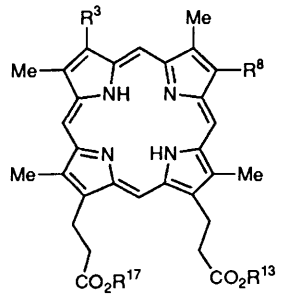
Benzoporphyrin Derivatives: Synthesis, Structure and Preliminary Biological Activity[1]

Isabelle Meunier,[a] Ravindra K. Pandey,*[a,b] Mathias O. Senge,[a] Thomas J. Dougherty[b] and Kevin M. Smith*[a]
[a] *Department of Chemistry, University of California, Davis, CA 95616, USA*
[b] *Chemistry Division, PDT Center, Department of Radiation Biology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA*

Starting from hematoporphyrin-IX dimethyl ester **1**, a series of isomerically pure so-called benzoporphyrin derivatives (BPDs) **20**, **23–25**, **27**, **28**, **31–33**, **35–37**, **39**, **40**, **42**, **44** and **45** have been synthesized. The bis-porphyrins **46** and **47** with carbon–carbon linkages were also prepared by treating 3- and 8-(1-hydroxyethyl)benzoporphyrin derivatives **24** and **32** with triflic acid. In preliminary *in vivo* studies, the hexyl ether derivatives **27**, **35**, **40** and **45** (as diastereoisomeric mixtures) appear to have better photosensitizing efficacy than the benzoporphyrin derivative mono-carboxylic acid (BPD-MA; mixture of **21** and **22**). Under similar doses and treatment conditions, other BPDs **23**, **25**, **26**, **31**, **33** and **34**, along with bis-porphyrins **46** and **47** did not show any significant tumourcidal activity. The structures of the ring 'A' modified BPD isomers **20** (*cis*) and **36** (*trans*) were confirmed by single crystal X-ray studies.

The so-called 'benzoporphyrin derivative'† mono-carboxylic acid (BPD-MA), currently one of the more promising photosensitizers for photodynamic therapy (PDT),[2] is prepared by first treating protoporphyrin-IX dimethyl ester **3** with dimethyl acetylenedicarboxylate (DMAD)[3] after which the Diels–Alder adduct (obtained as a mixture) is rearranged to a mixture of ring 'A' and ring 'B' reduced isomers **20** and **28**, respectively. The isomeric mixture is then separated into individual isomers by column chromatography. Partial hydrolysis of the methyl ester derivatives **20** and **28** mainly gave **21**, **22** from **20**, and **29**, **30** from **28**. Among these isomers the monomethyl ester derivatives as a mixture of **21** and **22** (the so-called BPD-MA) has been reported to be more effective than the ring 'B' modified isomers **29** and **30**.[4] BPD-MA has a strong absorption peak at 700 nm which potentially should allow deeper tissue penetration and greater activation than Photofrin®. Earlier studies in animal tumour models have also confirmed that BPD-MA is an effective photosensitizer if the animals are treated 3 h post intravenous (i.v.) injection of the drug.[5] At similar or higher doses, no tumour response was observed if the treatment was done 24 h post i.v. injection. In order to understand the structure activity relationships among BPDs, and also to avoid the tedious separation of the various isomers in the last steps of the synthesis, we have developed an efficient alternate approach for the synthesis of such analogues.

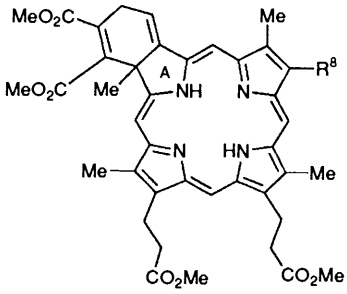
In our synthetic approach, hematoporphyrin-IX dimethyl ester **1**, obtained by the reaction of commercially available hematoporphyrin-IX dicarboxylic acid **2** with diazomethane was used as the starting material. Partial oxidation of **1** with tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide gave a mixture of mono-acetyl-mono-(1-hydroxyethyl)-porphyrins which were efficiently separated into individual isomers **4** and **5** by preparative HPLC‡ in gram quantities.[6,7] The mono(1-hydroxyethyl)porphyrins were then individually converted into the corresponding mono-acetyl-mono-vinyl (**6** and **7**) and mono-ethyl-mono-vinyl analogues **12** and **13** in a number of steps by following the literature procedure.[6] In brief, for the preparation of 8-acetyl-3-vinyldeuteroporphyrin-IX dimethyl ester **6** (IUPAC nomenclature), 8-acetyl-3-(1-hydroxyethyl)deuteroporphyrin-IX dimethyl ester **4** was refluxed with *o*-dichlorobenzene in the presence of toluene-*p*-sulfonic acid to afford 8-acetyl-3-vinyldeuteroporphyrin-IX dimethyl ester **6** in 90% yield. 3-Acetyl-8-vinyldeuteroporphyrin-IX dimethyl ester **7** was prepared from the porphyrin **5** by following the methodology as discussed for the preparation of **6**. For the



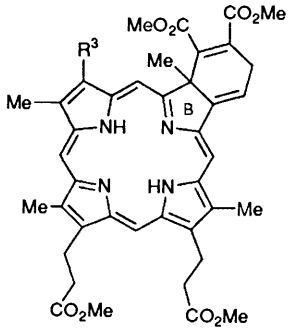
1 $R^3 = R^8 = CH(OH)Me$, $R^{13} = R^{17} = Me$
2 $R^3 = R^8 = CH(OH)Me$, $R^{13} = R^{17} = H$
3 $R^3 = R^8 = CH{=}CH_2$, $R^{13} = R^{17} = Me$
4 $R^3 = CH(OH)Me$, $R^8 = CH(OH)Me$, $R^{13} = R^{17} = Me$
5 $R^3 = R^8 = COMe$, $R^3 = R^{17} = Me$
6 $R^3 = CH{=}CH_2$, $R^8 = COMe$, $R^{13} = R^{17} = Me$
7 $R^3 = COMe$, $R^8 = CH{=}CH_2$, $R^{13} = R^{17} = Me$
8 $R^3 = Et$, $R^8 = COMe$, $R^{13} = R^{17} = Me$
9 $R^3 = COMe$, $R^8 = Et$, $R^{13} = R^{17} = Me$
10 $R^3 = Et$, $R^8 = CH(OH)Me$, $R^{13} = R^{17} = Me$
11 $R^3 = CH(OH)Me$, $R^8 = Et$, $R^{13} = R^{17} = Me$
12 $R^3 = Et$, $R^8 = CH{=}CH_2$, $R^{13} = R^{17} = Me$
13 $R^3 = CH{=}CH_2$, $R^8 = Et$, $R^{13} = R^{17} = Me$

† As pointed out by a referee, the 'benzoporphyrin derivative' described widely in the literature is neither a benzo derivative nor a porphyrin. 'So-called' is, therefore, appropriate in the first use of the term in this paper.

‡ HPLC conditions: (Preparative) Waters Associates Prep LC3000 system attached to a Waters 1000 PrepPak module with PrepPak-500 silica gel cartridge: solvent, 2.5% THF in CH_2Cl_2; 50.0 cm^3 min^{-1}; Waters 484 tunable absorbance detector set at 405 nm. (Analytical) Waters Associates 510 pump, 600E solvent delivery system; Waters Porasil 10 μm stainless steel column (30 cm × 3.9 mm i.d.); solvent, 3% THF in CH_2Cl_2; 3.5 cm^3 min^{-1}; Waters 490E programmable multiwavelength detector set at 405 nm; retention times: **4**, 16 min; **5**, 19 min.



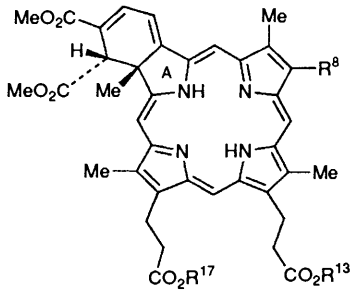
14 R^8 = CH=CH_2
15 R^8 = COMe
16 R^8 = Et



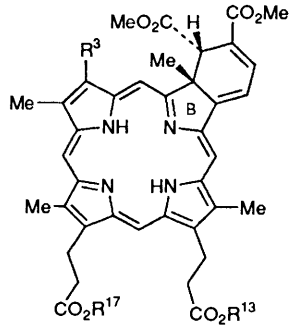
17 R^3 = CH=CH_2
18 R^3 = COMe
19 R^3 = Et

synthesis of 3-ethyl-8-vinyldeuteroporphyrin dimethyl ester **12**, the zinc(II) complex of 8-acetyl-3-vinyldeuteroporphyrin-IX dimethyl ester **6** was hydrogenated over Pd-C to give the corresponding 3-ethylporphyrin (Zn complex) in quantitative yield. Removal of zinc from the latter was easily achieved by briefly treating it with trifluoroacetic acid. The acetylporphyrin **8** was then converted into 3-ethyl-8-vinyldeuteroporphyrin-IX dimethyl ester **12** by sodium borohydride reduction, followed by dehydration of the resulting 3-ethyl-8-(1-hydroxyethyl)porphyrin. Along similar lines, starting from 3-acetyl-8-vinyldeuteroporphyrin **7**, 8-ethyl-3-vinylporphyrin **13** was also prepared in 56% overall yield.

For the preparation of the ring 'A' modified 8-acetylbenzoporphyrin derivatives **23** and **37**, 8-acetyl-3-vinyldeuteroporphyrin-IX dimethyl ester **6** was treated with DMAD, using toluene as a solvent. The reaction was monitored by spectrophotometry, and the 'intermediate' Diels–Alder adduct **15** so obtained was isolated pure in 50% yield. Treatment of the intermediate adduct with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), following the literature,[3b] gave the rearranged *cis* isomer **23** in 45% yield after tedious chromatographic separation. However, when the intermediate adduct was rearranged with triethylamine, the *trans* isomer was isolated in 50% yield after simple column chromatography. The *trans* isomer **37**, upon further treatment with DBU, conveniently gave the *cis* isomer **23** in almost quantitative yield.[1] In order to prepare a series of vinyl-BPDs **20**, **28**, **36** and **41** (*i.e. cis*- and *trans*-isomers) the acetyl derivatives **23**, **31**, **37** and **42** were first reduced to the corresponding (1-hydroxyethyl) analogues **24**, **32**, **38** and **43**, respectively, and then refluxed with *o*-dichlorobenzene containing a catalytic amount of toluene-*p*-sulfonic acid. The desired vinyl-BPDs were obtained in excellent yields. The 3-ethyl- and 8-ethyl-benzoporphyrin derivatives **25**,



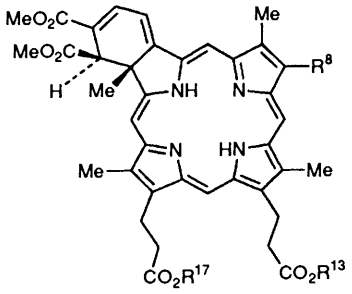
20 R^8 = CH=CH_2, R^{13} = R^{17} = Me
21 R^8 = CH=CH_2, R^{13} = H, R^{17} = Me
22 R^8 = CH=CH_2, R^{13} = Me, R^{17} = H
23 R^8 = COMe, R^{13} = R^{17} = Me
24 R^8 = CH(OH)Me, R^{13} = R^{17} = Me
25 R^8 = Et, R^{13} = R^{17} = Me
26 R^8 = CHO, R^{13} = R^{17} = Me
27 R^8 = CH(O-hexyl) Me, R^{13} = R^{17} = Me



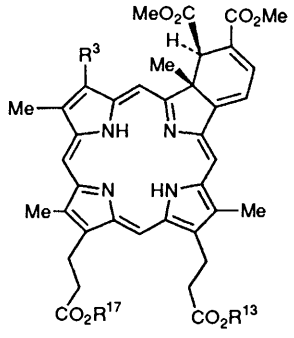
28 R^3 = CH=CH_2, R^{13} = R^{17} = Me
29 R^3 = CH=CH_2, R^{13} = H, R^{17} = Me
30 R^3 = CH=CH_2, R^{13} = Me, R^{17} = H
31 R^3 = COMe, R^{13} = R^{17} = Me
32 R^3 = CH(OH)Me, R^{13} = R^{17} = Me
33 R^3 = Et, R^{13} = R^{17} = Me
34 R^3 = CHO, R^{13} = R^{17} = Me
35 R^3 = CH(O-hexyl) Me, R^{13} = R^{17} = Me

33, **39** and **44** were obtained by reacting the vinylporphyrins **12** and **13** with DMAD and then treating them consecutively with triethylamine and DBU. In the pyropheophorbide series, we had already observed[8] that replacement of the vinyl group at position 3 with a formyl substituent made a significant difference in biological activity. In order to investigate the effect of such a formyl substituent in the BPD series, 3-vinyl- and 8-vinyl-BPDs **20** and **28** were first treated with sodium periodate and osmium tetroxide (catalytic amount)[8] to give the resulting formyl-BPDs **26** and **34** in > 80% yields. Like acetyl-BPDs, the formyl derivatives also have a strong absorption at 696 nm.

It has been shown, in a number of porphyrins, chlorins, pheophorbides, pyropheophorbides, and purpurins, that conversion of substituent vinyl group(s) into alkyl ether side chain(s), tends to increase the PDT efficacy over that of the parent vinyl-pigment.[8-11] Among such alkyl ether derivatives, it has been observed that biological activity increases with the length of carbon chain, with hexyl and heptyl being the most effective; further increasing the length of carbon chain usually resulted in a significant decrease in biological activity. In order to further investigate the alkyl ether structural hypothesis, we prepared the hexyl ether derivatives of the *cis*- and *trans*-isomers of both ring 'A' and ring 'B' modified benzoporphyrin derivatives, and these were compared with the biological activity of the corresponding vinyl analogues **20**, **28**,



36 $R^8 = CH{=}CH_2$, $R^{13} = R^{17} = Me$
37 $R^8 = COMe$, $R^{13} = R^{17} = Me$
38 $R^8 = CH(OH)Me$, $R^{13} = R^{17} = Me$
39 $R^8 = Et$, $R^{13} = R^{17} = Me$
40 $R^8 = CH(O\text{-hexyl})\,Me$, $R^{13} = R^{17} = Me$



41 $R^3 = CH{=}CH_2$, $R^{13} = R^{17} = Me$
42 $R^3 = COMe$, $R^{13} = R^{17} = Me$
43 $R^3 = CH(OH)Me$, $R^{13} = R^{17} = Me$
44 $R^3 = Et$, $R^{13} = R^{17} = Me$
45 $R^3 = CH(O\text{-hexyl})\,Me$, $R^{13} = R^{17} = Me$

36 and **41**, respectively. For the preparation of the hexyl ether derivatives, **27** and **35** (the *cis* isomers of ring 'A' and ring 'B' modified BPDs), the 3- and 8-vinylbenzoporphyrin derivatives **20** and **28** were separately treated with 30% HBr–acetic acid; the intermediate (1-bromoethyl) derivatives were not isolated but were immediately treated with hexanol under a nitrogen atmosphere. The respective (1-hexyloxyethyl) derivatives **27** or **35** were obtained in approximately 50% yield. BPD derivatives **40** and **45** (*trans* isomer) were obtained from corresponding (1-hydroxyethyl) derivatives **38** and **43** which, in turn, were obtained from the corresponding acetyl analogues **37** and **42**, and also from related vinyl analogues **36** and **41**.

For the syntheses of benzoporphyrin derivatives with variable substituents, 3- and 8-vinyl-BPDs were initially prepared by following the literature method.[3] In order to confirm the structure of the ring 'A' and ring 'B' modified derivatives, the vinyl group was transformed into a formyl substituent. Nuclear Overhauser enhancement (NOE) studies on the formyl derivatives confirmed the structural assignments for both of the starting materials. Interestingly, the NMR studies of the hexyl ether derivatives of ring 'A' and ring 'B' modified isomers (**27**, **35**, **40** and **45**; *cis*- and *trans*-) provided an independent verification of the precise (ring A or ring B) isomer involved. As can be seen from Fig. 1, in the NMR spectrum (A, C) of the ring 'B' reduced isomer **35** and **45** (as a mixture of diastereoisomers), there are two quartets for CH(O-hexyl)CH at 5.98 and 6.18 ppm, each integrating for one proton. However, in BPD derivatives **27** and **40**, both of these protons of the diastereoisomeric mixture resonate at 6.12 ppm as a broad multiplet, integrating for two protons. This is clear evidence that the chiral centres in **35** and **45** are closer to each other than

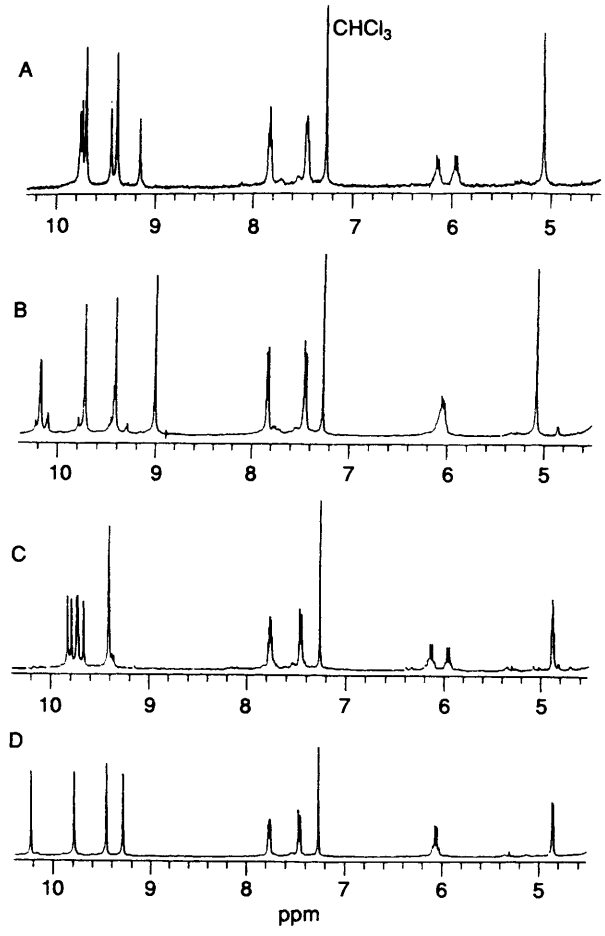


Fig. 1 The ^1H NMR spectrum (δ 4.5–10.5 region), in $CDCl_3$, of hexyl ether BPDs: (A) ring B modified compound **35**, (B) ring A modified compound **27**, (C) ring B modified compound **45**, and (D) ring A modified compound **40**

they are in **27** and **40**, and further reinforce the structural assignments. Interestingly, in the meso proton region (9.00–10.20 ppm) in **35** and **45** (Fig. 1A and 1C) the *meso* protons are less separated than for BPD derivatives **27** and **40**.

In the porphyrin series, we have shown that certain porphyrins which were found to be poor photosensitizers as monomers, when converted into carbon-linked bis-porphyrins showed significant increase in photosensitizing efficacy.[12–14] With this in mind, we prepared dimers **46** and **47** from 8-(1-hydroxyethyl)- and 3-(1-hydroxyethyl)-BPD, **24** and **32**, respectively, by following our own methodology.[12] Thus, **24** and **32** were individually treated with triflic acid, and the acid was quenched with pyridine before work-up. The desired bis-porphyrins were isolated in about 50% yield.

The structure and stereochemistry of the *cis* and *trans* isomers of ring 'A' reduced BPDs [as dimethyl esters **20** (*cis* isomer) and **36** (*trans* isomer)] were confirmed by single-crystal X-ray studies. The atomic coordinates for both compounds can be found in the Supplementary Material.* The molecular structures of the two isomeric forms are shown in Figs. 2 and 3. Both structures clearly show the ring A adduct structure, evidenced by the site of the vinyl group in ring B. The unsaturated character of the C(81)–C(82) bond is clearly shown

* Full lists of bond lengths and angles, tables of atomic coordinates, hydrogen atom coordinates, thermal parameters and further details of the structure determinations have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1994, issue 1.

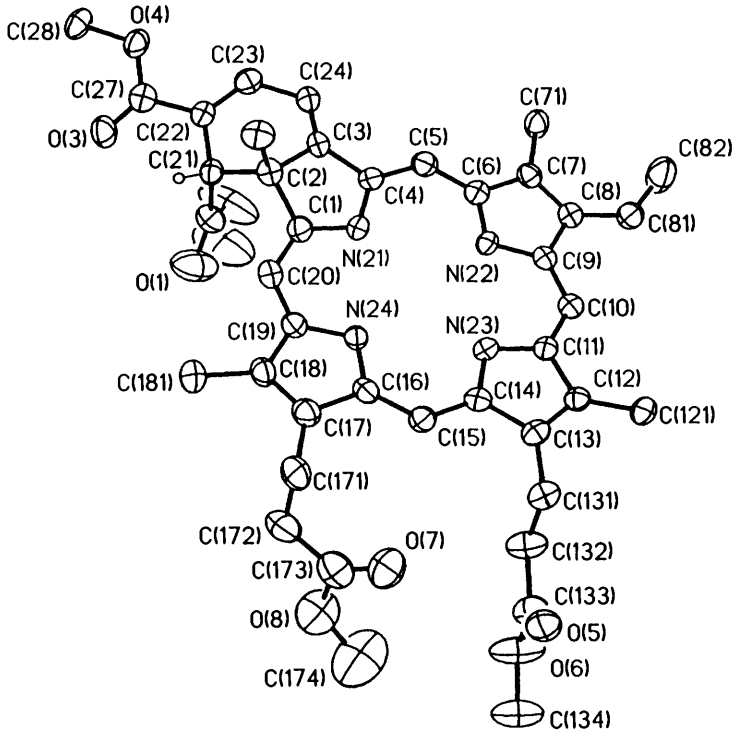


Fig. 2 Computer generated plot of **36**. Ellipsoids are drawn for 50% occupancy.

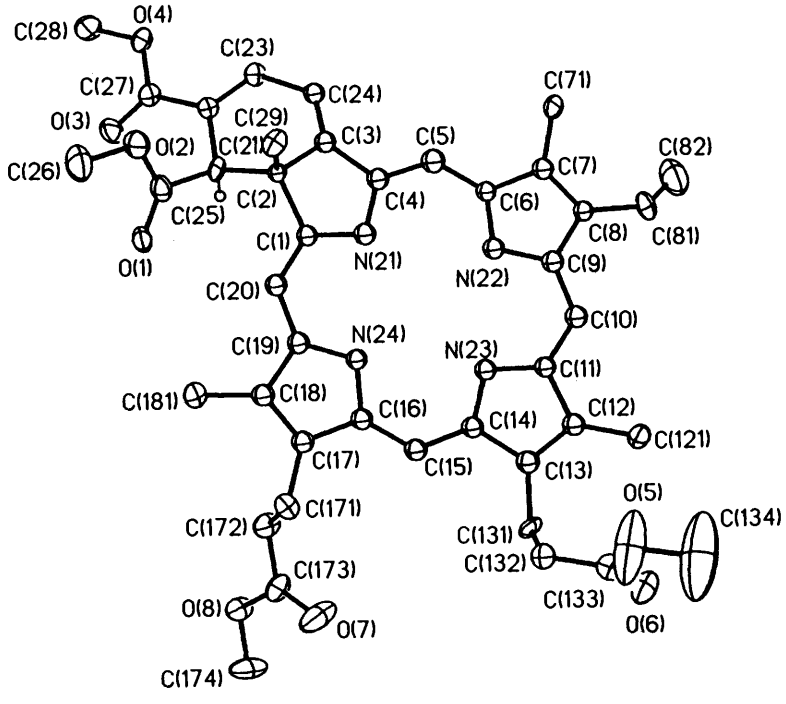
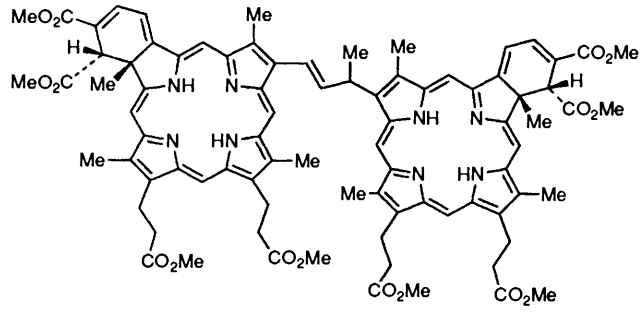


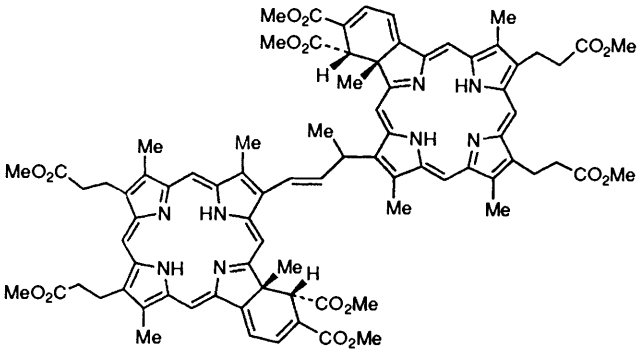
Fig. 3 Computer generated plot of **20**. Ellipsoids are drawn for 50% occupancy.

by the short bond lengths of 1.291(7) and 1.363(12) Å in **36** and **20**, respectively. The stereochemistry of the methoxycarbonyl and methyl substituents at C(21) and C(2) can clearly be elucidated as *cis* for **36** and *trans* for **20**. The orientation of the double bonds in the fused six-membered ring on pyrrole ring A can be delineated on the basis of the respective bond lengths. In **36** C(2)–C(21) [1.548(6) Å], C(21)–C(22) [1.519(6) Å], and C(23)–C(24) [1.456(8) Å] are obviously single bonds, while C(22)–C(23) [1.346(7) Å] and C(24)–C(3) [1.334(6) Å] have double-bond character. A similar situation is found in the structure of **20**. Both molecular structures differ somewhat in their macrocycle conformation. While in **36** the fused six-membered ring lies below the porphyrin macrocycle plane, this situation is reversed in **20**. The average deviation of the porphyrin macrocycle atoms from their least-squares plane is not very significant, with 0.07 Å in the structure of **36**. The structure of **20**, however, shows a significant ring ruffling with an average deviation of the 24 core atoms of 0.14 Å. The larger ring distortion in the latter structure is also evidenced by an alternating displacement of the meso-positions by 0.24 Å above and below the mean plane; this is in contrast to a meso-atom displacement of 0.06 Å found in **36**.

All the new BPDs discussed here are being evaluated for their *in vivo* photosensitizing efficacy, and the final results will be reported elsewhere.[10] Briefly, preliminary results indicate that among new photosensitizers, the (1-hexyloxy)ethyl derivatives **27**, **35**, **40** and **45** (as dimethyl esters) showed better anti-tumour activity than BPD-MA [mixture of **21** and **22**, obtained from Quadralogic Technologies (QLT), Vancouver, Canada]. The hexyl ether derivatives **27**, **35**, **40** and **45** were found to be active at a dose of 1.0 mg kg^{-1} (mice were treated 3 h post i.v. injection of the drug). So far, only photosensitizer **40** has been studied in detail, and has shown excellent anti-tumour activity if the mice were treated at a dose of 5.0 mg kg^{-1} 24 h post i.v. injection of the drug. Under similar conditions, BPD-MA did not show any activity. The photosensitizer **40** has also shown reduced skin phototoxicity compared with BPD-MA and Photofrin®.[10] The bis-porphyrins **46** and **47** showed no significant anti-tumour activity.



46



47

This work represents the first study in which a series of isomerically pure BPDs have been synthesized, characterized by single-crystal X-ray studies, and evaluated for their *in vivo* PDT activity. We conclude that as with porphyrins,[9] chlorins, and pheophorbides[9] replacement of the vinyl group with a hexyl ether side-chain in the BPD series results in a remarkable improvement in biological activity. A comparison of the *in vivo* data among the *cis*- and *trans*-isomers leads to the conclusion that in the generic BPD series, the conformation of the modified ring (either ring 'A' or ring 'B') does not make a significant difference in biological activity. However, in general, the ring 'A' reduced BPDs were found to be more active than the ring 'B' modified analogues. Currently, we are modifying the polarity of these tetrapyrrole sensitizers further by replacing the methyl esters with aspartyl amide side-chains, by varying the substituents, or by increasing the length of the carbon chain in alkyl ethers at peripheral positions of the nucleus. These studies are in progress and will be reported in due course.

Experimental

M.p.s, measured on a Thomas/Bristoline microscopic hot-stage apparatus, are uncorrected. Silica gel 60 (70–230 and 230–400 mesh, Merck) or neutral alumina (Merck; usually Brockmann Grade III, *i.e.* deactivated with 6% water) were used for column chromatography. Preparative thin layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck G 254 silica gel (1 mm thick). Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 silica gel (precoated sheets, 0.2 mm thick). Reactions were monitored by TLC and spectrophotometry and were carried out under nitrogen and in the dark. ^1H NMR spectra were obtained in deuteriochloroform solution at 300 MHz using a General Electric QE300 spectrometer; chemical shifts are expressed in ppm relative to chloroform (7.258 ppm). Elemental analyses were performed at the Midwest Microlab, Ltd., Indiana, USA. Unless stated otherwise, electronic absorption spectra were measured in dichloromethane solution using a Hewlett-Packard 8450A spectrophotometer. Mass spectra were obtained at the Mass Spectrometry Facility, University of California, San Francisco and at the Department of Biophysics, Roswell Park Cancer Institute, Buffalo.

Syntheses

3-Acetylbenzoporphyrin Derivative (Ring 'B' Modified) **31** (cis *Isomer*) *and* **42** (trans *Isomer*).—3-Acetyl-8-vinyldeuteroporphyrin-IX dimethyl ester **7** (100 mg, 0.165 mmol) was dissolved in degassed toluene (30 cm^3). Dimethyl acetylenedicarboxylate (0.101 cm^3) was added rapidly to the solution and the reaction mixture was heated at 120 °C during 13 d, while being monitored by TLC. After evaporation of the mixture to dryness under high vacuum, the major product was separated using preparative silica plates, eluting with 2% methanol in dichloromethane. The residue obtained after evaporating the extraction solvent was crystallized from dichloromethane–hexane to give **18** (50 mg, 40%), m.p. 192–194 °C; λ_{max}/nm 412 (ε/dm^3 mol^{-1} cm^{-1} 163 300), 506 (27 000), 536 (19 000), 616 (19 100) and 670 (41 500); δ_H 9.82, 9.70, 9.53, 9.18 (each s, 1 H, meso H), 7.39 (d, 2 H, CH_2) 7.26 (s, 1 H, $CHCO_2Me$), 4.25 (t, 2 H, $CH_2CH_2CO_2Me$), 4.15 (s, 3 H, Me or OMe), 4.00 (t, 2 H, $CH_2CH_2CO_2Me$), 3.89, 3.80, 3.66, 3.65, 3.43, 3.38 and 3.30 (each s, 3 H, Me or OMe), 3.21 and 3.13 (each t, 2 H, $CH_2CH_2CO_2Me$), 2.15 (s, 3 H, Me) and −1.80 (br s, 2 H, NH). Treatment of **18** with triethylamine (0.3 cm^3) in dichloromethane (10.0 cm^3) overnight under N_2 gave the BPD **42** (*trans* isomer): m.p. 235–237 °C (Found: C, 65.6; H, 5.9; N, 7.15. $C_{42}H_{44}N_4O_9 \cdot H_2O$ requires C, 65.76; H, 6.05; N, 7.30); λ_{max}/nm 418 (ε/dm^3 mol^{-1} cm^{-1} 84 800), 512 (8400), 516 (8100), 566 (8600), 636 (4600) and 690 (20 100); δ_H 9.75, 9.73, 9.51 and 9.17 (each s, 1 H, meso H), 7.69 (dd, 1 H, CCHCH), 7.36 (d, 1 H, CHCH), 4.76 (d, 1 H, $CHCO_2Me$), 4.24, 4.10 (each t, 2 H, $CH_2CH_2CO_2Me$), 4.32 (s, 3 H, Me or OMe), 3.93, 3.78, 3.66, 3.65, 3.42, 3.36 and 3.31 (each s, 3 H, Me and OMe), 3.19 and 3.15 (each t, 2 H, $CH_2CH_2CO_2Me$), 1.64 (s, 3 H, Me) and −1.99 (s, 2 H, NH). Treatment of the intermediate **18** (20 mg) with DBU (3 drops) in dichloromethane (10.0 cm^3) at room temperature for 15 min gave the BPD **31** (*cis* isomer) in quantitative yield, m.p. 238–240 °C; λ_{max}/nm 420 (ε/dm^3 mol^{-1} cm^{-1} 70 700), 506 (9900), 574 (10 500), 638 (6700) and 696 (24 600); δ_H 9.77, 9.59, 9.52 and 9.22 (each s, 1 H, meso H), 7.80 and 7.44 (each d, 1 H, CH=CH), 5.05 (s, 1 H, $CHCO_2Me$), 4.24 and 4.11 (each t, 2 H, $CH_2CH_2CO_2Me$), 3.98, 3.79, 3.65, 3.64, 3.42, 3.37 and 3.34 (each s, 3 H, Me and OMe), 3.18 and 3.13 (each t, 2 H, $CH_2CH_2CO_2Me$), 3.02 and 1.79 (each s, 3 H, Me) and −1.72 (br s, 2 H, NH) [Found: *m/z* (HRMS), 748.3101. $C_{42}H_{44}N_4O_9$ requires 748.3108].

By following the same approach, **23** and **37** (ring 'A' modified)

were obtained in 42 and 45% yield, respectively. *8-Acetylbenzoporphyrin derivative* **23** (cis *isomer, ring 'A' modified*). M.p. 242–244 °C; λ_{max}/nm 422 (ε/dm^3 mol^{-1} cm^{-1} 72 000), 508 (10 000), 572 (11 500), 638 (7000) and 696 (25 000); δ_H 10.29, 9.57, 9.44 and 8.93 (each s, 1 H, meso H), 7.80 and 7.47 (each d, 1 H, CH=CH), 5.05 (s, 1 H, C*H*CO_2Me), 4.27, 4.11 (each t, 2 H, C*H*$_2$CH$_2$CO$_2$Me), 3.99, 3.70, 3.67, 3.60, 3.46, 3.35 and 3.26 (each s, 3 H, Me and OMe), 3.20 and 3.13 (each t, 2 H, CH$_2$C*H*$_2$CO$_2$Me), 3.01 (s, 3 H, COMe), 1.81 (s, 3 H, Me), −1.70 and −2.00 (each br s, 1 H, NH) [Found: *m/z* (HRMS), 748.3100. $C_{42}H_{44}N_4O_9$ requires 748.3108].

8-Acetylbenzoporphyrin derivative **37** (trans *isomer, ring 'A' modified*). M.p. 238–240 °C; λ_{max}/nm 418 (ε/dm^3 mol^{-1} cm^{-1} 85 000), 514 (8000), 566 (8000), 636 (4600) and 690 (22 000); δ_H 10.23, 9.56, 9.08 and 8.93 (each s, 1 H, meso H), 7.55 (dd, 1 H, CH=CH), 6.90 (d, 1 H, CH=CH); 4.58 s, 1 H, C*H*CO_2Me), 4.25 and 4.00 (each t, 2 H, C*H*$_2$CH$_2$CO$_2$Me), 4.24, 3.97, 3.51, 3.45 and 3.41 (each s, 3 H, Me and OMe), 3.01 (s, 6 H, Me), 3.24 (m, 4 H, CH$_2$C*H*$_2$CO$_2$Me), 3.17 (s, 3 H, COMe), 1.43 (s, 3 H, Me) and −2.75 (br s, 2 H, NH).

8-(1-Hydroxyethyl)benzoporphyrin Derivative **24** (cis *Isomer, Ring 'A' Modified*).—8-Acetylbenzoporphyrin **23** (100 mg, 0.133 mmol) was dissolved in dichloromethane (50 cm^3) and the solution cooled in an ice-bath. A suspension of sodium borohydride (150 mg, 3 equiv.) in cold methanol (5 cm^3) was added rapidly to the solution which was then stirred for 1 h at room temperature after which the reaction was found to be complete (TLC). The mixture was treated with glacial acetic acid (2 cm^3) to quench the excess of sodium borohydride after which it was extracted with dichloromethane. The extract was washed with water to pH 7, dried (Na_2SO_4) and evaporated to give a residue which was crystallized from dichloromethane–hexane to afford the benzoporphyrin **24** (91 mg, 89%) as a mixture of diastereoisomers; m.p. 130–135 °C (Found: C, 66.8; H, 6.1; N, 7.3. $C_{42}H_{46}N_4O_9$ requires C, 67.17, H, 6.17; N, 7.46); λ_{max}/nm 400 (ε/dm^3 mol^{-1} cm^{-1} 71 600), 578 (14 250), 622 (6300) and 682 (29 800); δ_H 10.03 and 10.01 (each s, 1 H, meso H), 9.71 (s, 2 H, meso H), 9.36 and 9.35 (each s, 1 H, meso H), 9.01 (s, 2 H, meso H), 7.83 (d, 2 H, CH=CH), 7.45 (d, 2 H, CH=CH), 6.45 [q, 1 H, CH(OH)], 6.35 [q, 1 H, CH(OH)], 5.08 [s, 2 H, MeO$_2$CC*H*C(CO$_2$Me)], 4.32 (t, 4 H, C*H*$_2$CH$_2$CO$_2$Me), 4.17 (t, 4 H, C*H*$_2$CH$_2$CO$_2$Me), 3.99–3.38 (7 s, 36 H, Me and OMe), 3.22 (t, 4 H, CH$_2$C*H*$_2$CO$_2$Me), 3.16 (t, 4 H, CH$_2$C*H*$_2$CO$_2$Me), 2.98 (s, 3 H, Me), 2.96 (s, 3 H, Me), 2.11 (d, 3 H, CHC*H*$_3$), 2.10 (d, 3 H, CHC*H*$_3$), 1.81 (s, 3 H, Me), 1.79 (s, 3 H, Me) and −2.42 (br s, 4 H, NH).

3-(1-Hydroxyethyl)benzoporphyrin Derivative **32** (cis *Isomer, Ring 'B' Modified*).—This compound was prepared from **31** by following the procedure described for **24** and was isolated as a mixture of stereoisomers in 90% yield, m.p. 214–215 °C (Found: C, 66.5; H, 6.2; N, 7.25. $C_{42}H_{46}N_4O_9$·1.5 H_2O requires C, 66.37; H, 6.49; N, 7.37); λ_{max}/nm 428 (ε/dm^3 mol^{-1} cm^{-1} 78 200), 578 (12 400), 624 (4300) and 682 (30 400); δ_H 9.74, 9.72, 9.696, 9.692 and 9.45 (each s, 1 H, meso H), 9.37 (s, 2 H, meso H), 9.28 (s, 1 H, meso H), 7.82 (d, 2 H, CH=CH), 7.44 (d, 2 H, CH=CH), 6.58 [q, 1 H, C*H*(OH)], 6.48 [q, 1 H, C*H*(OH)], 5.08, 5.06 (each s, 1 H, C*H*CO_2Me), 4.31 (t, 4 H, C*H*$_2$CH$_2$CO$_2$Me), 4.17 (t, 4 H, C*H*$_2$CH$_2$CO$_2$Me), 3.98–3.41 (6 s, 36 H, Me and OMe), 3.20 (t, 4 H, CH$_2$C*H*$_2$CO$_2$Me), 3.15 (t, 4 H, CH$_2$C*H*$_2$CO$_2$Me), 2.88 and 2.89 (each s, 3 H, Me), 2.25 and 2.19 [each d, 3 H, CH(OH)*Me*], 1.82, 1.81 (each s, 3 H, Me) and −2.37 and −2.33 (each br s, 2 H, NH).

8-Vinylbenzoporphyrin Derivative **20** (cis *Isomer, Ring 'A' Modified*).—Benzoporphyrin **24** (90 mg, 0.12 mmol) was dissolved in *o*-dichlorobenzene (50 cm^3) and the solution heated to 150 °C before addition of toluene-*p*-sulfonic acid (194 mg, 1.02 mmol). Nitrogen was bubbled through the solution during 45 min, and after cooling the solution was diluted with dichloromethane and washed with water (3 × 250 cm^3). The organic phase was dried (Na_2SO_4), filtered, and treated with an excess of ethereal diazomethane. After evaporation of the solvents, compound **20** was crystallized from dichloromethane–hexane and isolated (82 mg, 93%), m.p. 134–136 °C (Found: C, 68.8; H, 6.05; N, 7.4. $C_{42}H_{44}N_4O_8$ requires C, 68.82; H, 6.05; N, 7.64); ν_{max}/nm 418 (ε dm^3 mol^{-1} cm^{-1} 75 600), 580 (11 500), 626 (3600) and 688 (28 500); δ_H 9.83, 9.69, 9.42 and 8.99 (each s, 1 H, meso H), 8.16 (dd, 1 H, C*H*=CH$_2$), 7.82 (d, 1 H, CH=CH), 7.44 (d, 1 H, CH=CH), 6.35 (d, 1 H, CH=C*H*$_2$), 6.17 (d, 1 H, CH=C*H*$_2$), 5.07 (s 1 H, C*H*CO_2Me), 4.31 and 4.17 (each t, 2 H, C*H*$_2$CH$_2$CO$_2$Me), 3.99, 3.67, 3.66, 3.56, 3.49 and 3.39 (each s, 3 H, Me and OMe), 3.21 and 3.15 (each t, 2 H, CH$_2$C*H*$_2$CO$_2$Me), 2.96 (s, 3 H, Me), 1.81 (s, 3 H, Me) and −2.31 (br s, 2 H, NH).

3-Vinylbenzoporphyrin Derivative **28** (cis *Isomer, Ring 'B' Modified*).—The benzoporphyrin **28** was synthesized from compound **32** (80 mg) in 93% yield by following the procedure reported above for compound **20**; it had m.p. 212–214 °C (Found: C, 67.4; H, 6.2; N, 7.95. $C_{42}H_{44}N_4O_8$·H_2O requires C, 67.17; H, 6.17; N, 7.46); λ_{max}/nm 430 (ε/dm^3 mol^{-1} cm^{-1} 69 100), 582 (13 100), 628 (6050) and 690 (29 450); δ_H 9.76, 9.69, 9.36 and 9.14 (each s, 1 H, meso H), 8.12 (dd, 1 H, C*H*=CH$_2$), 7.82 (d, 1 H, CH=CH), 7.45 (d, 1 H, CH=CH), 6.37 (d, 1 H, CH=C*H*$_2$), 6.17 (d, 1 H, CH=C*H*$_2$), 5.06 (s, 1 H, C*H*CO_2Me), 4.32 and 4.18 (each t, 2 H, C*H*$_2$CH$_2$CO$_2$Me), 3.98, 3.66, 3.64, 3.60, 3.48 and 3.42 (each s, 3 H, Me and OMe), 3.20 and 3.16 (each t, 2 H, CH$_2$C*H*$_2$CO$_2$Me), 2.94 (s, 3 H, Me), 1.78 (s, 3 H, Me) and −2.29 (br s, 2 H, NH).

8-Vinylbenzoporphyrin Derivative **36** (trans *Isomer, Ring 'A' Modified*).—8-Acetylbenzoporphyrin derivative **37** (100 mg) was first reduced to the 1-hydroxyethyl derivative **38** by treatment with sodium borohydride (150 mg), as described for compound **24**. Next, compound **38** was heated with toluene-*p*-sulfonic acid (200 mg) in refluxing *o*-dichlorobenzene (50 cm^3) to give the title vinyl compound (79 mg, 80%), m.p. 138–142 °C; λ_{max}/nm 418 (ε/dm^3 mol^{-1} cm^{-1} 86 000), 570 (14 500), 620 (3500) and 680 (28 000); δ_H 9.78 (s, 2 H, meso-H), 9.43 and 9.30 (each s, 1 H, meso H), 8.18 (dd, 1 H, C*H*=CH$_2$), 7.84 (d, 1 H, CH=CH), 7.44 (d, 1 H, CH=CH), 6.34 (d, 1 H, CH=C*H*$_2$), 6.15 (d, 1 H, CH=C*H*$_2$), 5.00 (s, 1 H, C*H*CO_2Me), 4.32 and 4.22 (each t, 2 H, C*H*$_2$CH$_2$CO$_2$Me), 4.20, 3.86, 3.66, 3.64, 3.50, 3.42, 2.94 and 1.80 (each s, 3 H, Me and OMe), 3.16 and 3.12 (each t, 2 H, CH$_2$C*H*$_2$CO$_2$Me) and −2.30 (br s, 2 H, NH) [Found (HRMS): *m/z* 732.3150. $C_{42}H_{44}N_4O_8$ requires 732.3153].

Bis(benzoporphyrin) **46** (cis-*Isomer*).—The benzoporphyrin **24** (28 mg, 0.037 mmol) was dissolved in dichloromethane (10 cm^3) and trifluoromethanesulfonic acid (0.4 cm^3) was added to the mixture which was then stirred at room temperature under nitrogen for 3 h. After this, pyridine (1.0 cm^3) was added to the mixture and stirring was continued for a further 30 min. The reaction mixture was extracted with dichloromethane and the extract was washed with water (3 × 200 cm^3), dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by preparative chromatography on silica gel plates, eluting with 2% methanol in dichloromethane. The major product, **46**, was isolated (11.8 mg, 44%) as a mixture of stereoisomers, m.p. 184–186 °C; λ_{max}/nm 426 (ε/dm^3 mol^{-1} cm^{-1} 142 200), 580 (30 900), 622 (17 600) and 682 (55 300); δ_H(gross diastereoisomeric mixture) 10.32–8.28 (15 s, 8 H, meso H), 7.85–7.80 (m, 2 H, CH=CH), 7.50–7.18 (m, 4 H, MeO$_2$CCH=CH), 6.5–5.6 (4 m, 1 H, CHMe), 5.12 and 5.10 (each s, 1 H, MeO$_2$CC*H*), 5.06

(s, 1 H, MeO_2CCH), 4.33 and 4.12 (each m, total 32 H, $CH_2CH_2CO_2Me$), 4.00, 4.01, 3.98 and 3.97 (each s, 24 H, Me or OMe), 3.81, 3.67, 3.66, 3.65, 3.62, 3.57, 3.52, 3.51, 3.48 and 3.47 (each s, total 108 H, Me or OMe), 3.26, 3.23 and 3.22 (each s, total 36 H, Me or OMe), 2.97–2.93 (m, 32 H, $CH_2CH_2CO_2Me$), 2.89, 2.61, 2.47 and 2.07 (each d, 3 H, $CHMe$), 1.86, 1.84 and 1.78 (each s, total 24 H, Me) and −2.20, −2.35 and −2.49 (br s, total 16 H, NH) [Found (LRMS): $[M + H]^+$, 1465.4. $C_{84}H_{88}N_8O_{16}$ requires 1464.6].

Bis(benzoporphyrin) **47** (cis *Isomer*).—The bis(benzoporphyrin) **47** was obtained from compound **32** by the procedure used for the foregoing dimer and was isolated in 58% yield; m.p. 195–197 °C; δ_H(gross diastereoisomeric mixture) 9.95, 9.94, 9.76, 9.75, 9.71, 9.68, 9.66, 9.65, 9.42, 9.39, 9.38, 9.37, 9.33, 9.30, 8.28 and 8.22 (each s, total 32 H, meso H), 7.87–7.78 (m, 16 H, CH=CH), 7.49–7.43 (m, 16 H, CH=CH), 6.01 (q, 2 H, CHMe), 5.90 (q, 2 H, CHMe), 5.22–5.05 (6 s, total 8 H, MeO_2CCH), 4.34 and 4.16 (m, total 32 H, $CH_2CH_2CO_2Me$), 4.02, 4.01, 3.99, 3.98, 3.94, 3.92 and 3.80 (each s, total 48 H, 16 Me or OMe), 3.67, 3.66, 3.65 and 3.64 (each s, total 54 H, 18 Me or OMe), 3.49 and 3.47 (each s, total 36 H, Me or OMe), 3.37 and 3.27 (each d, total 12 H, $CHMe$), 3.21–3.15 (m, total 38 H, $CH_2CH_2CO_2Me$ and 6 Me or OMe), 2.99, 2.92, 2.89, 2.85 and 2.83 (each s, total 18 H, Me), 2.67 (t, total 8 H, $CH_2CH_2CO_2Me$), 2.60 (t, total 4 H, $CH_2CH_2CO_2Me$), 1.94, 1.84, 1.79, 1.77 and 1.65 (each s, total 18 H, 6 Me), −2.31 (br s, 16 H, NH) [Found (LRMS): $[M + H]^+$: 1465.8. $C_{84}H_{88}N_8O_{16}$ requires 1464.6].

8-*Ethylbenzoporphyrin Derivative* **25** (*Ring 'A' Modified,* cis *Isomer*).—8-Ethyl-8-vinyldeuteroporphyrin-IX dimethyl ester **13** (400 mg, 0.675 mmol) was dissolved in degassed toluene (130 cm^3) and dimethyl acetylenedicarboxylate (0.42 cm^3, 3.37 mmol) was added to the solution which was then stirred at 120 °C under a N_2 atmosphere for 5 d. Solvent was evaporated from the reaction mixture and the intermediate **16** was isolated by a combination of silica gel column chromatography, eluting with 1.5% methanol in dichloromethane, followed by silica gel preparative plates eluting with the same solvent mixture. The intermediate Diels–Alder adduct **16**, after crystallization from dichloromethane–hexane, was obtained as a brown crystalline solid (173 mg, 43%), m.p. 113–115 °C (Found: C, 68.4; H, 6.2; N, 7.6. $C_{42}H_{46}N_4O_8$ requires C, 68.63; H, 6.31; N, 7.62); λ_{max}/nm 400 (ε/dm^3 mol^{-1} cm^{-1} 191 900), 498, (21 350), 502 (21 300), 532 (22 100), 598 (14 200), 626 (13 200) and 654 (47 200); δ_H 9.77, 9.71, 9.34 and 9.10 (each s, 1 H, meso H), 7.39 (dd, 2 H, CH_2CH), 7.29 (d, 1 H, CH_2CH), 4.35 and 4.22 (each t, 2 H, $CH_2CH_2CO_2Me$), 4.02 and 3.90 (each s, 3 H, Me or OMe), 4.01 (q, 2 H, CH_2CH_3), 3.67 (s, 6 H, Me or OMe), 3.51, 3.48 and 3.43 (each s, 3 H, Me or OMe), 3.22 and 3.19 (each t, 2 H, $CH_2CH_2CO_2Me$), 2.09 (s, 3 H, Me), 1.79 (t 3 H, CH_2CH_3) and −2.66 and −2.64 (each br s, 1 H, NH) [Found (HRMS): *m/z* 734.3409. $C_{42}H_{46}N_4O_8$ requires 734.3315].

The intermediate **16** (120 mg, 0.16 mmol) was dissolved in dichloromethane (40 cm^3) and DBU (5 drops) was added to the solution which was then kept at room temperature for 15 min, whilst being spectrophotometrically monitored. After this the mixture was evaporated to dryness and the residue recrystallized from dichloromethane–hexane to give compound **25** (107 mg, 89% yield), m.p. 125–130 °C (Found: C, 66.6; H, 6.3; N, 7.5. $C_{42}H_{46}N_4O_8 \cdot H_2O$ requires C, 66.99; H, 6.42; N, 7.44%); λ_{max}/nm 416 (ε/dm^3 mol^{-1} cm^{-1} 72 300), 580 (17 400), 620 (11 100) and 680 (31 200); δ_H 9.72, 9.70, 9.38 and 9.00 (each s, 1 H, meso H), 7.83 and 7.44 (each d, 1 H, CH=CH), 5.08 (s, 1 H, $CHCO_2Me$), 4.33 and 4.19 (each t, 2 H, $CH_2CH_2CO_2Me$), 3.99 (s, 3 H, Me or OMe), 3.98 (q, 2 H, CH_2CH_3), 3.68 (s, 6 H, Me or OMe), 3.50, 3.46 and 3.43 (each s, 3 H, Me or OMe), 3.22 and 3.19 (each t, 2 H, $CH_2CH_2CO_2Me$), 2.94 (s, 3 H, Me), 1.80 (s, 3 H, Me), 1.77 (t, 3 H, CH_2CH_3) and −2.46 (br s, 1 H, NH). [Found (HRMS): *m/z* 734.3323. $C_{42}H_{46}N_4O_8$ requires 734.3315].

2-*Ethylbenzoporphyrin Derivative* **33** (*Ring 'B' Modified,* cis *Isomer*).—This compound was synthesized from the porphyrin **12** by the procedure discussed above for **25**, and was isolated in 52% yield, m.p. 178–181 °C (Found: C, 65.7; H, 6.75; N, 7.6. $C_{42}H_{46}N_4O_8 \cdot 2H_2O$ requires C, 65.42; H, 6.53; N, 7.26); λ_{max}/nm 414 (ε/dm^3 mol^{-1} cm^{-1} 54 500), 580 (11 200), 620 (5300) and 680 (23 000); δ_H 9.71, 9.70, 9.39 and 8.99 (each s, 1 H, meso H), 7.83 and 7.44 (each d, 1 H, CH=CH), 5.07 (s, 1 H, $CHCO_2Me$), 4.33 and 4.19 (each t, 2 H, $CH_2CH_2CO_2Me$), 3.99 (s, 3 H, Me or OMe), 3.92 (q, 2 H, CH_2CH_3), 3.65, 3.64, 3.52, 3.49 and 3.42 (each s, 3 H, Me or OMe), 3.20 and 3.16 (each t, 2 H, $CH_2CH_2CO_2Me$), 2.90 (s, 3 H, Me), 1.80 (s, 3 H, Me), 1.78 (t, 3 H, CH_2CH_3) and −2.46 and −2.60 (each br s, 1 H, NH) [Found (HRMS): *m/z* 734.3307. $C_{42}H_{46}N_4O_8$ requires 734.3315].

2-*Ethylbenzoporphyrin Derivative* **44** (*Ring 'B' Modified,* trans-*Isomer*).—The intermediate Diels–Alder adduct **19** obtained after the reaction of **12** with DMAD [compound **19**, m.p. 174–176 °C (Found: C, 68.6; H, 6.4; N, 7.57. $C_{42}H_{46}N_4O_8$ requires C, 68.63; H, 6.31; N, 7.62); λ_{max}/nm 400 (ε/dm^3 mol^{-1} cm^{-1} 183 800), 504 (9500), 532 (10 600), 598 (2600), 626 (1700) and 654 (38 400); δ_H 9.77, 9.71, 9.35 and 9.12 (each s, 1 H, meso H), 7.40 (dd, 2 H, CH_2CH), 7.29 (d, 1 H, CH_2CH), 4.34 and 4.20 (each t, 2 H, $CH_2CH_2CO_2Me$), 4.02 and 3.90 (each s, 3 H, Me or OMe), 3.96 (q, 2 H, CH_2CH_3), 3.67, 3.66, 3.55, 3.51 and 3.43 (each s, 3 H, Me or OMe), 3.22 and 3.17 (each t, 2 H, $CH_2CH_2CO_2Me$), 2.08 (s, 3 H, Me), 1.78 (t, 3 H, CH_2CH_3) and −2.70 and −2.65 (each br s, 1 H, NH)] was dissolved in dichloromethane and then treated with triethylamine to give the title compound (95%), m.p. 224–226 °C (Found: C, 68.7; H, 6.4; N, 7.5. $C_{42}H_{46}N_4O_8$ requires C, 68.63; H, 6.31; N, 7.62); λ_{max}/nm 414 (ε/dm^3 mol^{-1} cm^{-1} 78 300), 570 (14 100), 614 (4700) and 672 (23 500); δ_H 9.77 (s, 2 H, meso H), 9.42 and 9.29 (each s, 1 H, meso H), 7.75 and 7.43 (each d, 1 H, $MeO_2CC{=}CHCH$), 4.86 (d, 1 H, $CHCO_2Me$), 4.35 and 4.20 (each t, 2 H, $CH_2CH_2CO_2Me$), 4.27, 3.94, 3.66, 3.65, 3.54, 3.52 and 3.44 (each s, 3 H, Me or OMe), 3.94 (q, 2 H, CH_2CH_3), 3.20 and 3.15 (each t, 2 H, $CH_2CH_2CO_2Me$), 1.80 (t, 3 H, CH_2CH_3), 1.64 (s, 3 H, Me) and −2.62 and −2.69 (each br s, 1 H, NH).

8-(1-*Hexyloxyethyl*)*benzoporphyrin Derivative* **27** (*Ring 'A' Modified,* cis-*Isomer*).—BPD **20** (30 mg, 0.041 mmol) was stirred with 30% hydrogen bromide–acetic acid (3 cm^3) under an atmosphere of N_2 at room temperature for 2 h after which it was evaporated to dryness. Hexanol (3.0 cm^3, 23.9 mmol) was rapidly added to the green bromoethyl residue and the solution was stirred at room temperature for 2 h and then diluted with dichloromethane (150 cm^3). The organic phase washed with water, saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), filtered and evaporated. The residue was treated with an excess of ethereal diazomethane after which the solvent was evaporated; the residual hexanol was removed under high vacuum. The residue was purified by preparative TLC, eluting with 1.5% methanol in dichloromethane as mobile phase. Two bands were separated; the most mobile band, a minor component, was not identified. The more polar fraction was characterized as the title compound **27** (17 mg, 50%); λ_{max}/nm 422 (ε/dm^3 mol^{-1} cm^{-1} 62 100), 576 (16 150), 576 (16 150), 622 (9800) and 682 (27 200); δ_H 10.18, 10.17, 9.72, 9.41 and 9.00 (each s, total 4 H, meso H), 7.82 and 7.43 (each d, 1 H, $MeCO_2C{=}CHCH$), 6.02 [q, 1 H, $CH(CH_3)O$], 5.08 (s, 1 H, $MeO_2CCHCCO_2Me$), 4.33 and 4.19 (each t, 2 H, $CH_2CH_2CO_2Me$), 3.99, 3.68, 3.54, 3.50, 3.46, 3.42, 2.94 and 2.93 (each s,

total 24 H, Me, OMe), 3.23 and 3.16 (each t, 2 H, $CH_2CH_2CO_2Me$), 2.16 (d, 3 H, CH*Me*), 2.00–0.76 [m, total 13 H, $(CH_2)_5Me$] and −2.40 (br s, 2 H, NH) [Found (HRMS): *m/z* 834.4210. $C_{48}H_{58}N_4O_9$ requires 834.4203].

3-(1-*Hexyloxyethyl*)*benzoporphyrin Derivative* **35** (*Ring 'B' Modified,* cis-*Isomer*).—This BPD was synthesized from **28** by following the method described above, and was obtained in 50% yield as a mixture of diastereoisomers, m.p. 94–95 °C; λ_{max}/nm 426 (ε/dm^3 mol^{-1} cm^{-1} 63 200), 578 (17 300), 624 (10 700) and 682 (30 700); δ_H 9.75, 9.73, 9.69, 9.45, 9.38 and 9.15 (each s, total 8 H, meso H), 7.83 and 7.45 (each pseudo t, 4 H, $MeO_2CC{=}CH{-}CH$), 6.21 and 5.95 (each q, 1 H, C*H*O-hexyl), 5.07 (s, 2 H, C*H*CO_2Me), 4.32 and 4.19 (each t, 8 H, CH_2CH_2Me), 3.99 (s, 6 H, Me), 3.65, 3.64, 3.48, 3.47, 3.42 and 2.90 (each s, 42 H, Me, OMe), 3.21 and 3.16 (each t, total 8 H, $CH_2CH_2CO_2Me$), 2.22 and 2.09 [each d, 3 H, CH(C*H*$_3$)O-hexyl], 1.85–0.75 (m, 26 H, Me and O-hexyl) and −2.30 and −2.40 (br s, 4 H, NH) [Found (HRMS): *m/z* 834.4206. $C_{48}H_{58}N_4O_9$ requires 834.4203]. An unidentified minor component was also isolated, but not further characterized.

8-(1-*Hexyloxyethyl*)*benzoporphyrin Derivative* **40** (*Ring 'A' Modified,* trans-*Isomer*).—BPD **36** (30 mg, 0.041 mmol) was stirred with 30% hydrogen bromide–acetic acid (3 cm^3) under a N_2 atmosphere, following the procedure described above, to give the title compound (50%), m.p. < 60 °C (Found: 68.5; H, 7.05; N, 6.5. $C_{48}H_{58}N_4O_9{\cdot}0.5H_2O$ requires: C, 68.31; H, 7.04; N, 6.64); λ_{max}/nm 426 (ε/dm^3 mol^{-1} cm^{-1} 69 000), 498, (8500), 568 (16 300), 616 (8200) and 674 (24 800); δ_H 10.22, 9.78, 9.45 and 9.28 (each s, 1 H, meso H), 7.76 and 7.44 (each d, 1 H, $MeCO_2C{=}CHCH$), 6.05 [q, 1 H, C*H*(CH$_3$)O], 4.84 (d, 1 H, $MeO_2CCHCCO_2Me$), 4.36 (t, 2 H, $CH_2CH_2CO_2Me$), 4.27 (s, 3 H, Me), 4.21 (t, 2 H, C*H*$_2$CH$_2$CO$_2$Me), 4.92–3.44 (each s, total 18 H, Me, OMe), 3.21 (t, 2 H, $CH_2CH_2CO_2Me$), 3.18 (t, 2 H, $CH_2CH_2CO_2Me$), 2.17–0.76 [m, total 19 H, Me and $(CH_2)_5Me$] and −2.57 (br s, 2 H, NH) [Found (HRMS): *m/z* 834.4213. $C_{48}H_{58}N_4O_9$ requires: 834.4203].

3-(1-*Hexyloxyethyl*)*benzoporphyrin Derivative* **45** (*Ring 'B' Reduced,* trans-*Isomer*).—3-Vinyl-BPD **41** (20 mg, 0.03 mmol) was converted into the title compound by following the procedure described for the foregoing BPD, the product being isolated as a mixture of diastereoisomers (55%), m.p. 95–97 °C; λ_{max}/nm 422 (ε/dm^3 mol^{-1} cm^{-1} 69 400), 568 (8600), 568 (16 800), 618 (9200) and 676 (25 200); δ_H 9.83, 9.79, 9.73, 9.72 and 9.66 (each 1s, 5 H, meso H), 9.39, 9.40 and 9.41 (each s, 1 H, meso H), 7.73–7.77 (m, 2 H, $MeO_2CC{=}CHCH$), 7.44 (d, 2 H, $MeO_2C{-}C{=}CHCH$), 6.13 (q, 1 H, C*H*O-hexyl), 5.95 (q, 1 H, C*H*O-hexyl), 4.87 (m, 2 H, $MeO_2CCHCCO_2Me$), 4.34 (t, 4 H, C*H*$_2$CH$_2$CO$_2$Me), 4.34 (s, 3 H, Me), 4.29 (s, 3 H, Me), 4.19 (t, 4 H, C*H*$_2$CH$_2$CO$_2$Me), 3.94–3.44 (8s, 36 H, Me, OMe), 3.22 (t, 4 H, $CH_2CH_2CO_2Me$), 3.17 (t, 4 H, C*H*$_2$CH$_2$CO$_2$Me), 2.23 [d, 3 H, CH(C*H*$_3$)O-hexyl], 2.18 [d, 3 H, CH(C*H*$_3$)O-hexyl], 1.73–0.72 (m, 32 H, Me and O-hexyl), −2.54 (br s, 2 H, NH) and −2.61 (br s, 2 H, NH) [Found (HRMS): *m/z* 834.4228. $C_{48}H_{58}N_4O_9$ requires 834.4203].

8-*Formylbenzoporphyrin Derivative* **26** (*Ring 'A' Modified,* cis-*Isomer*).—8-Vinylbenzoporphyrin derivative **20** (80 mg, 0.11 mmol) was dissolved in tetrahydrofuran (40 cm^3) and osmium tetraoxide (20 mg) in carbon tetrachloride (1 cm^3) together with sodium periodate (320 mg) in water (15 cm^3) and dioxane (15 cm^3) were added to the solution. The mixture was stirred under a N_2 atmosphere for 45 min at room temperature, after which the reaction was judged to be complete (spectrophotometry, disappearance of peak at 680 and appearance of new peak at 689 nm in dichloromethane). The mixture was diluted with dichloromethane (200 cm^3), washed with water (3 × 200 cm^3), dried (Na_2SO_4) and evaporated to give a residue which was chromatographed on silica gel plates, eluting with 5% methanol in dichloromethane. The major band was collected and the product was crystallized from dichloromethane–hexane to give the title compound (65 mg, 80%), m.p. 250–252 °C; λ_{max}/nm 434 (ε/dm^3 mol^{-1} cm^{-1} 85 000), 514 (8000), 566 (7200), 638 (6000) and 696 (24 000); δ_H 11.27 (s, 1 H, CHO), 10.06, 9.48, 9.02 and 8.74 (each s, 1 H, meso H), 7.54 (dd, 1 H, $MeO_2CC{=}CHCH$), 6.86 (d, 1 H, $MeO_2CC{=}CHCH$), 4.54 (d, 1 H, C*H*CO_2Me), 4.06 (m, 4 H, C*H*$_2$CH$_2$CO$_2$Me), 4.24, 3.99, 3.43 and 3.28 (each s, 3 H, Me or OMe), 3.68 (s, 9 H, Me, OMe), 3.20 and 3.12 (each t, 2 H, $CH_2CH_2CO_2Me$), 1.37 (s, 3 H, Me) and −2.15 (br s, 2 H, NH) [Found (HRMS): *m/z* 734.2948. $C_{41}H_{42}N_4O_9$ requires 734.2945].

3-*Formylbenzoporphyrin Derivative* **34** (*Ring 'B' Modified,* cis-*Isomer*).—3-Vinylbenzoporphyrin derivative **28** (80 mg, 0.11 mmol) was treated with osmium tetraoxide/sodium periodate as described above for compound **26** to give the title compound (66 mg, 82%), m.p. 242–245 °C; λ_{max}/nm 434 (ε/dm^3 mol^{-1} cm^{-1} 85 000), 512 (8500), 566 (7500), 638 (6500) and 696 (24 000); δ_H 11.48 (s, 1 H, CHO), 9.78, 9.70, 9.45 and 9.05 (each s, 1 H, meso H), 7.66 (dd, 1 H, C=CHC*H*), 7.32 (d, 1 H, C=C*H*CH), 4.69 (d, 1 H, C*H*CO_2Me), 4.23, 4.09 (each t, 2 H, C*H*$_2$CH$_2$CO$_2$Me), 4.34, 3.94, 3.82, 3.69, 3.65, 3.39 and 3.30 (each s, 3 H, Me or OMe), 3.19–3.09 (m, 4 H, $CH_2CH_2CO_2Me$), 1.65 (s, 3 H, Me) and −1.60 and −1.80 (each br s, 1 H, NH) [Found (HRMS): *m/z* 734.3000. $C_{41}H_{42}N_4O_9$ requires 734.2945].

Crystallography.—Crystals of compound **36** were grown by slow diffusion of hexane into a concentrated solution of the porphyrin in dichloromethane. The *cis* compound **20** was crystallized from chloroform–hexane. The crystals were mounted on a glass fibre using the method described by Hope.[15]

Crystal data. Compound **36**. $C_{42}H_{44}N_4O_8$, M = 732.8, triclinic, a = 10.695(6), b = 13.895(5), c = 14.188(5) Å, α = 71.22(3), β = 71.57(4), γ = 72.41(4)°, U = 1846 Å^3 (by least-squares refinement on diffractometer angles for 19 automatically centred reflections, λ = 0.7107 Å), space group $P\bar{1}$, Z = 2, D_c = 1.318 g cm^{-3}, F(000) = 776. Red block, 0.4 × 0.35 × 0.31 mm, μ(Mo-Kα) = 0.092 mm^{-1}.

Compound **20**. $C_{42}H_{44}N_4O_8$, M = 732.8, triclinic, a = 8.467(4), b = 13.863(6), c = 15.718(10) Å, α = 89.33(4), β = 85.04(4), γ = 81.31(4)°, U = 1817 Å^3 (by least-squares refinement on diffractometer angles for 22 automatically centred reflections, λ = 1.541 78 Å), space group $P\bar{1}$, Z = 2, D_c = 1.339 g cm^{-3}, F(000) = 776. Brown parallelepiped, 0.21 × 0.15 × 0.05 mm, μ(Cu-Kα) = 0.763 mm^{-1}.

Data collection and processing. Compound **36**. Siemens R3m/V diffractometer, 130 K, ω mode with ω scan range 2.0°, ω scan speed 6.01° min^{-1}, graphite-monochromated Mo-Kα radiation; 7665 reflections measured ($0 < 2\theta \leqslant 52°$, $+/-h$, $+/-k$, $+l$), giving 4194 reflections with $F > 4\sigma(F)$. The intensities are corrected for Lorentz, polarization, and absorption effects; extinction was disregarded.

Compound **20**. Siemens P4 diffractometer equipped with a rotating anode operating at 50 kV and 300 mA, 120 K, 2θ–θ mode with a scan range of 2.2° plus Kα separation, scan speed 29.3° min^{-1}, Cu-Kα radiation; 4567 reflections measured ($0 < 2\theta \leqslant 108.5°$, $+/-h$, $+/-k$, $+l$), giving 3224 reflections with $F > 4\sigma(F)$.

Structure analysis and refinement. Compound **36**. The structure was solved by direct methods followed by full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens in calculated positions using a riding model. The weighting scheme used was $w^{-1} = \sigma^2(F) + 0.0002\,F^2$; refinement of 487 parameters gave final R and R_w

values of 0.083 and 0.079. Programs and computers used and sources of scattering factor data are given in ref. 16.

Compound **20**. Only the peripheral side-chain non-hydrogen atoms were refined with anisotropic thermal parameters. The weighting scheme used was $w^{-1} = \sigma^2(F) + 0.1260\ F^2$; refinement of 362 parameters gave final R and R_w values of 0.111 and 0.133. Structure solution and other refinement details were as reported for compound **36**.

Acknowledgements

This work was supported by grants from the National Institutes of Health (CA 55791, HL 22252) and Oncologic Foundation of Buffalo. Mass spectrometric analyses were performed by the University of California, San Francisco, Mass Spectrometry (A. L. Burlingame, Director) supported by the Biomedical Research Technology Program of the National Center for Research Resources, NIH NCRR BRTP 01614, and at the Department of Biophysics, Roswell Park Cancer Institute, Buffalo. We thank Mr. Adam Sumlin for his assistance in antitumour bioassay.

References

1 Preliminary Communication: I. Meunier, R. K. Pandey, M. M. Walker, M. O. Senge, T. J. Dougherty and K. M. Smith, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 1575.
2 For a review see: R. K. Pandey, D. F. Majchrzycki, T. J. Dougherty and K. M. Smith, *Proc. SPIE*, 1989, **1065**, 164.
3 (*a*) H. L. Callot, A. W. Johnson and A. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1424; (*b*) A. R. Morgan, V. S. Pangka and D. Dolphin, *J. Chem. Soc., Chem. Commun.*, 1984, 1047; (*c*) R. K. Pandey, F.-Y. Shiau, K. Ramachandran, T. J. Dougherty and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1377.
4 A. M. Richter, B. Kelly, J. Chow, J. D. Liu, G. H. N. Towers, J. Levy and D. Dolphin, *J. Natl. Cancer Inst.*, 1990, **52**, 501.
5 A. M. Richter, E. Waterfield, A. K. Jain and B. Allison, *Br. J. Cancer*, 1991, **63**, 87.
6 R. K. Pandey, K. M. Smith and T. J. Dougherty, *J. Med. Chem.*, 1990, **33**, 2032.
7 F.-Y. Shiau, R. K. Pandey, S. Ramaprasad, T. J. Dougherty and K. M. Smith, *J. Org. Chem.*, 1990, **55**, 2190.
8 R. K. Pandey, F.-Y. Shiau, A. B. Sumlin, T. J. Dougherty and K. M. Smith, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 491.
9 (*a*) R. K. Pandey, D. A. Bellnier, K. M. Smith and T. J. Dougherty, *Photochem. Photobiol.*, 1991, **53**, 65; (*b*) D. A. Bellnier, B. W. Henderson, R. K. Pandey, W. R. Potter and T. J. Dougherty, *J. Photochem. Photobiol. Part B: Biol.*, 1993, **20**, 55.
10 R. K. Pandey, W. Potter, I. Meunier, A. B. Sumlin and K. M. Smith, *Photochem. Photobiol.*, submitted.
11 J. F. Evenson, S. Sommer, C. Rimington and J. Moan, *Br. J. Cancer*, 1987, **55**, 483.
12 R. K. Pandey, F.-Y. Shiau, C. J. Medforth, T. J. Dougherty and K. M. Smith, *Tetrahedron Lett.*, 1990, **31**, 789.
13 R. K. Pandey, T. J. Dougherty, D. Dolphin, F.-Y. Shiau, I. Meunier and K. M. Smith, unpublished results.
14 R. K. Pandey, M. G. H. Vicente, F.-Y. Shiau, T. J. Dougherty and K. M. Smith, *Proc. SPIE*, 1991, **1426**, 356.
15 H. Hope, *ACS Symp. Ser.*, 1987, **357**, 257.
16 M. O. Senge, H. Hope and K. M. Smith, *J. Chem. Soc., Perkin Trans. 2*, 1993, 11.

Paper 3/06984B
Received 23rd *November* 1993
Accepted 7th *January* 1994