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Synthesis of novel texaphyrins containing lanthanides and boron

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Abstract—Texaphyrin macrocycles that contain gadolinium or lutetium, such as motexafin gadolinium and motexafin lutetium, are versatile anticancer therapeutics and diagnostics. Gadolinium texaphyrins substituted with carborane clusters could also find application in combined gadolinium and boron neutron capture therapy (GdB-NCT). The synthesis and characterization of novel texaphyrins containing gadolinium or lutetium in the pentaaza core and two carborane clusters bound to opposite pyrrol units of the macrocycle are described.
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Texaphyrins, such as motexafin gadolinium and motexafin lutetium, are applicable in various cancer therapeutic and diagnostic modalities including radiation sensitization in conventional photon radiation therapy, photodynamic therapy (PDT), magnetic resonance imaging (MRI), and fluorescence imaging.[1,2] Since these structures have a tendency to localize selectively in tumors,[1] texaphyrins that contain gadolinium and/or boron also would have applicability to neutron capture therapy (NCT) of cancer.[3] There are two types of NCT, boron neutron capture therapy (^{10}BNCT) and gadolinium neutron capture therapy (^{157}GdNCT).[4] In the case of ^{10}BNCT, a neutron capture reaction occurs when a stable ^{10}B isotope is irradiated with low energy thermal neutrons to produce helium- (α-particle) and lithium nuclei, both of which can kill cancer cells primarily by the induction of DNA double strand breaks.[5] The particles have pathlengths of approximately one cell diameter (<10 μm), which effectively limits damage to cells that have been targeted with ^{10}B. Recently, there has been an increased interest in ^{157}GdNCT, especially in the context of nanotechnology,[6] because ^{157}G has a significantly higher neutron capture cross section than ^{10}B (254,000 b vs 3800 b) and it can be effectively quantified/imaged by MRI. The ^{157}Gd neutron capture reaction produces a mixture of γ-, X-, and β-radiation.[7]

In this Letter, we present the synthesis and characterization of two texaphyrins containing Gd^{3+} in the pentaaza core and either two *para*- (**1**) or two *meta*-carborane clusters (**2**) attached through propylene spacer to opposite pyrrol units of the macrocycle (GdB-texaphyrins, Fig. 1). These structures potentially could be used for combined gadolinium and boron neutron capture therapy (GdB-NCT). On a very small scale, a *meta*-carboranyl lutetium texaphyrin (LuB-texaphyrin, **3**) was also prepared. Overall, synthetic strategies that are typical for texaphyrin- and carborane chemistry were applied

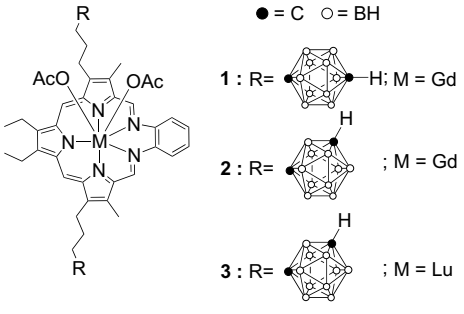

Figure 1. Structures of GdB- and LuB-texaphyrins.

Keywords: Gadolinium and boron neutron capture therapy (GdB-NCT); Carboranyl pyrroles; Boronated gadolinium- and lutetium texaphyrins (GdB- and LuB-texaphyrins).

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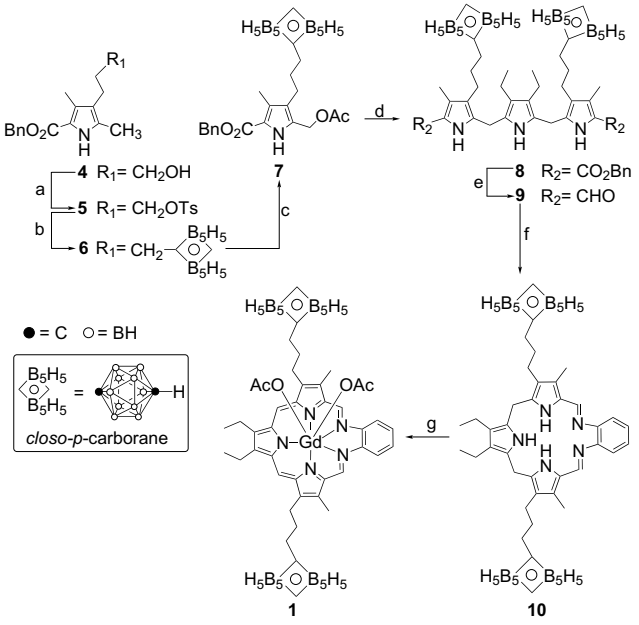

Scheme 1. Synthesis of *p*-carboranyl GdB-texaphyrin **1**. Reagents and conditions: (a) TsCl, Et_3N, CH_2Cl_2; (b) *n*-BuLi, *p*-carborane, THF; (c) SO_2Cl_2, NaOAc, tetra-*n*-butylammonium acetate, CH_2Cl_2; (d) 3,4-diethylpyrrole (0.5 equiv), *p*-TsOH, EtOH, 75–80 °C; (e) (i) Pd/C (10%), H_2, THF/MeOH (1:1); (ii) TFA, CH_2Cl_2; (iii) $CH(OEt)_3$; (f) 1,2-phenylenediamine, MeOH, HCl; (g) $Gd(OAc)_3$, Et_3N, air, MeOH, reflux.

for the preparation of these compounds.[8,9] The general synthetic route is shown in Scheme 1 using GdB-texaphyrin **1** as an example. Compound **4**[10] was converted to tosylate **5** in 68% yield by treatment with *p*-toluenesulfonylchloride/triethylamine at room temperature. The lithium salt of *p*-carborane then was reacted with **5** to afford the boronated pyrrole **6** in 45% yield. Reaction of compound **6** with SO_2Cl_2 in CH_2Cl_2 followed by addition of NaOAc and tetra-*n*-butylammonium acetate produced compound **7** in 82% yield. The acid catalyzed condensation of freshly prepared 3,4-diethyl pyrrole[11] with 2 equiv of **7** gave tripyrrole **8** in 40% yield. Compound **5** as well as the *p*-carboranyl compounds **6**–**8** and their *m*-carboranyl isomers had wax-like consistencies and were characterized by ^1H NMR, ^{13}C NMR, and HR-ESI MS. Compound **9** was prepared according to previously reported procedures for the synthesis of diformyltripyrroles.[12] Debenzylation of **8** was carried out by hydrogenolysis in THF/MeOH (1:1) using 10% Pd/C as the catalyst. Decarboxylation of the crude product with TFA/CH_2Cl_2 was followed by a Clezy-type formylation[13] with triethyl orthoformate to afford crude *p*-carboranyl diformyltripyrrole **9** in 45% yield. The crude product was characterized by HR-ESI MS ($C_{32}H_{60}B_{20}O_2Na$ $[M+Na]^+$ calcd 757.6500; found 757.6494) and ^1H NMR showing the characteristic signals for the aldehydes proton at δ 9.5 ppm. Formation of a Schiff base using crude **9** and *o*-phenylenediamine produced macrocycle **10**, which was partially purified by precipitation from CH_2Cl_2/Et_2O/hexanes (2:1:1.5 v/v/v). Compound **10** was characterized by HR-ESI MS ($C_{38}H_{61}B_{20}N_5$ $[M+H]^+$ calcd 807.7148; found 807.7161) and ^1H NMR showing an apparent singlet for both imine protons at δ 8.04 ppm as well as the four protons from the bridging methylene groups at δ 3.65 ppm due to symmetry of the macrocycle. Compounds **9** and **10** as well as their *m*-carboranyl analogues appeared to be unstable during purification and storage, and therefore, they were used as crude or partially purified materials. Instability of reduced texaphyrin macrocycles was reported previously.[14] Simultaneous oxidation and metallation of compound **10** was carried out with 1.5 equiv Gd(III) acetate hydrate, excess triethylamine, and air in refluxing methanol for 17 h. The solvent was evaporated, the dark residue dried in vacuo for 6–8 h, and purified by silica gel column chromatography using a MeOH/$CHCl_3$ gradient (0–15%) containing 0.2% triethylamine. The silica gel was pre-treated with 6 mL water/20 mL MeOH before use. First, a dark reddish fraction was eluted from the column, which was followed by a dark green fraction containing product. Anion-exchange using Ambersep-900-OH resin, pretreated with AcOH, produced the oxidized texaphyrin macrocycle **1** as a dark green solid in 26% yield. Product purity was conveniently checked by normal-phase silica gel TLC using *n*-BuOH/AcOH/H_2O (4:1:2 v/v/v) as the solvent system.

The *m*-carboranyl GdB-texaphyrin **2** was synthesized according to the procedure described for **1** and yields for intermediates and final product were comparable, except for the *m*-carboranyl analogue of **7**, which was obtained in 65% yield. LuB-texaphyrin **3** (HR-ESI MS: $C_{40}H_{61}B_{20}LuN_5O_2$ $[M-OAc]^+$ calcd 1034.6239; found 1034.6248) was synthesized by reacting the *m*-carboranyl analogue of **10** with 1.5 equiv Lu(III) acetate, triethylamine, and air in refluxing methanol.

Compounds **1** and **2** were analyzed by HR-ESI MS, UV–vis, and ^{11}B NMR (Figs. 2 and 3).[15] MS produced molecule ion signals consistent with the loss of one acetate counterion $[M-OAc]^+$, as has been described previously for other texaphyrins.[16] Due to the isotropic shift of paramagnetic complexes,[17] compounds **1** and **2** were not characterized by ^1H and ^{13}C NMR. The UV–vis absorption spectrum of compound **1** showed a Soret-like band at 430 nm ($\varepsilon = 43{,}362$) and a Q-like band at 770 nm ($\varepsilon = 20{,}893$) along with low intensity bands at 336 nm, 566 nm, and 704 nm. Excitation at both wavelengths resulted in fluorescence emission maximum at 825 nm. The UV–vis spectra of compounds **2** and **3** were similar to those of **1**.

Compounds **1** and **2** were glassy light-sensitive compounds that were soluble in organic solvents such as DMSO, THF, acetone, methanol, ethanol, dichloromethane, and chloroform. They were stable in methanol, ethanol, and alcohol/water mixtures at neutral and slightly basic pH at least for several weeks but decomposed even in the absence of light at pH 2–5. Dark decomposition of **1** and **2** was observed especially in dichloromethane and chloroform, presumably due to minor acidic residues in these solvents.

In summary, we have synthesized and characterized novel *m*- and *p*-carboranyl GdB- and LuB-texaphyrins.

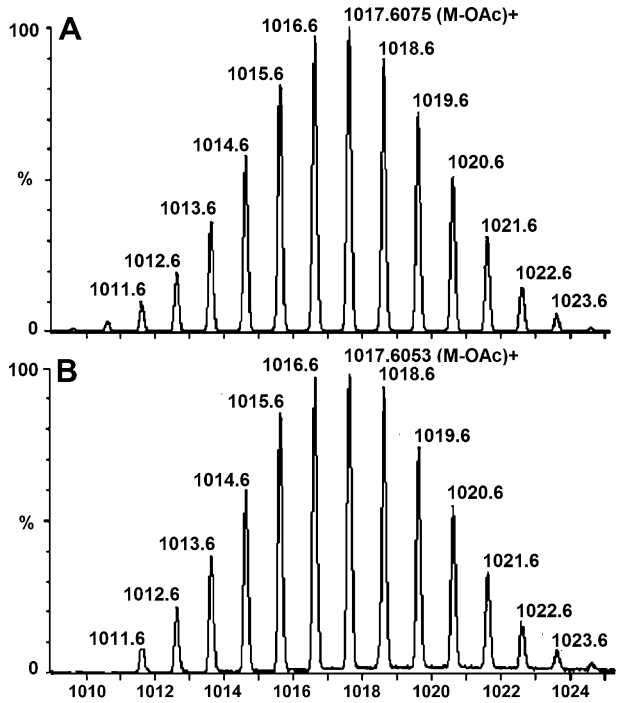

Figure 2. (A) Theoretical MS isotope pattern of GdB-texaphyrin **1** generated with software available at http://www.geocities.com/junhuayan/pattern1.htm. (B) Observed HR-ESI MS of GdB-texaphyrin **1** (positive mode).

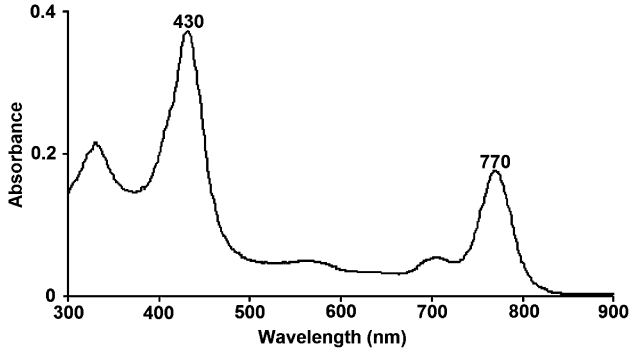

Figure 3. UV–vis absorption spectrum of GdB-texaphyrin **1** (10^{-5} M solution in MeOH).

These macrocycles could be used in GdB-NCT, PDT, MRI, and near-infrared imaging (NIRI). Further structural modification could make these structures especially attractive in the context of nanotechnology.[18] The biological and preclinical evaluation of these agents is underway in our laboratories.

Acknowledgments

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15. Compound **1**: ^{11}B NMR (CD_3OD, decoupled, internal standard: $BF_3{\cdot}OEt_2$) δ −10.42, −12.78, 1.40; UV–vis [(MeOH) λ_{max}, nm] 336.0, 430.0, 566.0, 704.0, 770.0; MS (HR-ESI) $C_{40}H_{61}B_{20}GdN_5O_2$ $[M-OAc]^+$ calcd 1017.6075; found: 1017.6053. Compound **2**: ^{11}B NMR (CD_3OD, decoupled, internal standard: $BF_3{\cdot}OEt_2$) δ −1.32, −8.04, −10.58, −12.31; UV–vis [(MeOH) λ_{max}, nm] 333.0, 433.0, 707.5, 772.5; MS (HR-ESI) $C_{40}H_{61}B_{20}GdN_5O_2$ $[M-OAc]^+$ calcd 1016.6084; found 1016.6122. For compounds **1**, **2**, **3**, **9**, and **10**, the value of the most abundant peak of the isotope pattern is reported as HR signal.
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