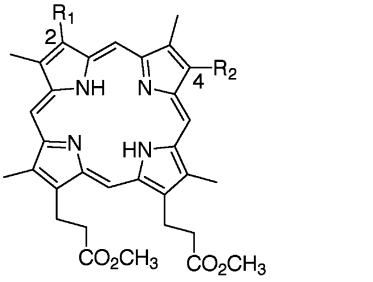
[12]. Detailed structural studies of the chemical nature of Photofrin®-II have revealed that the major tumor-localizing fraction contains dimers and trimers with ether linkages connected between the 2- and 4-positions of hematoporphyrin IX (**2**) (Fig. 1). Regioisomerically pure ether-linked porphyrin dimers and trimers have been synthesized and characterized by several groups [12–16]. It has also been observed that ester-linked porphyrin dimers are biologically inactive and found to be unstable and readily cleaved under both acidic and basic conditions at ambient temperature [15,16]. However, work with carbon–carbon-linked hematoporphyrin dimers indicated that the dimer joined at the 4-position was extremely active as an anticancer agent, while the dimer linked at the 2-position showed little activity [17], indicating a strong relationship between molecular shape and tumor-localizing ability.

These results prompted us to synthesize regiochemically pure porphyrin dimers connected with both ether and carbon–carbon linkages for evaluation as binary sensitizers. The porphyrin units were linked specifically at the 4-position of the macrocycle with both the free porphyrin ring 2-positions and linker-functional group atoms providing potential templates for attachment of polyhedral carborane group attachment. Fig. 2 shows an example of one such target compound, an ether-linked hematoporphyrin dimer, bearing four covalently bound *o*-carborane cages.

2. Results and discussion

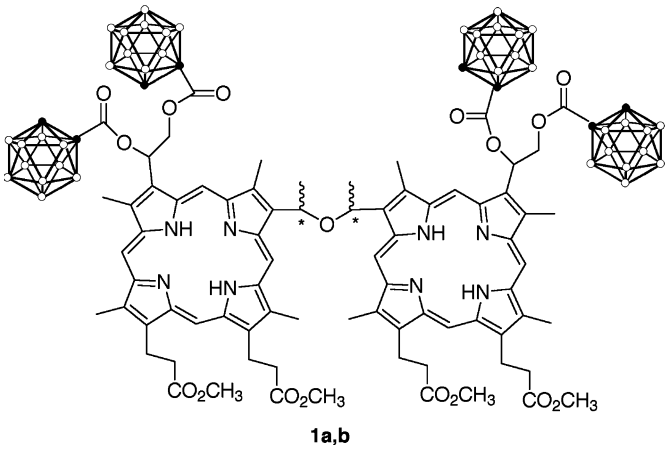
2.1. Synthesis of boronated ether-linked dimers

Three basically similar strategies were apparent for the preparation of boronated ether-linked dimers such as **1a** and **1b** (Fig. 2), each relying on the initial



2 R_1 = $CH(OH)CH_3$ R_2 = $CH(OH)CH_3$
3 R_1 = $CH(OH)CH_3$ R_2 = $COCH_3$
4 R_1 = $COCH_3$ R_2 = $CH(OH)CH_3$
5 R_1 = $COCH_3$ R_2 = $COCH_3$
6 R_1 = $CH=CH_2$ R_2 = $COCH_3$
7 R_1 = $CH=CH_2$ R_2 = $CH(OH)CH_3$
8 R_1 = $CH(OH)CH_2OH$ R_2 = $COCH_3$
9 R_1 = $COCH_3$ R_2 = $CH=CH_2$

Fig. 1. Porphyrin monomers prepared regioselectively in preparation for ether-linked porphyrin dimers.

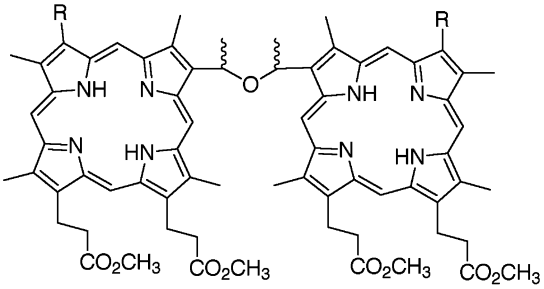


1a,b

Fig. 2. Carboranyl ether-linked porphyrin dimer target compounds.

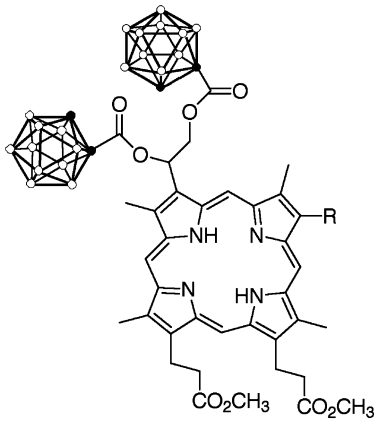
preparation of regiochemically pure monomers. Since we had previous success with exhaustive acylation of glycol porphyrins [18], the most direct and appealing route was to start with the 2-(vinyl)-4-(hydroxyethyl)-deuteroporphyrin monomer (**7**), dimerize to divinyl dimer (DVD) isomers **10a** and **10b** (Fig. 3), convert the vinyl groups into glycols **11a** and **11b** by osmylation and finally acylate with carborane acid chloride. This route seemed the most direct, but as the light sensitivity of vinyl porphyrins is well established, a second alternative was considered. Beginning with acetyl monomer **4**, dimerization would give diacetyl dimer **12a** and **12b**, followed by reduction of the acetyl carbonyls to 1-hydroxyethyl groups as in **13a** and **13b**. Dehydration to DVDs **10a** and **10b** would then be followed as with the first method by osmylation and carborane acylation. Lastly, a third route would begin by acylating glycol monomer **8** to provide the carboranyl porphyrin monomer **14** (Fig. 4). Reduction of the 4-acetyl ketone to monomer **15** and dimerization would then lead to the desired target compounds, regiochemically pure dimers **1a** and **1b** (Fig. 2). Only one of these three strategies proved successful.

The sequence of monomeric porphyrin compounds prepared for the first approach is shown in Fig. 1.



10a,b R = $CH=CH_2$
11a,b R = $CH(OH)CH_2OH$
12a,b R = $COCH_3$
13a,b R = $CH(OH)CH_3$

Fig. 3. Diastereomeric ether-linked porphyrin dimers.



14 R = $COCH_3$
15 R = $CH(OH)CH_3$

Fig. 4. Carboranyl porphyrin monomers.

Commercially available hematoporphyrin IX dihydrochloride (Porphyrin Products) was esterified with diazomethane to give the starting material hematoporphyrin IX dimethyl ester (**2**) in excellent yields (90%). The usual esterification procedure for hematoporphyrin dimethyl ester using methanol/trimethylorthoformate/sulfuric acid gave variable yields [19]. The strongly acidic conditions caused dehydration of the hydroxyl group producing protoporphyrin IX, thereby decreasing the yield of the esterified product and necessitating an additional purification step. The preparation of regiochemically pure dimers requires the synthesis and separation of the pure monomeric regioisomers 4-acetyl-2-(1-hydroxyethyl) deuteroporphyrin IX dimethyl ester (**3**) and 2-acetyl-4-(1-hydroxyethyl)-deuteroporphyrin IX dimethyl ester (**4**) [14]. Partial oxidation of the benzylic-like hydroxyl group of **2** was carried out smoothly using manganese (IV) oxide [19]. This reaction gave a mixture of products **3**, **4** and **5** which was easily separated by silica gel column chromatography. The use of *N*-methylmorpholine oxide (NMO) as the oxidizing agent with a catalytic amount of tetra-*N*-propyl ammonium perruthenate (TPAP) has also been reported previously [14,21]. In our hands, this reaction gave varying amounts of the two regioisomers. This reaction is also considerably faster than oxidation with MnO_2 but resulted in uncontrolled formation of the partially oxidized regioisomers. The completely oxidized by-product 2,4-diacetyldeuteroporphyrin IX dimethyl ester (**5**) eluted first from silica gel, then regioisomer **3** followed closely by regioisomer **4**. The fully oxidized product 2,4-diacetyl-deuteroporphyrin IX dimethyl ester (**5**) can be reduced back to hematoporphyrin dimethyl ester (**2**) with sodium borohydride. Controlled reduction of **5** using an equimolar amount of sodium borohydride can be utilized to yield regioisomers **3** and **4**, but this method failed to give consistent yields. Pure 4-acetyl-2-(1-hydroxyethyl)-deuteroporphyrin IX dimethyl ester (**3**) was then dehydrated with benzoyl chloride in DMF to give 4-acetyl-2-vinyl-deuteroporphyrin IX dimethyl ester (**6**) in quantitative yield. Reduction of the acetyl group of **6** with sodium borohydride gave monomer **7**, the desired precursor to DVD **10**.

Formation of the 4-linked dimer **10** was achieved using published procedures [13,15,21]. The hydroxyl group of porphyrin **7** was transformed into its triflate with trifluoroacetic anhydride and then converted to its 1-bromoethyl derivative with LiBr. The bromo derivative was not isolated, but immediately condensed with the same starting alcoholic monomer **7** to obtain the desired dimer as a mixture of diastereomers **10a** and **10b** in 60% total yield. A similar procedure was used utilizing methanesulfonyl chloride in which the hydroxyl group of porphyrin **7** was converted into its mesylate, which was not isolated, but was immediately reacted with the original monomer **7**. The reaction with trifluoroacetic anhydride gave a slightly better yield (66%) than the procedure using mesyl chloride and there were fewer side products making product isolation easier. Size exclusion chromatography can effectively separate the dimers from the monomers, but silica gel column chromatography was used to separate the diastereomeric dimers (formed in about 1:2 ratio). Due to the presence of the vinyl groups, dimers **10a** and **10b** were extremely light-sensitive compared to vinyl-containing monomers; hence column chromatography was performed in the dark.

The origin of these dimeric isomers is of particular note. Mironov and coworkers [22,23] noted a ''remarkable observation'' in their preparation of dimer **13** from 2-acetyl-4-(1-hydroxyethyl) monomer **4**. When the resulting dimer was subjected to TLC, it was found to consist of two stable isomers of significantly differing chromatographic mobilities, melting points, UV spectra and, presumably, molecular shapes. Similarly, we found that dimerization of 2-vinyl-4-(1-hydroxyethyl) monomer **7** resulted in a pair of easily separable isomers. The mechanism through which dimerization proceeds is probably initiated when the triflate or mesylate leaves to form a stable 2° carbonium ion at the 1-position of the ethyl side chain. A molecule of unesterified alcohol monomer forms the ether linkage by attack at the planar sp^2 site. Since each monomer contains a chiral atom from the hydroxy ethyl side chain, the resulting dimer is composed of two pairs of enantiomers, i.e. a pair of separable diastereomers. Molecular models show that the potential orientations of the two planar porphyrin rings in these diastereomers are quite different. One direction of attack by the alcohol places the two porphyrins lying approximately parallel to each other. This results in the 2- and 2′-vinyl groups being oriented approximately parallel to each other with the porphyrin A, B, C and D rings similarly oriented in the two halves

of the dimer, i.e. with A ring above A′ ring and so forth in what might be described as an "eclipsed" manner. There is then a pseudomirror plane between the two porphyrin ring planes. This structure consists of the *R*,*S* diastereomer. The *R*,*R* diastereomer results from attack from the opposite side of the carbonium ion and produces a dimer in which the two porphyrins are anti-parallel. Such an arrangement leaves the D′ ring of the "upper" porphyrin oriented approximately above the A ring of the "lower" porphyrin and the 2,2′-substituents at a roughly 90–120° angle. Since the resulting diastereomers differ significantly in chromatographic mobility and hence in their potential tumor uptake, we have undertaken a systematic investigation of their respective structures by 2D ROESY and low-temperature proton-NMR and by molecular modeling. The results of this study will appear in a separate paper.

The question of molecular shape and charge distribution is of more than simple curiosity. Although the precise details of the structural requirements and mechanisms responsible for tumor cell localization of porphyrins are not completely understood, physicochemical properties such as molecular shape and hydrophobic character are known to play a major role [24]. In general, amphiphilic sensitizers constitute the most potent and largest class of PDT agents. These compounds tend to localize intracellularly and reach maximum tumor concentrations in 24–48 h after administration. There is substantial experimental evidence that this class of sensitizers becomes associated with lipoproteins on administration, particularly low (LDL)- and high-density lipoproteins (HDL). This binding is believed to be responsible for the resulting intracellular uptake, much like a Trojan horse. Allison et al. [25] have clearly demonstrated that LDL–porphyrin complexes are transported into cells via the LDL receptor, and we have demonstrated this to be the mode of BOPP uptake into malignant glioma cells [26]. Typical biodistribution patterns for amphiphilic porphyrins also mirror the LDL and HDL receptors abundance in organs with liver, spleen, kidney, adrenals and testes showing the highest levels of uptake. Very polar anionic compounds with high charge/volume ratios cannot associate with plasma lipoproteins due to repulsion between negative charges on the phospholipids on the lipoprotein surface and those on the sensitizer molecule. Polyanionic hydrophilic compounds, such as aluminum phthalocyanine tetrasulfonate ($AlPcS_4$), are freely soluble at physiologic pH and often show more rapid tumor uptake and clearance than amphiphilic porphyrins. They also provide good tumor:blood and tumor:normal tissue ratios. There are questions, however, as to whether these localize in stromal and vascular tumor tissue constituents or intracellularly; $AlPcS_4$ is most likely the former while the mono- and disulfonates the latter. Highly charged, pH-insensitive compounds such as $AlPcS_4$ are also found to be strongly associated with serum albumin, which may account for their extracellular locus. For hydrophobic sensitizers, i.e. those of negligible aqueous solubility, biodistribution data are strongly affected by the nature of the delivery vehicle and the resulting state of aggregation of the drug within its lipid environment, making structure-based generalizations difficult. Amphiphilic boronated porphyrins such as BOPP, where the carborane "end" of the molecule is hydrophobic and the propionate residues hydrophilic, are the ultimate targets of the present work.

The second route to boronated ether-linked dimers utilized the pure regioisomer, 2-acetyl-4-(1-hydroxyethyl) deuteroporphyrin IX dimethyl ester (**4**). This was reacted with HBr to form the corresponding brominated product, which was not isolated but was immediately reacted with an equimolar amount of **4** to give two chiral isomeric diacetyl dimers **12a** and **12b** formed in 1:3 ratio. These diastereomers were easily separated by silica gel chromatography since there was a significant difference in their chromatographic mobilities, the isomer **12a** being eluted first. Reduction of the acetyl group on each of the dimers **12a** and **12b** was carried out using sodium borohydride to obtain the dihematoporphyrin ether (DHE) dimers **13a** and **13b**, respectively. Conversion of the acetyl groups of **12a** and **12b** into hydroxyl groups in this manner introduces another set of stereocenters into the molecule and considerably complicates the ^{1}H-NMR spectrum, especially for **13b**. Dehydration of the 2° alcohols in **13a** and **13b** to give the desired DVDs **10a** and **10b** proved to be unsuccessful since the ether linkage was readily cleaved even under the mildest possible dehydration conditions.

The third approach to the desired compounds involved the initial attachment of the boron cages into the monomeric porphyrin units followed by dimerization. The vinyl group of porphyrin **6**, obtained by dehydration of 4-acetyl-2-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**3**), was readily converted to its glycol derivative **8** with OsO_4 [18]. Esterification with *o*-carborane carboxylic acid chloride gave only 20% yield of the disubstituted product **14** (Fig. 4). Prolonged reaction time and increased temperature did not improve the yield considerably. Reduction of **14** to **15** with $NaBH_4$, which would give the precursor to the boronated ether dimers **1a** and **1b**, produced a variety of different products that could not be identified. Hence this scheme proved unsuccessful. It was also observed that attaching the carborane molecules during the later stages of the synthetic scheme gave better yields and purification steps were easier. The boronated pophyrin products tend to streak on the plate or in the column and prolonged contact with silica gel resulted in decomposition. Using neutral alumina for purifying

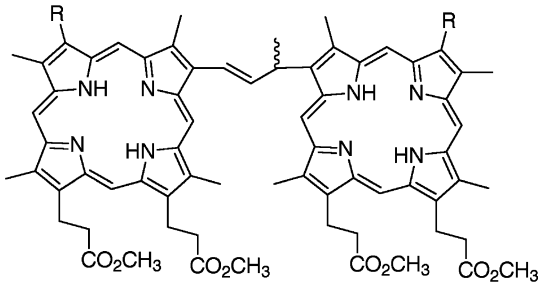
the boronated products did not provide any improvement.

Once the desired dimer precursors were in hand we were able to proceed to add the carborane cages. Divinyl dimers **10a** and **10b** were subjected to dihydroxylation with osmium tetroxide to give bis-glycol ether dimers **11a** and **11b**, respectively. Similar to **13a** and **13b**, the non-stereoselective introduction of two *cis*-hydroxyl substituents creates additional stereocenters in the molecule; thus, the NMR spectra of bis-glycols **11a** and **11b** are very complex. However, as with compounds **11a** and **11b**, this is not reflected in the appearance of additional chromatographically separable species. Attachment of the carborane cages was accomplished easily using a procedure [27] previously developed in our laboratory to give the BOPP ether dimer targets **1a** and **1b**. Passing the reaction mixture through a short silica gel column purified the products **1a** and **1b**. For both of the boronated isomers, a minor quantity of baseline material is always observed during the chromatographic separation in the column and on TLC plates. The IR spectra of **1a** and **1b** both gave a strong absorption at about 2570 cm^{-1}, characteristic of the B–H stretching frequency of the carborane cage. The mass spectrum indicated a molecular ion peak at 1948 and the molecular formula $C_{84}H_{122}N_8O_{17}B_{40}$ was confirmed by elemental analysis. The boron wt.% in these dimers is thus in excess of 22%. Comparison of the melting points of the dimers showed that the dimers **1a**, **10a**, **11a**, **12a** and **13a** all melted at a higher temperature than their corresponding diastereomers.

To ensure efficient transport and biodistribution for applications in binary cancer therapies, BOPP should be amphiphilic. In the case of the boronated dimer, water solubility can be achieved by hydrolysis of the propionate ester groups and then converting their corresponding carboxylic acids into their sodium or potassium salts. However, the ether linkage of boronated dimers **1a** and **1b** did not withstand the conditions for acidic hydrolysis, and the carborane cage, although stable in acidic media, decomposes into its open cage form in basic conditions. Although *nido* carborane cages are intrinsically water-soluble, they are also often associated with significantly increased toxicity. Since our results showed instability and extreme acid sensitivity of the ether linkage of the boronated dimer, we turned our attention to BOPP dimers joined by carbon–carbon bonds.

2.2. Synthesis of carbon–carbon-linked BOPP dimers

Triflic acid (trifluoromethane sulfonic acid) treatment of porphyrins has been reported to give carbon–carbon-linked dimers (Fig. 5) [17]. Such methodology was utilized in the present work, but the reaction time was increased to 5 days from the reported time of 30 min.



16 R = $COCH_3$
17 R = $CH{=}CH_2$

Fig. 5. Carbon–carbon-linked porphyrin dimers.

The regioisomer 2-acetyl-4-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**4**) in dry dichloromethane was reacted with freshly opened triflic acid to give in 90% yield the carbon–carbon-linked diacetyl dimer **17**, the structure of which was confirmed by ^{1}H-NMR and mass spectroscopies. The proposed mechanism for the coupling reaction involves initial protonation of the hydroxyl substituent, which is eventually lost as a water molecule. The porphyrin can form either a vinyl group through proton elimination or remain a stabilized carbocation. Dimerization occurs when the vinyl group acting as a nucleophile attacks the carbonium ion formed from another molecule. During the course of the reaction, the stable by-product, 2-acetyl-4-vinyl-deuteroporphyrin IX dimethyl ester (**9**) (the dehydrated form of **4**), was observed as a faster-moving band than dimer **16**. This stable vinyl-substituted intermediate **9** can be isolated and, when subjected to the same reaction with triflic acid, carbon–carbon-linked porphyrin dimer **16** was also formed under the same reaction conditions. Conversion into the carbon–carbon-linked DVD **17** was performed easily by sodium borohydride reduction of **16** to the corresponding diol followed by the usual method of dehydration with benzoyl chloride in dimethylformamide to give **17** in 80% yield. The ''propene'' dimer linkage is very stable under these acidic conditions and no evidence of dimer cleavage was observed. Dimer **17** has three alkene groups that can be transformed into dihydroxy-substituted functional groups. Indeed, dihydroxylation with osmium tetroxide gave the corresponding hexaol **18** (Fig. 6). Despite having five tetrahedral stereocenters, both **18** and **19** appeared as single spots upon thin-layer chromatography (TLC). Esterification of **18** with carboranyl acid chloride using the procedure described above gave the desired carbon–carbon-linked BOPP dimer **19**, which has six carborane cages appended. The boron wt.% of this dimer is ~28%. Subsequent acidic hydrolysis of **19** gave product **20** (Fig. 7), which was found by mass spectral analysis to contain one less carborane cage, indicating that one of the ester bonds is acid-labile, presumably one located in the carbon–carbon linkage. This implies that two

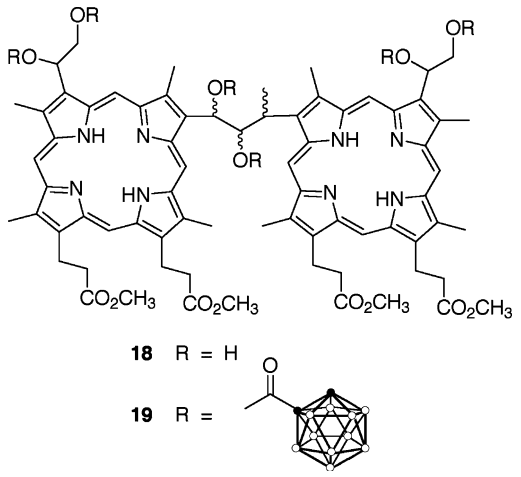


Fig. 6. Carbon-linked porphyrin dimers bearing four or six *o*-carborane cages.

positional isomers **20a** and **20b** are formed. The fact that the dimer is still intact means that the linkage survived this extremely acidic dehydration condition. Exchanging the ionizable proton by passing the compound in an ion-exchange column gave sodium salts **21a** and **21b**, which prove to have surprisingly good solubility in water (~ 2 mg ml^{-1}). Complete assignment of ^{1}H-NMR spectra of the hydrolyzed products **20a** and **20b** and their corresponding salts **21a** and **21b** is not possible due to the presence of broad peaks. These are likely results of positional isomers at the linkage sites brought about by the hydrolysis reaction, as well as the presence of multiple stereocenters. Further studies evaluating the in vitro and in vivo behavior of this remarkable compound are currently underway.

3. Conclusions

Porphyrin dimers are potentially useful as boron delivery agents for BNCT or as photosensitizers in PDT. We have synthesized a series of ether-linked diastereomeric porphyrin dimers joined at the 4-position, culminating in a diastereomeric pair of boronated dimers in which four *closo* carborane cages are appended. The resulting diastereomers, containing 40 boron atoms, were found to be acid-labile at the ether link and thus unsuitable for use in binary cancer therapies. In contrast, carbon–carbon-linked dimers bearing up to six carborane cages (60 boron atoms) were prepared and found to be acid-stable. Further in vitro and in vivo investigation of these compounds is currently in progress.

4. Experimental

4.1. General

Melting points were measured on Thomas Hoover capillary melting point apparatus. Electronic absorption spectra were obtained on a Hewlett-Packard 8452A spectrophotometer using solutions in dichloromethane. Routine NMR spectra (^{1}H- and ^{13}C-NMR) were

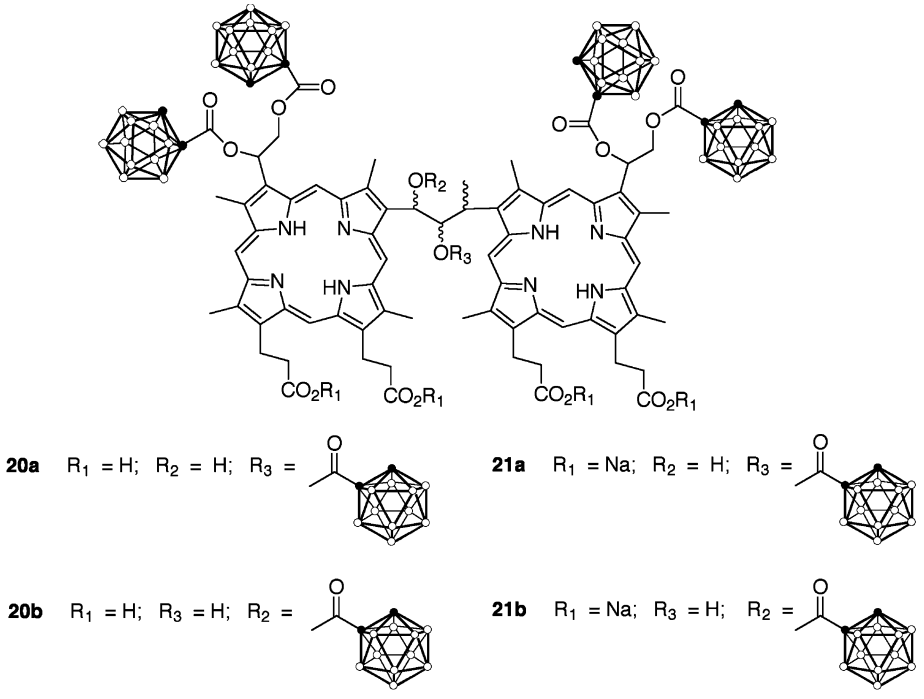


Fig. 7. Carboranyl porphyrin dimer target compounds.

obtained in $CDCl_3$ or DMSO at 300 MHz (GE QE300) with chemical shifts reported in ppm relative to internal standards of tetramethylsilane (0 ppm) or chloroform (7.258 ppm). Reactions were monitored using TLC on commercially available Eastman-Kodak silica sheets. Gravity and flash column chromatography employed either Camag Brockman neutral alumina (70–230-mesh) or Merck silica gel 60. For preparative TLC, Analtech 1500 μ Silica Gel GF was used and for gel permeation chromatography, Bio-Beads S-X1 (200–400-mesh) was utilized.

4.2. 4-Acetyl-2-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (3) and 2-acetyl-4-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (4)

Hematoporphyrin IX dimethyl ester (**2**, 1.00 g) (obtained by diazomethane esterification of commercially available hematoporphyrin IX) was dissolved in dichloromethane (400 ml). Manganese (IV) oxide (MnO_2, 3.0 g) was added and the mixture stirred overnight. The reaction monitored by TLC was stopped when almost all the starting porphyrin disappeared. The black precipitate was filtered-off and the solvent removed. The product was purified by silica gel column chromatography, eluting with 1% MeOH in methylene chloride. The first band was 2,4-diacetylporphyrin IX dimethyl ester (**5**) which was collected and evaporated to dryness to give 95 mg of **5** (9.5% yield from **2**). The major band contained the desired isomers; each was separated and crystallized from dichloromethane/hexane. (A) Fast-running band: 4-acetyl-2-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**3**)—320 mg (32% yield from **2**); m.p.: 213–215 °C (lit. [20], 229–230 °C); λ_{max} (nm) (CH_2Cl_2): 410 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 172 000), 508 (10 000), 548 (11 000), 578 (7000), 632 (900); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.67, 10.02, 9.79, 9.77 (4H, s, *meso*-H), 6.14 (1H, q, $-CH(OH)-CH_3$), 4.33–4.23 (4H, each t, $CH_2CH_2CO_2Me$), 3.69, 3.68, 3.67, 3.49, 3.40 (18H, each s, ring Me and CO_2CH_3), 3.30 (4H, t, $CH_2CH_2CO_2Me$), 3.19 (3H, s, $CH_3C{=}O$), 2.40 (1H, br s, O*H*), 1.98 (3H, d, $CH(OH)CH_3$), −4.11 (2H, br s, N*H*). (B) Slow-moving band: 2-acetyl-4-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**4**)—350 mg (35% yield from **2**); m.p.: 240–242 °C (lit. [20], 247–249 °C); λ_{max} (nm) (CH_2Cl_2): 410 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 175 000), 508 (10 900), 548 (12 000), 578 (7500), 632 (1600); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.62, 10.22, 9.85 (4H, s, *meso*-H), 6.40 (1H, q, $-CH(OH)-CH_3$), 4.36, 4.27 (4H, each t, $CH_2CH_2CO_2Me$), 3.72, 3.69, 3.66, 3.57, 3.49, 3.47 (18H, each s, ring Me and CO_2CH_3), 3.26 (4H, t, $CH_2CH_2CO_2Me$), 3.24 (3H, s, $CH_3C{=}O$), 2.75 (1H, br s, O*H*), 2.15 (3H, d, $CH(OH)CH_3$), −4.06 (2H, br s, N*H*).

4.3. 4-Acetyl-2-vinyldeuteroporphyrin IX dimethyl ester (6)

4-Acetyl-2-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**3**) (400 mg) was dissolved in anhydrous dimethyl formamide (120 ml) and benzoyl chloride (4.6 ml) was added to the solution. The solution was heated at 95 °C for 1 h. The mixture was allowed to cool and then poured into 3% aqueous triethylamine (460 ml). The purple black precipitate was filtered in a sintered glass funnel and then washed with water several times. The product was dissolved with methylene chloride and the filtrate was dried over sodium sulfate. The solvent was evaporated to give 390 mg of **6** (98% yield). m.p.: 190–191 °C (lit. [21], 160–163 °C); λ_{max} (nm) (CH_2Cl_2): 412 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 171 000), 510 (12 000), 550 (9900), 580 (6900), 632 (3800); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.72, 10.21, 9.98, 9.96 (4H, s, *meso*-H), 8.26–8.20 (1H, dd, $-CH{=}CH_2$), 6.44–6.23 (2H, dd, $CH{=}CH_2$), 4.43–4.32 (4H, each t, $CH_2CH_2CO_2Me$), 3.85, 3.71, 3.67, 3.55 (18H, each s, ring Me and CO_2CH_3), 3.31 (3H, s, $CH_3C{=}O$), 3.27 (4H, t, $CH_2CH_2CO_2Me$), −3.64 (2H, br s, N*H*); *m*/*z*: 607.2 (100%, MH^+).

4.4. 4-(1-Hydroxyethyl)-2-vinyldeuteroporphyrin IX dimethyl ester (7)

4-Acetyl-2-vinyldeuteroporphyrin IX dimethyl ester (**6**) (300 mg) was dissolved in dry methylene chloride (100 ml) and the solution was stirred under argon. A suspension of sodium borohydride (160 mg) in dry methanol (10 ml) was added to the mixture. The reaction was monitored by TLC. When the reaction was complete, pouring the solution into water quenched excess sodium borohydride. The organic portion was washed with aqueous solution of sodium bicarbonate and then twice with water. The organic layer was dried over sodium sulfate and then concentrated to give 300 mg of the reduced product **7** (100% yield). m.p.: 195–196 °C (lit. [21], 164–166 °C); λ_{max} (nm) (CH_2Cl_2): 402 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 109 000), 502 (8700), 536 (6300), 572 (3800), 626 (2200); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.09, 9.96, 9.90, 9.89 (4H, s, *meso*-H), 8.24–8.14 (1H, dd, $-CH{=}CH_2$), 6.35–6.14 (2H, dd, $CH{=}CH_2$), 6.05 (1H, q, $CH(OH)CH_3$), 4.30 (4H, each t, $CH_2CH_2CO_2Me$), 3.66, 3.67, 3.61, 3.51, 3.49, 3.35 (18H, each s, ring Me and CO_2CH_3), 3.23 (4H, t, $CH_2CH_2CO_2Me$), 2.11 (1H, br s, $CH(OH)CH_3$), 2.02 (3H, d, $CH(OH)CH_3$), −4.08 (2H, br s, N*H*); *m*/*z*: 609.2 (100%, MH^+).

4.5. Bis {1-[2-vinyldeuteroporphyrin IX 13,17-dimethyl ester-8-yl]ethyl} ether or DVD (10a and 10b)

4-(1-Hydroxyethyl)-2-vinyldeuteroporphyrin IX dimethyl ester (**7**) (600 mg) was dissolved in trifluoroacetic

anhydride (180 ml). After stirring the solution under argon for 15 min, the solvent was evaporated under vacuum protected from light. The residue was dissolved in dry dichloromethane (180 ml) after which 600 mg of **7** dissolved in dry dichloromethane (180 ml) was added to the original mixture. The solution was stirred for 8 h under argon at room temperature (r.t.), then diluted with methylene chloride (100 ml) and washed with water (2 ×). The organic layer was dried over Na_2SO_4 and the solvent was removed. The residue was subjected to silica gel column chromatography in the dark using 2% tetrahydrofuran (THF) in dichloromethane as the eluent and increasing to 4% THF in dichloromethane to yield two fractions in 1:2 mixture (66% total yield). (A) Fast-running band, DVD **10a** (156 mg; 26% yield)—m.p.: 255–257 °C (decomposed); λ_{max} (nm) (CH_2Cl_2): 404 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 230 000), 504 (26 000), 530 (17 000), 572 (10 000), 622 (4600); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.19, 10.14, 9.91 (6H, each s, *meso*-H), 9.80 (2H, br s, *meso*-H), 8.32–8.22 (2H, each dd, –C*H*=CH_2), 6.38–6.12 (4H, each dd, CH=C*H*$_2$), 6.27–6.20 (2H, q, C*H*(O)CH_3), 4.48 (8H, br t, C*H*$_2$$CH_2CO_2Me$), 3.93, 3.79, 3.72, 3.64 (30H, each s, ring Me and CO_2CH_3), 3.34 (8H, m, $CH_2CH_2CO_2Me$), 2.35–2.37 (6H, d, CH(O)C*H*$_3$), 2.09 (6H, br s, 10-C*H*$_3$), −3.67 (4H, br s, N*H*); *m*/*z*: 1199.4 (100%, MH^+); Anal. Calc. for $C_{72}H_{78}N_8O_9$: C, 72.08; H, 6.56; N, 9.35. Found: C, 71.84; H, 6.51; N, 9.15%. (B) Slow-moving band, DVD **10b** (320 mg, 40% yield)—m.p.: 127–130 °C; λ_{max} (nm) (CH_2Cl_2): 398 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 200 000), 504 (19 000), 538 (12 000), 576 (6200), 628 (2600); ^{1}H-NMR ($CDCl_3$, δ ppm): 9.96, 9.63, 9.36 (6H, each s, *meso*-H), 9.81 (2H, br s, *meso*-H), 8.06–7.96 (2H, each dd, –C*H*=CH_2), 6.65–6.59 (2H, q, C*H*(O)CH_3), 6.22–6.03 (4H, each dd, CH=C*H*$_2$), 4.40 (4H, br t, C*H*$_2$$CH_2CO_2Me$), 3.70, 3.69, 3.49, 3.34 (30H, each s, ring Me and CO_2CH_3), 3.40 (4H, br t, C*H*$_2$$CH_2CO_2Me$), 3.24 (4H, overlapping m, $CH_2CH_2CO_2Me$), 2.52–2.50 (6H, d, CH(O)C*H*$_3$), 2.40 (4H, br m, $CH_2CH_2CO_2Me$), 2.01 (6H, s, 10-C*H*$_3$), −4.78 (4H, br s, N*H*); *m*/*z*: 1199.5 (100%, MH^+); Anal. Calc. for $C_{72}H_{78}N_8O_9\cdot 2H_2O$: C, 70.00; H, 6.69; N, 9.07. Found: C, 70.36; H, 6.59; N, 8.92%.

4.6. Bis{1-[2-(1,2-dihydroxyethyl)deuteroporphyrin IX 13,17-dimethyl ester-8-yl]ethyl} ether or bis-glycol dimer (*11a* and *11b*)

To DVD **10a** (200 mg) was added dioxane (60 ml) and pyridine (18 drops). Argon was bubbled through the solution for 20 min. A solution of osmium tetroxide (200 mg) in diethyl ether (28 ml) was added to the mixture and the resulting solution was stirred overnight under argon atmosphere. The reaction flask was protected from light by wrapping with aluminum foil. After 16 h of stirring in the dark, sodium sulfite (800 mg) in water (8 ml) was added and the mixture heated at 75 °C for 1 h. The black precipitate was filtered-off and discarded. The filtrate was subjected to evaporation under vacuum and the residue was purified by preparative TLC using 2% methanol in dichloromethane as the solvent. The major band was the dimer glycol which was collected to give 75 mg of the product **11a** (35% yield). m.p.: > 270 °C; λ_{max} (nm) (CH_2Cl_2): 402 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 219 000), 502 (19 200), 534 (10 400), 570 (6600), 624 (2200); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.33, 10.08, 10.01, 9.97 (8H, each s, *meso*-H), 6.24 (4H, br m, –C*H*(OH)CH_2OH and C*H*(O)CH_3), 4.56, 4.20, 4.05 (4H, m, C*H*$_2$OH), 4.45 (8H, br t, –C*H*$_2$$CH_2CO_2Me$), 3.67, 3.34 (36H, each s, ring Me and CO_2CH_3), 2.36 (8H, m, $CH_2CH_2CO_2Me$), 2.23 (6H, d, CH(O)C*H*$_3$), 2.11 (4H, br s, O*H*), −3.67 (4H, br s, N*H*); *m*/*z*: 1268.6 (100%, MH^+); Anal. Calc. for $C_{72}H_{82}N_8O_{13}\cdot 3H_2O$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.43; H, 6.57; N, 8.46%.

The same procedure was followed to give 85 mg of the product **11b** from 200 mg of **10b** (40% yield). m.p.: 250 °C (decomposed); λ_{max} (nm) (CH_2Cl_2): 390 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 195 000), 502 (24 200), 534 (18 500), 570 (17 300), 622 (13 300); ^{1}H-NMR ($CDCl_3$, δ ppm): 9.89, 9.78, 9.54, 9.51, 9.35 (8H, each s, *meso*-H), 6.64–6.38 (4H, br m, –C*H*(OH)CH_2OH and C*H*(O)CH_3), 5.26–4.91 (4H, br m, CH(OH)C*H*$_2$OH), 4.38 (4H, br t, –C*H*$_2$$CH_2CO_2Me$), 3.79, 3.67, 3.60, 3.34 (36H, each s, ring Me and CO_2CH_3 and 4H, C*H*$_2$$CH_2CO_2Me$), 3.30 (4H, br t, –$CH_2CH_2CO_2Me$), 2.53 (6H, d, CH(O)C*H*$_3$), 2.49 (4H, m, $CH_2CH_2CO_2Me$), 2.20 (4H, br s, OH), −5.07 (4H, br s, N*H*); *m*/*z*: 1267.7 (100%, MH^+); Anal. Calc. for $C_{72}H_{82}N_8O_{13}\cdot 3H_2O$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.39; H, 6.40; N, 8.52%.

4.7. Bis{1-[2-(1,2-di-o-carboranyl-1-carboxyethyl)deuteroporphyrin IX 13,17-dimethyl ester-8-yl]ethyl} ether or ether-linked BOPP (*1a* and *1b*)

To bis-glycol dimer **11a** (70 mg) in dichloromethane (10 ml) was added carboranyl acid chloride (70 mg). The solution was stirred for 10 min under argon at r.t. DMAP (35 mg) was added and stirring was continued for another hour while the reaction was monitored. When the starting glycol disappeared as shown by TLC, the solution was washed twice with water. The residue after the solvent was removed was redissolved in a small amount of dichloromethane and then purified by passing through a short silica gel column using 4% THF in methylene chloride as the eluent. The faster-moving band, which was the major component, was collected to give 38 mg (36% yield) of BOPP ether dimer **1a**. m.p.: 190–192 °C; λ_{max} (nm) (CH_2Cl_2): 400 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 257 000), 504 (24 900), 538 (18 600), 572 (14 000), 628 (7000); IR (in KBr, cm^{-1}): 2607, 2571 (B–H stretch), 1731 (C=O stretch); ^{1}H-NMR ($CDCl_3$, δ

ppm): 10.49, 10.24, 9.95 (6H, each s, *meso*-H), 9.73 (2H, v br s, *meso*-H), 6.37 (2H, m, –C*H*(O)CH_3), 6.34 (4H, br m, CH_2–OC=O), 6.13 (2H, br m, C*H*–OC=O), 5.46, 4.99 (4H, br m, –COOCH–CH_2–OCO), 4.51 (8H, m, –$CH_2CH_2CO_2$Me), 4.09 (4H, br s, carborane C*H*), 3.70, 3.59, 3.37 (36H, br s, ring Me and CO_2CH_3), 2.29 (6H, d, CH(O)CH_3), 2.20 (40 H, v br s, *BH*), *2*.14 and 2.18 (8H, each m, $CH_2CH_2CO_2$Me), −3.68 (4H, br s, N*H*); *m*/*z*: 1949.2 (100%, MH^+); Anal. Calc. for $C_{84}H_{122}N_8O_{17}B_{40}$: C, 51.78; H, 6.31; N, 5.75. Found: C, 52.15; H, 6.00; N, 6.13%.

The same procedure as above was followed to give 65 mg of the product **1b** from 70 mg of **11b** (62% yield) except 3% THF in CH_2Cl_2 was used to elute the product from the silica gel column. m.p.: 165–168 °C; λ_{max} (nm) (CH_2Cl_2): 399 (ε (dm^3 mol^{-1} cm^{-1}): 236 000), 505 (23 000), 540 (19 300), 572 (16 500), 624 (12 100); IR (in KBr, cm^{-1}): 2610 (B–H stretch), 1739 (C=O stretch); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.20, 10.16, 10.09, 9.94, 9.86, 9.85, 9.32, 9.12 (8H, each s, *meso*-H), 7.58, 7.49 (2H, br dd, –COO–C*H*–CH_2–OCO), 6.60 (2H, m, –C*H*(O)CH_3), 5.98, 5.45, 5.24 (4H, br m, –COO–CH_2–OCO), 4.39 (8H, m, –$CH_2CH_2CO_2$Me), 4.07 (4H, br s, carborane C*H*), 3.73, 3.71, 3.66, 3.55, 3.41 (36H, br s, ring Me and CO_2CH_3), 3.28 (8H, m, $CH_2CH_2CO_2$Me), 2.53 (6H, d, CH(O)CH_3), 2.23 (40H, v br s, B*H*), −3.99 (4H, br s, N*H*); *m*/*z*: 1949.3 (55%, MH^+); Anal. Calc. for $C_{84}H_{122}N_8O_{17}B_{40}$: C, 51.78; H, 6.31; N, 5.75. Found: C, 52.20; H, 6.52; N, 5.72%.

4.8. Bis{1-[2-acetyldeuteroporphyrin IX 13,17-dimethyl ester-8-yl]ethyl} ether or diacetyl ether dimer (DAD) (**12a** and **12b**)

2-Acetyl-4-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**4**) (100 mg) was dissolved in dry methylene chloride (80 ml). HBr was bubbled into the solution for 5 min and the solution stirred for another 10 min. The solvent was evaporated and the residue was dissolved in dry methylene chloride (80 ml) after which a solution of 100 mg of the starting monomeric alcohol **4** (100 mg) in dry methylene chloride (20 ml) was added. The resulting mixture was stirred for 20 min, then diluted with methylene chloride (100 ml). The solution was washed with water, then with aqueous sodium bicarbonate, then again with water. The solution was concentrated and the dimers were separated from the monomers by using gel permeation chromatography. The dimeric fraction was eluted first with dichloromethane followed by the monomeric fraction. The diastereomeric dimers were separated by silica gel chromatography eluting with 4% THF in dichloromethane to give two fractions. (A) Faster-moving fraction—DAD **12a**, 20 mg (20% yield); m.p.: 271–272 °C (lit. [23], 293–294 °C); λ_{max} (nm) (CH_2Cl_2): 408 (ε (dm^3 mol^{-1} cm^{-1}): 242 000), 512 (24 500), 548 (23 400), 578 (15 200), 628 (5900); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.84, 10.28, 9.83 (6H, each s, *meso*-H), 9.64 (2H, br s, *meso*-H), 6.25 (2H, q, –C*H*(O)CH_3), 4.50 (8H, t, –$CH_2CH_2CO_2$Me), 4.00, 3.77, 3.69, 3.63 (30H, br s, ring Me and CO_2CH_3), 3.35 (6H, s, CH_3C=O), 3.26 (8H, br t, $CH_2CH_2CO_2$Me), 2.33 (6H, d, CH_3CHO), 2.11 (6H, br s, 10-CH_3), −3.54 (4H, br s, N*H*); ^{13}C-NMR: 199.7 (CH_3C=O), 173.4 (CH_3OC=O), 140.0, 138.9, 138.6, 136.6, 135.7 (aromatic porphyrin), 101.7, 98.2, 97.2, 95.9 (*meso*-C), 69.4 (*C*H(O)CH_3), 51.8, 51.7 (CO_2CH_3), 36.8 ($CH_2CH_2CO_2$Me), 36.4 (CH_3C=O), 24.7 (CH_3CHO), 21.1, 21.7 ($CH_2CH_2CO_2$Me), 14.5, 11.6, 11.4, 10.5 (ring Me); *m*/*z*: 1231.8 (100%, MH^+); Anal. Calc. for $C_{72}H_{78}N_8O_{11}$: C, 68.23; H, 6.52; N, 8.84. Found: C, 67.81; H, 6.41; N, 8.55%. (B) Slower-moving fraction—DAD **12b**, 60 mg (60% yield); m.p.: 217–218 °C (lit. [23], 265 °C decomposed); λ_{max} (nm) (CH_2Cl_2): 406 (ε (dm^3 mol^{-1} cm^{-1}): 213 000), 512 (20 100), 536 (19 400), 578 (14 000), 636 (6300); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.33, 9.96, 9.07 (6H, each s, *meso*-H), 9.54 (2H, br s, *meso*-H), 6.59 (2H, q, –C*H*(O)CH_3), 4.33 (4H, t, –$CH_2CH_2CO_2$Me), 3.90, 3.71, 3.64, 3.54, 3.47 (30H, each s, ring Me and CO_2CH_3), 3.37 (4H, m, $CH_2CH_2CO_2$Me), 3.22 (6H, s, CH_3C=O), 3.18 (4H, m, $CH_2CH_2CO_2$Me), 2.52 (6H, d, CH_3CHO), 2.39 (4H, m, $CH_2CH_2CO_2$Me), 2.04 (6H, br s, 10-CH_3), −4.96 (4H, br s, N*H*); ^{13}C-NMR: 199.3 (CH_3C=O), 173.2 (CH_3OC=O), 138.3, 137.1, 136.2 (aromatic porphyrin), 100.8, 97.4, 94.7 (*meso*-C), 71.2 (*C*H(O)CH_3), 51.7, 51.5 (CO_2CH_3), 36.6, 35.9 ($CH_2CH_2CO_2$Me), 33.1 (CH_3C=O), 24.2 (CH_3CHO), 21.6, 20.8 ($CH_2CH_2CO_2$Me), 14.4, 11.9, 11.6, 10.2 (ring Me); *m*/*z*: 1230.7 (100%, M^+); Anal. Calc. for $C_{72}H_{78}N_8O_{11}$: C, 70.23; H, 6.38; N, 9.10. Found: C, 69.96; H, 6.57; N, 9.02%.

4.9. Bis{1-[2-(1-hydroxyethyl)deuteroporphyrin IX 13,17-dimethyl ester-8-yl]ethyl} ether or DHE dimer (**13a** and **13b**)

These compounds (**13a** and **13b**) were prepared in quantitative yield from diacetyl porphyrin dimer **12a** and **12b**, respectively, using sodium borohydride as the reducing agent. The procedure for the preparation of **7** was followed. (A) DHE **13a**—m.p.: 289–291 °C; λ_{max} (nm) (CH_2Cl_2): 404 (ε (dm^3 mol^{-1} cm^{-1}): 185 000), 502 (20 500), 534 (11 500), 572 (7520), 622 (4700); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.46, 10.40, 10.16, 9.93 (6H, each s, *meso*-H), 9.78 (2H, br s, *meso*-H), 6.56 (2H, br q, –C*H*(OH)CH_3), 6.32 (2H, br q, –C*H*(O)CH_3), 4.47 (8H, t, –$CH_2CH_2CO_2$Me), 3.71, 3.69, 3.64 (36H, each s, ring Me and CO_2CH_3), 3.35 (8H, br t, $CH_2CH_2CO_2$Me), 3.16, 2.92 (2H, br s, O*H*), 2.35 (6H, d, CH(OH)CH_3), 2.22 (6H, d, CH(O)CH_3), −3.72 (4H, br s, N*H*); *m*/*z*: 1235.6 (100%, M^+); Anal. Calc. for $C_{72}H_{82}N_8O_{11}\cdot 2H_2O$: C, 68.01; H, 6.82; N, 8.81. Found: C, 67.75; H, 6.52; N, 8.59%. (B) DHE **13b**—m.p.: 198–

200 °C; λ_{max} (nm) (CH_2Cl_2): 396 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 195 000), 502 (18 800), 534 (10 600), 570 (9500), 622 (4500); ^{1}H-NMR ($CDCl_3$, δ ppm): 9.94, 9.93, 9.91, 9.86, 9.68, 9.43, 9.31 (8H, each s, *meso*-H), 6.62, 6.58 (2H, br q, –C*H*(OH)CH_3), 6.07, 5.93 (2H, br q, –C*H*(O)CH_3), 4.40 (8H, t, –C$H_2$$CH_2CO_2Me$), 3.73, 3.69, 3.50 (36H, each s, ring Me and CO_2CH_3), 3.27 (8H, br t, $CH_2CH_2CO_2Me$), 2.94 (2H, br s, O*H*), 2.48 (6H, d, CH(OH)CH_3), 2.22 (6H, d, CH–O–CH_3), −4.80, −4.90, −4.98 (4H, each br s, N*H*); *m*/*z*: 1235.7 (100%, MH^+); Anal. Calc. for $C_{72}H_{82}N_8O_{11}\cdot 2H_2O$: C, 68.01; H, 6.82; N, 8.81. Found: C, 68.38; H, 6.54; N, 8.62%.

4.10. 4-Acetyl-2-(1,2-dihydroxyethyl)deuteroporphyrin IX dimethyl ester (*8*)

This compound was prepared from **6** similar to the preparation of **1** in 30% yield with osmium tetroxide as the hydroxylating agent. m.p.: 210–211 °C; λ_{max} (nm) (CH_2Cl_2): 410 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 141 000), 508 (9400), 546 (8300), 576 (5700), 634 (1600); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.52, 9.68, 9.52, 8.98 (4H, each s, *meso*-H), 5.08 (1H, br t, –C*H*(OH)CH_2OH), 4.47 (4H, each t, –C$H_2$$CH_2CO_2Me$), 3.68, 3.59, 3.42, 3.15, 2.97, 2.82 (18H, each s, ring Me and CO_2CH_3), 3.76 (2H, br d, CH(OH)CH_2OH), 3.20 (4H, overlapping t, $CH_2CH_2CO_2Me$), 2.25, 2.10 (2H, br s, O*H*), −4.62 (2H, br s, N*H*); *m*/*z*: 641.2 (100%, MH^+).

4.11. 4-Acetyl-2-(1,2-dicarboranyl)deuteroporphyrin IX dimethyl ester (*14*)

This product was prepared from **8** similar to the preparation of **1** in 30% yield. m.p.: 165–167 °C; λ_{max} (nm) (CH_2Cl_2): 410 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 141 000), 508 (9400), 546 (8300), 576 (5700), 634 (1600); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.81, 10.33, 10.09, 10.04 (4H, each s, *meso*-H), 7.65 (1H, t, –C*H*(O)CH_2O–), 5.78, 5.01 (2H, d, –CH(O)CH_2–O–), 4.35 (4H, t, C$H_2$$CH_2CO_2Me$), 4.18, 4.12 (2H, each br s, carborane C–*H*), 3.99, 3.79, 3.64, 3.37 (18H, each s, ring Me and CO_2CH_3), 3.27 (3H, s, CH_3C=O), 3.20 (4H, overlapping t, $CH_2CH_2CO_2Me$), 2.63 (20H, br, B*H*), −3.48 (2H, br s, N*H*); *m*/*z*: 981.6 (100%, MH^+).

4.12. Bis[1-(2-acetyldeuteroporphyrin IX 13,17-dimethyl ester-8-yl)]-3-methylpropene or carbon–carbon-linked diacetyl dimer (CCD) (*16*)

2-Acetyl-4-vinyldeuteroporphyrin IX dimethyl ester (**4**) (400 mg) was dissolved in dry methylene chloride (40 ml). Argon was bubbled through the solution and triflic acid (4 ml) was added. The green-colored mixture was stirred for 5 days. The solution was neutralized slowly with aqueous solution of sodium bicarbonate and the product was extracted with methylene chloride. The organic layer was washed several times with water and then dried over sodium sulfate. After evaporation, the residue was treated with diazomethane. The product was purified on a short pad of silica gel eluting with chloroform to remove monomeric fraction and then the eluting solvent was changed to 2% MeOH/$CHCl_3$ to elute the second band which is the dimeric fraction to yield 350 mg of **16** (88% yield). m.p.: 240–242 °C; λ_{max} (nm) (CH_2Cl_2): 410 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 297 000), 512 (27 100), 548 (20 800), 578 (17 400), 636 (5000); ^{1}H-NMR ($CDCl_3$, δ ppm): 11.03, 10.82, 10.68, 10.22, 10.10, 10.07, 10.04, 9.90 (8H, each s, *meso*-H), 8.43 (1H, d, –C*H*=CH–CH), 8.00 (1H, dd, –CH=C*H*–CH), 5.99 (1H, br m, –CH=CH–C*H*), 4.49, 4.31, 4.23, 4.09 (8H, t, –C$H_2$$CH_2CO_2Me$), 4.05, 3.94, 3.86, 3.76, 3.71, 3.64, 3.61, 3.55, 3.53, 3.38, 3.36 (36H, each s, ring Me and CO_2CH_3), 3.28 (6H, s, CH_3C=O), 3.31, 3.23, 3.12, 3.03 (8H, br t, $CH_2CH_2CO_2Me$), 2.72 (3H, d, CH=CH–CHCH_3), −3.42, −3.61 (4H, br s, N*H*); *m*/*z*: 1213.6 (100%, MH^+); Anal. Calc. for $C_{72}H_{76}N_8O_{10}$: C, 71.25; H, 6.32; N, 9.24. Found: C, 70.80; H, 6.39; N, 8.86%.

4.13. 2-Acetyl-4-vinyldeuteroporphyrin IX dimethyl ester (*9*)

This is the monomeric fraction isolated upon formation of the above CCD **16**. m.p.: 250–252 °C (lit. [21], 256–258 °C); λ_{max} (nm) (CH_2Cl_2): 414 (ε ($dm^3\ mol^{-1}\ cm^{-1}$): 140 000), 512 (13 000), 550 (12 000), 582 (7000), 634 (3500); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.82, 10.08, 9.96 (4H, each s, *meso*-H), 8.32–8.22 (1H, dd, C*H*=CH_2), 6.46–6.22 (2H, dd, CH=CH_2), 4.45–4.28 (4H, each t, C$H_2$$CH_2CO_2Me$), 3.87, 3.75, 3.67, 3.54 (18H, each s, ring Me and CO_2CH_3), 3.31 (3H, s, CH_3C=O), 3.25 (4H, t, $CH_2CH_2CO_2Me$), −3.65 (2H, br s, N*H*); *m*/*z*: 607.3 (100%, MH^+); Anal. Calc. for $C_{36}H_{38}N_4O_5$: C, 71.27; H, 6.31; N, 9.23. Found: C, 70.78; H, 6.42; N, 9.13%.

4.14. Bis[1-(2-vinyldeuteroporphyrin IX 13,17-dimethyl ester-8-yl)]-3-methylpropene or carbon–carbon-linked divinyl dimer (CCDV) (*17*)

To a solution of CCD **16** (300 mg) in dry methylene chloride (80 ml) was added sodium borohydride (300 mg) and dry methanol (10 ml). The solution was stirred at r.t. under argon atmosphere and the progress of the reaction monitored by TLC. When only one slow-moving spot was observed, the reaction was quenched by pouring the solution into water. The organic layer was washed twice with aqueous sodium bicarbonate, dried over sodium sulfate, solvent removed and the residue dissolved in anhydrous dimethyl formamide (90 ml). Benzoyl chloride (3.6 ml) was added and the mixture was heated at 95 °C for 1 h under argon atmosphere. After the solution was allowed to cool, it

was poured into a cold solution of 3% aqueous triethylamine (400 ml). The precipitate was filtered-off and it was purified in a short pad of silica gel to obtain 230 mg of the product **17** (80% yield). In some instances when precipitation of the product did not occur, it was extracted with dichloromethane from the aqueous solution. m.p.: >270 °C; λ_{max} (nm) (CH_2Cl_2): 408 (ε (dm^3 mol^{-1} cm^{-1}): 244 000), 504 (25 800), 540 (20 500), 576 (12 100), 636 (4350); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.77, 10.84, 10.22, 10.20, 10.18, 10.10, 9.98 (8H, each s, *meso*-H), 8.54–8.49 (1H, d, –C*H*=CH–CH), 8.38, 8.26 (2H, each dd, –C*H*=CH_2), 7.97–7.91 (1H, dd, –CH=C*H*–CH), 6.46, 6.17 (4H, each dd, –CH=CH_2), 5.99 (1H, br m, –CH=CH–C*H*), 4.46, 4.38, 4.26, 4.19 (8H, each t, –C$H_2$$CH_2CO_2$Me), 4.01, 3.66, 3.63, 3.58, 3.53, 3.44 (36H, each s, ring Me and CO_2CH_3), 3.32, 3.25, 3.08, 3.01 (8H, each t, CH_2C$H_2$$CO_2$Me), 2.70 (3H, d, CH=CH–CHCH_3), −3.54, −3.73 (4H, br s, N*H*); *m*/*z*: 1181.5 (100%, MH^+), 591.2 (28%); Anal. Calc. for $C_{72}H_{76}N_8O_8 \cdot 3H_2O$: C, 70.00; H, 6.69; N, 9.07. Found: C, 70.39; H, 6.46; N, 8.67%.

*4.15. Bis{1-[2-(1,2-dihydroxyethyl)deuteroporphyrin IX 13,17-dimethyl ester-8-yl]}-1,2-dihydroxy-3-methylpropane or Tris–glycol carbon–carbon-linked dimer (**18**)*

To CCDV **17** (350 mg) was added of dioxane (75 ml) and pyridine (12 drops). Ar was bubbled into the solution for 20 min. A solution of osmium tetroxide (500 mg) in diethyl ether (30 ml) was added to the previous mixture and then the resulting solution was stirred overnight under argon atmosphere. The reaction flask was protected from light by wrapping with aluminum foil. After 16 h of stirring in the dark, sodium sulfite (1.0 g) in water (15 ml) was added to the mixture and then heated at 75 °C for 1 h. The black precipitate was filtered-off and then discarded. The filtrate was subjected to evaporation under vacuum and the residue was passed through a short silica gel pad washing with chloroform and a small amount of THF. The solvent was evaporated and the residue was again purified by preparative TLC using 10% methanol in dichloromethane as the solvent. The major band was the dimer Tris–glycol which was collected to give 120 mg of the product **18** (35% yield). m.p.: 217–219 °C; λ_{max} (nm) (CH_2Cl_2): 392 (ε (dm^3 mol^{-1} cm^{-1}): 205 000), 502 (19 000), 536 (10 900), 572 (8200), 622 (3600); ^{1}H-NMR ($CDCl_3$, δ ppm): 10.52, 10.46, 10.28, 10.19, 10.01 (8H, each s, *meso*-H), 6.38–6.15 (4H, br m, –C*H*(OH)CH_2OH and C*H*(OH)C*H*(OH)–CHMe), 6.20 (4H, br m, –CH_2OH), 5.54 (1H, br m, –C*H*(Me)CH-OH), 5.20 (6H, br s, O*H*), 4.34 (8H, br t, –C$H_2$$CH_2CO_2$Me), 3.68, 3.59, 3.47, 3.38 (36H, each s, ring Me and CO_2CH_3), 2.94 (3H, br s, –CH(OH)–CH–CH_3), 2.31 (8H, each m, CH_2C$H_2$$CO_2$Me), −4.24 (4H, br s, N*H*); *m*/*z*: 1283.7 (100%, MH^+); Anal. Calc. for $C_{72}H_{82}N_8O_{14}$: C, 67.36; H, 6.44; N, 8.73. Found: C, 67.64; H, 6.24; N, 8.87%.

*4.16. Bis{1-[2-(1,2-di-o-carboranyl-1-carboxyethyl)-deuteroporphyrin IX 13,17-dimethyl ester-8-yl]}-1,2-di-(o-carboranyl-1-carboxyl)-3-methylpropane or boronated carbon–carbon-linked dimer (CCDB) (**19**)*

The above porphyrin **18** was treated with carborane acid chloride following the procedure described for the preparation of **1** except that after stirring overnight, the reaction mixture was washed with H_2O, then with 0.1 M HCl and then twice with aqueous sodium bicarbonate. The residue was observed to contain unidentified boron-containing by-products which were detected when a TLC plate spotted with the sample was exposed to an acidic solution of $PdCl_2$. The fast-running BOPP was isolated using alumina column chromatography eluting with chloroform. The product obtained in 25% yield, however, was found to decompose on the column if allowed to remain longer and if a less-polar solvent such as dichloromethane was used. m.p.: 147–150 °C; λ_{max} (nm) (CH_2Cl_2): 386 (ε (dm^3 mol^{-1} cm^{-1}): 228 000), 506 (16 900), 538 (14 200), 570 (13 200), 624 (6000); IR (KBr, cm^{-1}): 2608, 2580 (B–H stretch), 1740 (C=O stretch); ^{1}H-NMR (DMSO, δ ppm): 10.24, 10.20, 10.15, 10.09, 10.01 (8H, each b s, *meso*-H), 6.40 (4H, br m, –C*H*(O)CH_2O– and C*H*(O)–C*H*(O)–CHMe), 6.30 (4H, br m, –CH_2O*H*), 5.00 (1H, br m, –C*H*(Me)CH–O), 4.31 (8H, m, C$H_2$$CH_2CO_2$Me), 4.10 (6H, br s, carborane CH), 3.65, 3.36 (36H, br s, ring Me and CO_2CH_3), 2.97 (3H, s, CH(O)–CH–CH_3), 2.32 (60H, v br s, –B–*H*), 2.31 (8H, each m, CH_2C$H_2$$CO_2$Me), −4.02 (4H, br s, N*H*); *m*/*z*: 2304.8 (30%, M^+), 679.4 (100%); Anal. Calc. for $C_{90}H_{142}N_8O_{20}B_{60} \cdot 4H_2O$: C, 45.47; H, 6.56; N, 4.71. Found: C, 44.15; H, 6.47; N, 4.59%.

*4.17. Bis{1-[2-(1,2-di-o-carboranyl-1-carboxyethyl)deuteroporphyrin IX 13,17-dicarboxylic acid-8-yl]}-1,2-di-(o-carboranyl-1-carboxyl)-2-hydroxy-3-methylpropane (**20**)*

The above porphyrin **19** was hydrolyzed by dissolving the compound (33 mg) in reagent grade anhydrous diethyl ether (12 ml) followed by adding 25% aqueous HCl (12 ml). The mixture was stirred overnight. Additional 25% aqueous HCl (25 ml) was added and the resulting reaction was monitored by TLC in 20% MeOH in methylene chloride. When the reaction was observed to be complete, ether (50 ml) was added and the solution was washed with H_2O (3 ×). The ether extract was then evaporated to obtain 10 mg of the hydrolyzed free acid product **20a** and **20b** (35% yield). m.p.: 190–193 °C; IR (KBr, cm^{-1}): 3444 (O–H stretch), 2585 (B–H stretch),

1730 (C=O stretch); ^{1}H-NMR (DMSO, δ ppm): 10.50–10.10 (8H, br s, *meso*-H and 4H, *COOH*), 7.5–6.5 (9H, br m, *CH*(O)–*CH*$_2$–O–, *CH*(O)–*CH*(O)–*CH*Me), 4.44, 4.43, 4.16 (8H, br m, *CH*$_2$CH$_2$CO$_2$H), 3.66, 3.55 (24H, each v br s, ring Me), 2.28 (50H, v br s, B–*H* and CH$_2$*CH*$_2$CO$_2$H), −4.00 (4H, br s, *NH*); *m*/*z*: 2079.8 (MH^+).

4.18. Bis{1-[2-(1,2-di-o-carboranyl-1-carboxyethyl)-deuteroporphyrin IX 13,17-dicarboxy-8-yl]}-1,2-di-(o-carboranyl-1-carboxyl)-2-hydroxy-3-methyl-propane tetrasodium salt (**21**)

Diacid **20** (10 mg) was dissolved in 80% acetone in water and was passed through a Dowex 50X2-400 ion-exchange resin (Aldrich). The eluate was passed through the ion exchanger again eluting with 50% acetone in water, and then once again through the resin with water. Acetone was removed and the product was lyophilized. The boronated dimer obtained in 95% yield was soluble in water: 2 mg ml^{-1}. m.p.: 230 °C (decomposed); λ_{max} (nm) (DMSO): 398 (ε (dm^3 mol^{-1} cm^{-1}): 185 000), 502 (29 400), 534 (22 100), 564 (18 500), 620 (16 100); IR (KBr, cm^{-1}): 2580 (B–H stretch), 1709, 1653 (C=O stretch).

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