Tetrahedron Letters, Vol.31, No.16, pp 2247-2250, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

PREPARATION OF CARBORANYL PORPHYRINS FOR BORON NEUTRON CAPTURE THERAPY

Michiko Miura*, Detlef Gabel#, Georg Oenbrink# and Ralph G. Fairchild

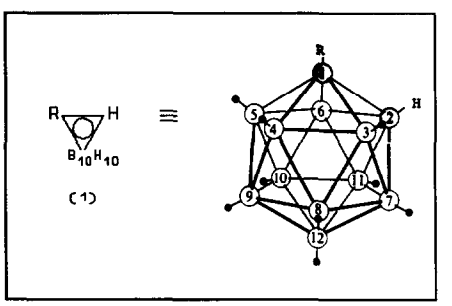
*Brookhaven National Laboratory, Medical Department, Upton, NY 11973, USA
#University of Bremen, Department of Chemistry, Box 330 440, D-2800 Bremen 33, FRG

Abstract: *The preparation of two structurally different boronated porphyrins is described for use in Boron Neutron Capture Therapy. One is a derivative of a natural porphyrin and the other is a derivative of tetraphenylporphyrin.*

Boron Neutron Capture Therapy (BNCT) is an anti-cancer treatment dependent on the $^{10}B(n,\alpha)^{7}Li$ reaction.[1,2] If ^{10}B can be localized in sufficient quantity in tumor tissue, subsequent irradiation with thermal or epithermal neutrons produces charged particles (α and ^{7}Li) that damage the mitotic potential of tumor cells.

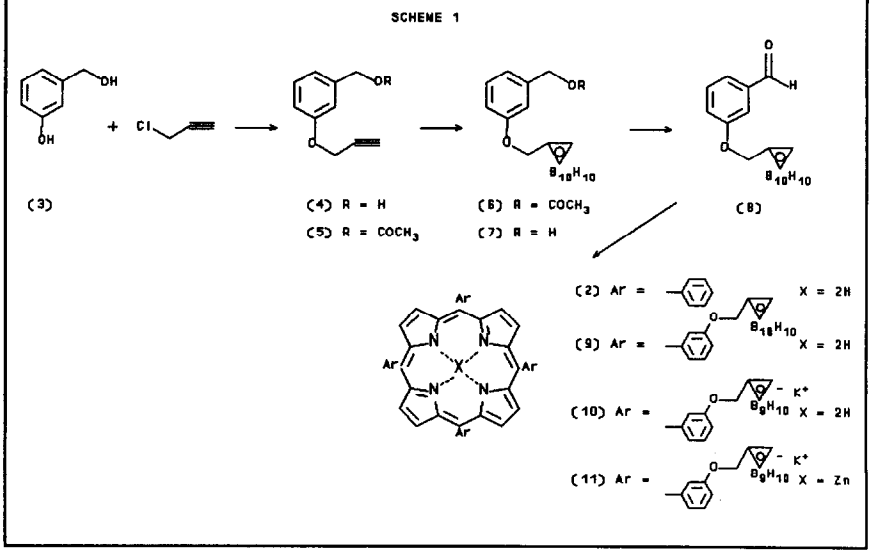
Clinical trials in the U.S. for the treatment of brain tumors by BNCT in the 1950's failed in part due to poor tumor-localization of boron-containing drugs. BNCT is currently used in Japan with an improved compound, a caged sulfhydryl boronohydride, $Na_2B_{12}H_{11}SH$.[3] Because the tumor-to-blood ratio is only ≈1.5 at the time of irradiation, better boron-transport drugs should be developed.

Porphyrins have been shown to have a great affinity for tumors and are used in a related radiotherapeutic modality, Photodynamic Therapy, (PDT).[4] We propose to use boronated porphyrins as a vehicle for boron transport to tumor for BNCT and possibly PDT. We now report the synthesis of two boronated porphyrins: a derivative of tetraphenylporphyrin, (TPP) and a boronated derivative of a natural porphyrin. The boron-containing moiety is an o-carborane cage, (1), where R can be various functional groups. The advantage of this cage is that it contains ten B atoms and that it can be chemically degraded to yield a hydrophilic, open-caged nido-carborane moiety.[5] There have been several carboranyl porphyrins reported previously and most have contained the TPP structure (2).[6,7,8]



The TPP derivative (9) was synthesized as shown in Scheme 1. Intermediate (4) was synthesized by treating 3-hydroxybenzylalcohol (3) with NaOMe/MeOH followed by propargyl chloride at reflux overnight. Carboranes can be synthesized via alkynes and decaborane ($B_{10}H_{14}$) but the latter reacts with alcohols. Therefore the hydroxy group in (4) was protected with acetic anhydride and the product (5) was isolated in 69% yield (b.p. 123°C at 5 mm) from (3).[8]

SCHEME 1

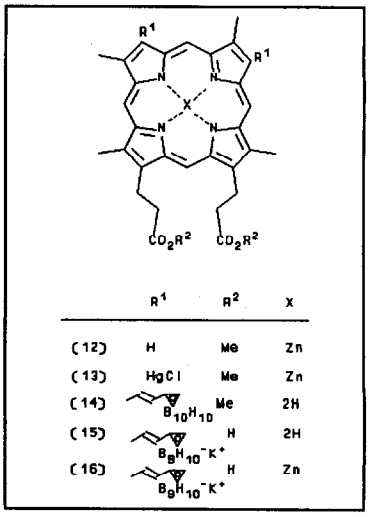


Decaborane (1 mol. eq.) MeCN/3h/r.t. was treated with (5) 80°C/3d. After quenching, (MeOH/.05N HCl /acetone/overnight /r.t.) the solvents removed and treated with toluene/100°C/15 min. The solution was filtered and evaporated to dryness. The acetyl groups of (6) were hydrolyzed using 1:80 (v/v) conc. HCl: MeOH/60°C/1h and the solvents removed in vacuo. Product (7) was purified by flash chromatography (SiO_2/CH_2Cl_2) and isolated in 65% yield from (5).[10]

The alcohol (7) was oxidized with pyridinium chlorochromate (1.5 mol. eq.) in CH_2Cl_2/0°C and was left to stir 2.5h/r.t. The product was extracted with CH_2Cl_2 and filtered through a pad of silica yielding aldehyde (8) in 81% yield.[11]

Cyclization to the corresponding porphyrin was carried out using the mild procedure recently reported by Lindsey et al.[12] The aldehyde (8) (20 mM in CH_2Cl_2), pyrrole (1 mol. eq.) and triethylorthoformate (1 mol. eq) were degassed with nitrogen for 30 min. $BF_3 \cdot EtO_2$ (2.5M, 0.1 mol. eq.) was added and the reaction stirred 2h/r.t. p-Chloranil (0.75 mol. eq.)/reflux/1h was used to oxidize the intermediate porphyrinogen. After purification by flash chromatography (SiO_2/35% pet ether/CH_2Cl_2), (9) was obtained in 42% yield.[13]

The carborane cages were then degraded in order to achieve water-solublity by using KOH/MeOH/reflux/2.5h. Porphyrin (10) was isolated using preparative TLC (0.5% HCO_2H in 1:1 acetone:CH_2Cl_2) in 50% yield.[14] The zinc analog (11) was synthesized by inserting zinc into porphyrin (9) followed by the degradation procedure.[15]



The natural porphyrin derivative was obtained more directly starting with zinc deuteroporphyrin IX dimethyl ester (12). This was mercurated and then treated with vinyl carborane (40 mol. eq.) in the presence of $LiPdCl_3$ to introduce olefinic groups at the 2 and 4 positions.[16] Porphyrin (14) was obtained in 42% yield after purification (flash chromatography, 50% hexane/CH_2Cl_2 - 2% MeOH/CH_2Cl_2), demetallation (trifluoroacetic acid) and recrystallization.[17]

In order to water-solubilize (14), the esters were hydrolyzed to the corresponding diacid. The product however was not highly soluble in water. A 10% DMSO aqueous solution of this diacid was administered to mice, but it appeared to have precipitated out in the area of injection. A more hydrophilic compound was necessary, therefore the nido analog was synthesized.

The cages were degraded with concomitant saponification of the esters using KOH/MeOH/THF/H_2O/2.5h/reflux. The crude mixture was purified by preparative TLC (0.5% HCOOH in 1:1 acetone CH_2Cl_2) followed by an ion exchange column (Dowex 50W K^+).[18] The zinc chelate (16) was prepared by treating the intermediate zinc dicarboranyldeuteroporphyrin IX DME directly with the degradation/saponification conditions.[19] In vitro experiments with (10) have shown high cellular uptake,[20] however preliminary murine biodistribution studies have shown both (10) and (11) to be too toxic for sufficient boron to be delivered to tumor. Porphyrin (15) is less toxic and yields therapeutic concentrations of boron in tumor.[21]

Acknowledgements: We are grateful to Professor Kevin M. Smith for suggesting (14), Ms. Peggy Micca for the improved yield of (7) and Drs. Charles Iden and Robert Rieger (SUNY Stony Brook) for mass spectral analyses. We thank the National Institutes of Health (1R01 CA38107-01A2), the Department of Energy (Contract No. DE-AC02-76CH00016) and the Deutsche Forschungsgemeinshaft for financial support.

References and Notes:

1. G.L. Locher, Am. J. Roentgenol. Radium Ther. Nucl. Med. **1936**, *36*: 1-13.
2. D.N. Slatkin, R.D. Stoner, K.M. Rosander, J.A. Kalef-Ezra, J.A. Laissue, Proc. Natl. Acac. Sci., USA, **1988**, *85*: 4020-4024.
3. H. Hatanaka in "Boron Neutron Capture Therapy for Tumors", H. Hatanaka (ed.). Nishimura Co. Ltd, Niigata, Japan, pp 349-379, 1986.
4. T. Dougherty, Photochem. Photobiol., **1987**, *45*: 879-889.
5. M.F. Hawthorne, R.A. Wiesboeck, J. Amer. Chem. Soc., **1964**, *86*, 1642-1643.
6. D. Gabel, R.G. Fairchild, M. Hillman, G. Oenbrink, R. Müller, "Proc. 2nd Int. Symp. Neutron Capture Therapy, pp 37-45. H. Hatanaka (ed.) Niigata, Japan: Nishimura Co., Ltd., 1986.
7. R.C. Haushalter, W.M. Butler, R.W. Rudolph, J. Amer. Chem. Soc., **1981**, *103*, 2620-2627.

8. S.B. Kahl, M.-S. Koo, B.H. Laster, R.G. Fairchild, Strahlenther. Onkol., 1989, *165*, 134-137.

9. (5): ^{1}H NMR ($CDCl_3$): δ ppm 6.9-7.5 (m, 4H, ArH); 5.05 (s, 2H, CH_2O); 4.63 (d, 2H, $CH_2C{\equiv}C$); 2.5 (t, 1H, C≡CH); 2.05 (s, 3H, CH_3). IR (NaCl): 2122 cm^{-1}, C≡C; 1742 cm^{-1}, C=O.

10. (7): ^{1}H NMR ($CDCl_3$): 6.7-7.5 (m, 4H, ArH); 5.1 (s, 2H, CH_2OCO); 4.3 (s, 2H, CH_2O); 4.1 (br. s, 1H, carborane CH); 2.15 (s, 3H, CH_3). IR (KBr): 2590 cm^{-1}, BH; 1730 cm^{-1}, C=O. High resolution mass spectrum, (HRMS): Calculated for $^{12}C_{10}{}^1H_{20}{}^{16}O_2{}^{10}B_2{}^{11}B_8$ 280.2466, found 280.2468.

11. (8): ^{1}H NMR ($CDCl_3$): 9.93 (s, 1H, CHO); 7.1-7.55 (m, 4H, ArH); 7.7 (m, 8H, ArH); 4.48 (s, 2H, CH_2); 4.12 (s, 1H, carborane CH); 1.5-3.3 (br.s, BH). IR (KBr): 2560 cm^{-1}, BH; 1685 cm^{-1}, C=O. HRMS: Calculated for $^{12}C_{10}{}^1H_{18}{}^{16}O_2{}^{10}B_2{}^{11}B_8$ 278.2308, found 278.2305.

12. J.S. Lindsey, I.C. Schreiman, H.C. Hsu, P.C. Kearney, A.M. Marguerettaz, J. Org. Chem., 1987, *52*, 827-836.

13. (9): ^{1}H NMR ($CDCl_3$): 8.83 (s, 8H, pyrrole H); 7.92 (m, 4H, ArH); 7.7 (m, 8H, ArH); 7.26 (m, 4H, ArH); 4.6 (s, 8H, CH_2O); 4.13 (s, 4H, carborane CH); 1.4-3.2 (br. s, BH); ~2.85 (s, 2H, NH). UV-Vis (CH_2Cl_2) λ_{max} nm: 416, 513, 547, 589, 647. Fast atom bombardment MS (m/e): 1305 (M^+ + H).

14. (10): ^{1}H NMR (d^6-acetone): 8.93 (s, 8H, pyrrole H); 7.77 (br. s, 8H, ArH); 7.66 (m, 4H, ArH), 7.36 (m, 4H, ArH); AB quartet, 4.34 (d, 4H, CH_2), 4.03 (d, 4h, CH_2); 2.13 (s, 4H, carborane CH); ~2.1-~2.9 (br. d, 2H, BH); -2.78 (s, 2H, NH). IR (KBr): 2508 cm^{-1}, BH. UV-Vis (EtOH): 413, 510, 545, 587, 645.

15. (11): UV-Vis (acetone): 421, 555, 585.

16. K.M. Smith, K.C. Langry, J. Org. Chem., 1983, *48*, 500-506.

17. (14): ^{1}H NMR ($CDCl_3$): 10.077 (s, 2H, meso); 9.982 (s, 1H, meso); 9.944 (s, 1H, meso); 8.421 (d, 2H, vinyl, J = 15.8 Hz); 6.924 (d, 1H, vinyl, J = 15.9 Hz); 6.907 (d, 1H, vinyl, J = 15.8 Hz); 4.395 (t, 4H, -$CH_2CH_2CO_2Me$); 4.113 (s, 2H, carborane CH); 3.656 (s, 9H, CH_3); 3.624 (s, 6H, CH_3); 3.617 (s, 3H, CH_3); 3.276 (t, 4H, CH_2CO_2Me); 3.8-1.5 (br. mult., 20 BH); ~3.623 (s, 2H, NH) Anal. Calcd. for $C_{40}H_{58}N_4O_4B_{20}$: C, 54.90; H, 6.68; N, 6.41; B, 24.70. Found: C, 55.30; H, 6.45; N, 6.31; B, 24.38. IR (CH_2Cl_2) 2600 (BH), 1725 cm^{-1} (C=O); UV-Vis (CH_2Cl_2) λ_{max} nm (ϵ): 416 (178,000), 511 (16,500), 546 (15,200), 580 (6,860), 634 (5,220)

18. (15): ^{1}H NMR (d^6-acetone): 10.369 (s, 1H, meso); 10.234 (s, 2H, meso); 10.186 (s, 1H, meso); 7.844 (d, 1H, vinyl J = 16.2 Hz); 7.818 (d, 1H, vinyl J = 15.9 Hz); 7.054 (d, 1H, vinyl J = 15.9 Hz); 7.027 (d, 1H, vinyl J = 15.9 Hz); 4.416 (m, 4H, $CH_2CH_2CO_2H$); 3.667 (s, 12H, CH_3); 3.259 (q, 4H, CH_2CO_2H) 2.132 (s, 2H, carborane CH); ~2.2 (br. s, 2H, BH^-); ~3.604 (s, 2H, NH). IR (acetone) 2520 cm^{-1} (BH). UV-Vis (MeOH): 400, 506, 546, 580, 630.

19. (16): UV-Vis (MeOH): 413, 547, 585.

20. G. Oenbrink, P. Jürgenlimke, D. Gabel, Photochem. Photobiol., 1988, *48*, 451-456.

21. M. Miura, D. Gabel, L.S. Warkentien, B.H. Laster, R.G. Fairchild, Strahlenther. Onkol., 1989, *165*, 131-134.

(Received in USA 16 January 1990)