Syntheses of Monosulfonated Phthalocyanines, Benzonaphthoporphyrazines and Porphyrins *via* the Meerwein Reaction

Svetlana V. Kudrevich, Hasrat Ali and Johan E. van Lier*
MRC Group in the Radiation Sciences, Faculty of Medicine, University of Sherbrooke, Sherbrooke (Québec), Canada J1H 5N4

A variety of monosulfonated phthalocyanine, benzonaphthoporphyrazine and porphyrin derivatives have been prepared as single positional isomers in moderate to high yield using modified Meerwein reaction conditions. These amphiphilic dyes have a potential application as photosensitizers in the photodynamic therapy of cancer.

Photodynamic therapy (PDT) is a promising new modality for the control and treatment of tumours.[1] This technique is based on the use of a photosensitizing dye which, upon localization at the tumour site and light activation in the presence of oxygen, produces cytotoxic species, including singlet oxygen, resulting in tumour necrosis. The dye preparation currently used in clinical trials consists of a complex mixture of haematoporphyrin dimers and oligomers (Photofrin II™, QLT Inc., Vancouver, Canada) which could be improved upon in terms of purity as well as tumour localization and photochemical properties. Several alternative classes of photosensitizers are being evaluated and among them phthalocyanines and their analogues receive increasing attention.[2] Their capacity to photoinactivate cancer cells *in vitro* as well as *in vivo* is well documented and particularly mono/disulfonated, amphiphilic phthalocyanines, chelated with diamagnetic metal ions have been shown to be capable of killing tumour cells directly.[2]

Published routes for preparing amphiphilic phthalocyanines mostly involve one of two methods:[3] (i) *in situ* synthesis of the phthalocyanine's macrocycle, *i.e.* condensation of two differently substituted precursors in the appropriate stoichiometric ratio and (ii) partial sulfonation of substituted metallophthalocyanines. These methods can be inconvenient for several reasons. Thus, syntheses of amphiphilic phthalocyanines *via* the mixed condensation method requires two types of precursors (hydrophilic and lipophilic), which differ substantially in their physical properties and reactivities, disfavouring selection of optimal reaction conditions and stoichiometry. Furthermore, the complexity of the resulting reaction mixture requires time-consuming and tedious chromatographic separation procedures. The second method results in even more complex isomeric mixtures due to sulfonation either at the 3- or the 4-position of the benzo rings of the phthalocyanine macrocycle.[4] Also, electrophilic substitution requires harsh reaction conditions which may affect substituents, or result in demetallation or decomposition of the macrocycle.

On such accounts we evaluated alternative synthetic procedures for the preparation of amphiphilic photosensitizers as pure isomeric compounds, featuring both lipophilic and hydrophilic substituents at selected positions of the chromophore. In order to avoid the problems associated with attempted reaction of incompatible hydrophilic and lipophilic precursors, sulfonate substituents were introduced onto the macrocycle as the final step in the reaction sequence, using the Meerwein procedure. In this work we apply the method to the synthesis of monosulfonated porphyrins, phthalocyanines and benzonaphthoporphyrazines.

Results and Discussion

In our procedure the basic macrocycle was obtained by the condensation of two different precursors of similar solubility, one featuring the selected lipophilic substituent and the other containing a nitro group. After subsequent reduction of the nitro to an amino group, the Meerwein procedure was employed to introduce the sulfo group. The applicability of the Meerwein procedure to a variety of compounds is well established[5] and its usefulness for our synthesis was evaluated by converting zinc 4-amino-11,18,25-tri(*tert*-butyl)phthalocyanine† **4a** to the zinc 11,18,25-tri(*tert*-butyl)-4-sulfophthalocyanine **5a**. Subsequently, we prepared a series of monoamino derivatives of different phthalocyanines, tetraphenylporphyrins and benzonaphthoporphyrazines featuring various central metal atoms and macro-ring substituents. Our choice of substituents was guided by the PDT potential of the final product and adequate solubility of the monoamine intermediate to allow for chromatographic purification. In addition to the 4-sulfophthalocyanine **5a**, we also prepared the analogous 3-sulfophthalocyanine **5b** which allowed us to evaluate the distinct chromatographic and biological properties of these closely related structures. Using the conventional condensation method we recently prepared the zinc hexadecafluorophthalocyanine and the mixed 3- and 4-isomer of the zinc dodecafluoromonosulfophthalocyanine analogue (unpublished data). In view of the good photodynamic properties of these derivatives we prepared the single isomeric zinc dodecafluoro-4-sulfophthalocyanine **21** using the present procedure. Benzonaphthoporphyrazines, which can be considered as hybrid structures composed of both phthalocyanine and naphthalocyanine moieties, have recently been reported as effective sensitizers for tumour cell and virus inactivation.[3a,b] In particular, the disulfobenzo derivatives, obtained *via* the condensation of naphthalene-2,3-carboxylic acid and 4-sulfophthalic acid with metal salts in the presence of urea, showed good biological activities whereas the monosulfonates were less active due to their strong tendency to aggregate. In order to enhance solubility and to reduce aggregation of the monosulfonato derivative, we applied the modified Meerwein procedure to the preparation of two monosulfobenzonaphthoporphyrazines substituted with three *tert*-butyl groups and one sulfonate group either on the benzo **10** or naphtho **15** ring.

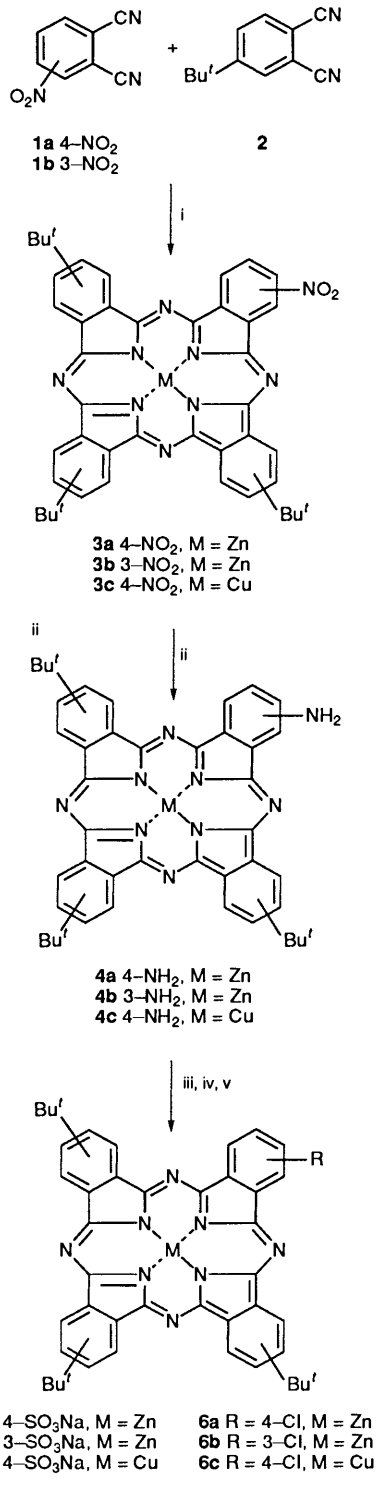
Preparation of Monoaminophthalocyanines and Monoaminobenzonaphthoporphyrazines.—Condensation of 4- or 3-nitrophthalonitrile **1a** or **1b** and 4-(*tert*-butyl)phthalodinitrile **2** with

† The original phthalonitrile numbering was retained.

zinc acetate (molar proportions 1:3:4; 3 h; 160 °C) gave a mixture of mono- through to tetra-nitrophthalocyanine derivatives. The reaction mixture was brought to dryness under reduced pressure, the residue was dissolved in dimethylformamide (DMF), and the solution was treated with $Na_2S·9H_2O$ to yield a mixture of mono- and poly-aminophthalocyanines (55–65% yield for the zinc complexes and 95% yield for the more stable copper complexes). Unlike the nitrophthalocyanines, the more polar amino derivatives were easily separated on a silica gel column, and gave the pure monoaminotri(*tert*-butyl)phthalocyanines **4b** and **4c** (Scheme 1). The analogous benzonaphthoporphyrazines **9** and **14** were prepared in a similar manner (Schemes 2 and 3). Identity of the final products was established by fast-atom bombardment (FAB) MS and UV-visible spectroscopy. Compounds **4a–c** exhibit a deep greenish blue colour. The addition of one auxochromic amino group per molecule induces a weak bathochromic shift of the absorption maxima in the red end of the spectrum.[6] Perturbation of the symmetry of the aromatic ring systems in the case of the monoaminobenzonaphthoporphyrazines, combined with the effect of the added amino group, results in further characteristic shifts of the absorption maxima (Table 1).

The synthesis of the zinc 4-aminododecafluorophthalocyanine **20** was complicated by difficulties encountered in reducing the nitro substituent. Sodium sulfide induced a nucleophilic substitution of the F atoms in a similar manner to that reported for the thiylation of compound **18** with PhS .[7] Other reducing agents tested, including acidic solutions of tin(II) chloride and titanium(III) chloride, induced decomposition of the zinc complex. Attempts to effect direct condensation of 4-aminophthalodinitrile likewise did not give the appropriate phthalocyanine.[8] Therefore, we modified the procedure by first protecting the amino group in 4-aminophthalodinitrile as an acetamido group (*i.e.*, compound **17**), followed by a mixed condensation with tetrafluorophthalodinitrile **18** to yield the monoacetamido derivative **19**. Compound **20** was subsequently obtained by acidic hydrolysis of amide **19** (Scheme 4).

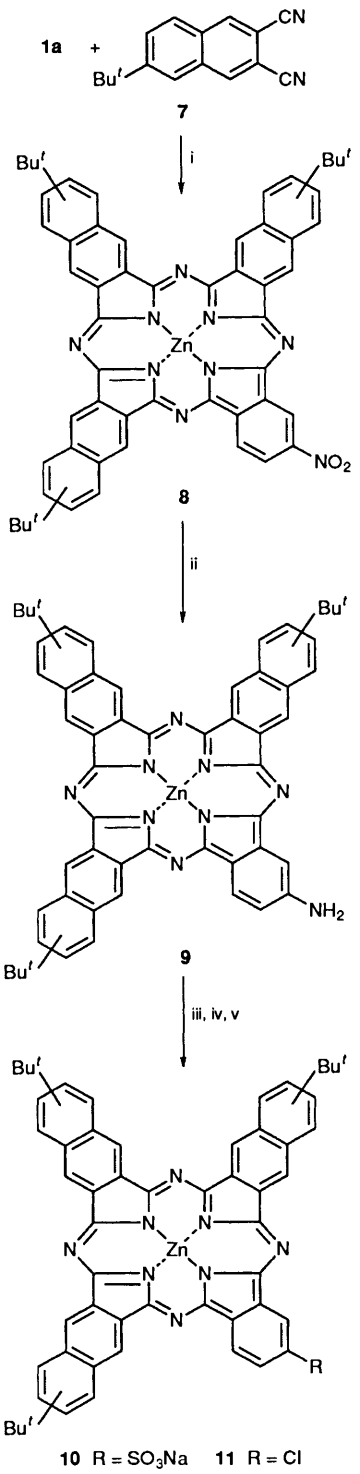
Preparation of Monosulfonato-phthalocyanines, -benzonaphthoporphyrazines and -tetraphenylporphyrins.—The method developed by Meerwein and co-workers for the conversion of aromatic amines into sulfonyl chlorides involves treatment of the diazonium chloride in conc. hydrochloric acid with sulfur dioxide in acetic acid, using the copper(II) ion as a catalyst.[9] We modified the procedure to accommodate the specific properties of the selected macrocyclic compounds. Owing to the low solubility of the monodiazonium salts of phthalocyanines, benzonaphthoporphyrazines and tetraphenylporphyrins in water (or aq. acetone), we used suspensions and established the completion of the reaction empirically. To optimize the use of the monodiazo compounds, we reversed the order by which reagents were added. For example, a solution of sulfur dioxide in acetic acid mixed with a solution of the catalyst, was added rapidly to a vigorously stirred, cold suspension of zinc 11,18,25-tri(*tert*-butyl)-4-diazophthalocyanine, freshly prepared from compound **4a**. Vigorous evolution of nitrogen, indicative of the reaction, started immediately. Precipitated material contained 55% of zinc 11,18,25-tri(*tert*-butyl)-4-(chlorosulfonyl)phthalocyanine and 25% of the monochloro derivative **6a** as a side product resulting from a competitive reaction of SO_2 and Cl^- with Ar^+. This mixture was hydrolysed in mol dm^{-3} aq. NaOH. The resulting monosulfonate **5a** was easily separated from the monochloro derivative **6a** by chromatography on a short silica gel column and was characterized by its combustion analyses data and its physicochemical properties. When dissolved in methanol, this



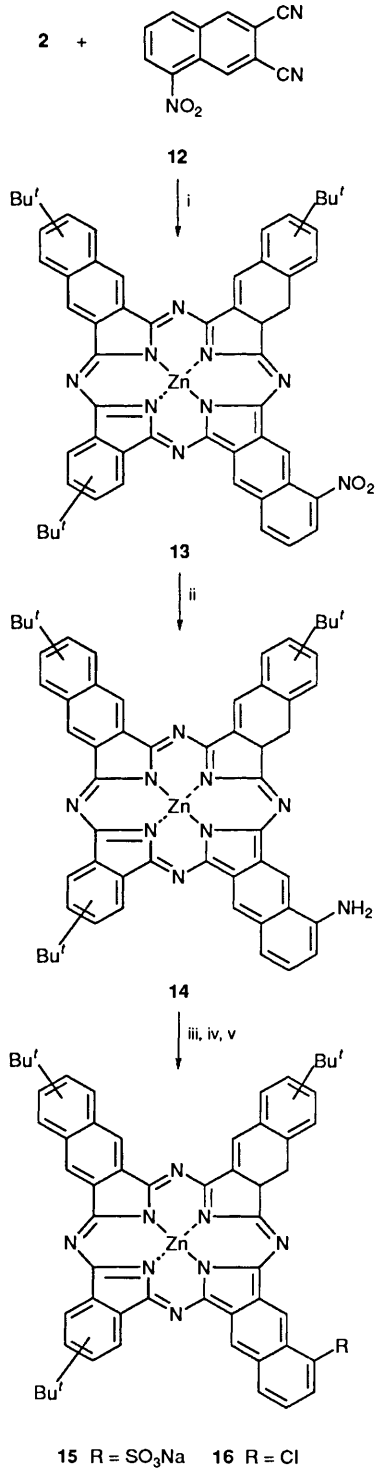
Scheme 1 *Reagents and conditions:* i, $Zn(OAc)_2·2H_2O$ or CuCl; ii, $Na_2S·9H_2O$ in DMF–THF; iii, $NaNO_2$, HCl, 0 °C; iv, SO_2 in AcOH, $CuCl_2$; v, 1 mol dm^{-3} aq. NaOH

compound is largely monomeric. The oxidative degradation of compound **5a**, followed by HPLC analysis,[4] gave a sulfophthalamide/*tert*-butylphthalamide ratio of 1:3.

The monosulfophthalocyanines **5b** and **5c**, the monosulfobenzonaphthoporphyrazines **10** and **15**, and the monosulfotetraphenylporphyrins **24a–c** were obtained by the same procedure (Table 2). All sulfochlorination products were hydrolysed with 1 mol dm^{-3} aq. NaOH prior to the separation of the final products by silica gel chromatography. The ratio between the monosulfonate and monochloro compounds was shown to depend strongly on the type of precursor used,



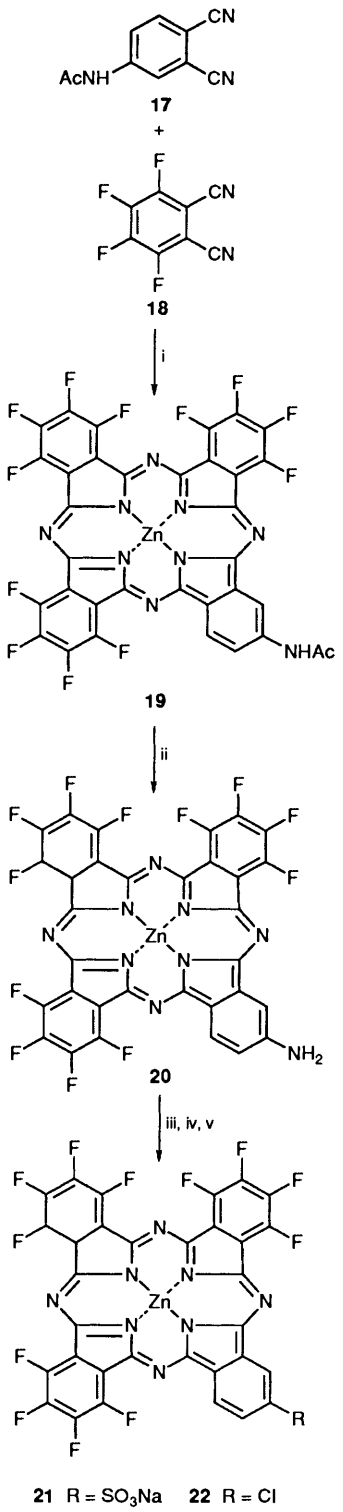
Scheme 2 *Reagents and conditions:* i, $Zn(OAc)_2 \cdot 2H_2O$; ii, $Na_2S \cdot 9H_2O$ in DMF–THF; iii, $NaNO_2$, HCl, 0 °C; iv, SO_2 in AcOH, $CuCl_2$; v, 1 mol dm^{-3} aq. NaOH



Scheme 3 *Reagents and conditions:* i, $Zn(OAc)_2 \cdot 2H_2O$; ii, $Na_2S \cdot 9H_2O$ in DMF–THF; iii, $NaNO_2$, HCl, 0 °C; iv, SO_2 in AcOH, $CuCl_2$; v, 1 mol dm^{-3} aq. NaOH

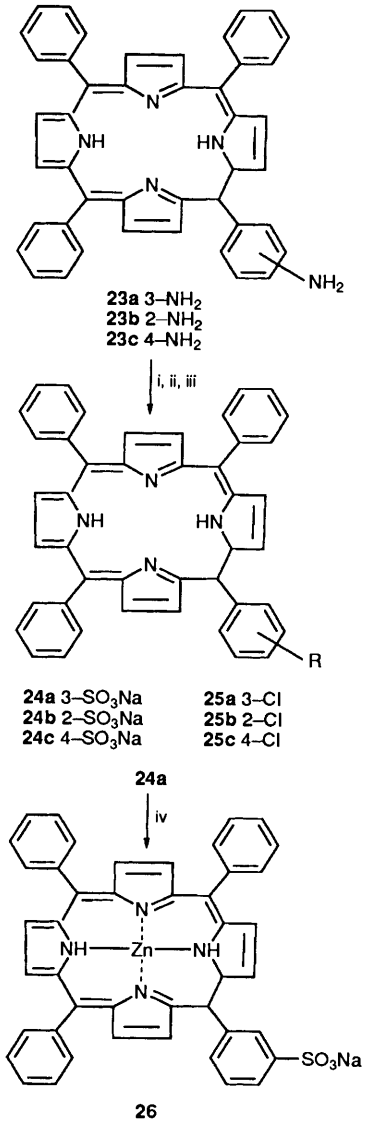
suggesting a dominant role of steric factors in the reaction mechanism (Table 3). The ratio between the 4-sulfo- and 4-chloro-phthalocyanines **5a** and **6a** was ~2:1, whereas in the case of the analogous 3-sulfo- and 3-chloro-phthalocyanines **5b** and **6b**, the latter was the major product. Furthermore, the relative amount of monosulfotetraphenylporphyrins *versus* the corresponding monochloro analogues was ~5:1 for the *para*-substituted **24c** and **25c**, 2:1 for the *meta*-substituted **24a** and **25a** and only 1:1 for the *ortho*-substituted **24b** and **25b**, reflecting the effect of the various degrees of steric hindrance on the reaction.

The degree of sulfonation of the monosulfonated products was confirmed by analytical reversed-phase HPLC. In all cases we observed a single peak with retention time *ca.* 30 min, which is characteristic for the monosulfonato derivatives.[4] It should be noted, however, that even when single HPLC peaks were observed, unresolved type isomers will be present for compounds **5a–c**, **10** and **15**, as evidenced by the broad ^1H NMR signals of the purified samples. It is evident that, owing to the general symmetry of dodecafluoro-phthalocyanine and -tetraphenylporphyrin, compounds **21**, **24a–c** and **26** were obtained



Scheme 4 *Reagents and conditions:* i, $Zn(OAc)_2 \cdot 2H_2O$; ii, 5 mol dm^{-3} HCl, reflux; iii, $NaNO_2$, HCl, 0 °C; iv, SO_2 in AcOH, $CuCl_2$; v, 1 mol dm^{-3} aq. NaOH

as single isomeric products (Scheme 5). All monosulfonates, with the exception of compound **10**, are very soluble in methanol. We observed a distinct difference in spectral properties between zinc phthalocyanines sulfonated at the 4- or 3-position (**5a** *vs.* **5b**). Compound **5b** appears to be more aggregated in methanol than is compound **5a** as demonstrated by the broadening and lower molar extinction of the Q-band (Fig. 1, Table 2).



Scheme 5 *Reagents and conditions:* i, $NaNO_2$, HCl, 0 °C; ii, SO_2 in AcOH, $CuCl_2$; iii, 1 mol dm^{-3} aq. NaOH; iv, $Zn(OAc)_2 \cdot 2H_2O$ in MeOH

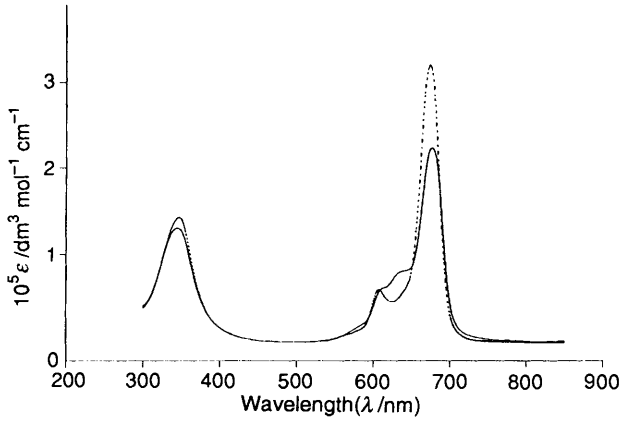


Fig. 1 UV-VIS spectra of tri(*tert*-butyl)monosulfophthalocyanines in methanol, **5a** (- - -) and **5b** (—)

The split maxima in the electronic spectra of the monosulfobenzonaphthoporphyrazine **10** in DMF at 751 nm and 733 nm are indicative of the asymmetrical character of this compound. When one of the four benzo groups in zinc tetra(*tert*-butyl)phthalocyanine is replaced by a 5-sulfonaphtho group (compound **15**), only one major absorption

Table 1 Monoaminophthalocyanines obtained from mononitrophthalocyanines

No.	Synthesis: Condensation conditions: metal salt employed, reaction temperature	Synthesis: Reduction conditions: solvent, time, yield (%)	Conditions of chromatographic purification: eluent, R_f	Molecular formula	FAB-MS	λ_{max}(DMF)/nm (log ε)
4a	$Zn(OAc)_2 \cdot 2H_2O$, 160 °C	DMF, 2 h, 65	Toluene–ethyl acetate (5:1), 0.72	$C_{44}H_{41}N_9Zn$	760 (M^+)	682 (5.35), 617 (4.68), 351 (4.95), 285 (4.61)
4b	$Zn(OAc)_2 \cdot 2H_2O$, 160 °C	DMF, 2 h, 68	Toluene–ethyl acetate (5:1), 0.7	$C_{44}H_{41}N_9Zn$	760 (M^+)	682 (5.28), 617 (4.60), 350 (5.0)
4c	CuCl, 180 °C	THF, 1 h, 95	Toluene–THF (3:1), 0.89	$C_{44}H_{41}CuN_9$	759 (M^+)	681 (5.4), 617 (4.7), 350 (5.0)
9	$Zn(OAc)_2 \cdot 2H_2O$, 190 °C	DMF, 2 h, 55	Ethyl acetate (0.88)	$C_{56}H_{47}N_9Zn$	911 (M^+)	770 (5.25), 724 (5.05), 698 (4.95), 648 (4.55), 390 (4.83)
14	$Zn(OAc)_2 \cdot 2H_2O$, 225 °C	DMF, 2 h, 60	Toluene–ethyl acetate (9:1), 0.44	$C_{48}H_{43}N_9Zn$	811 (M^+)	706 (5.21), 347 (4.87)

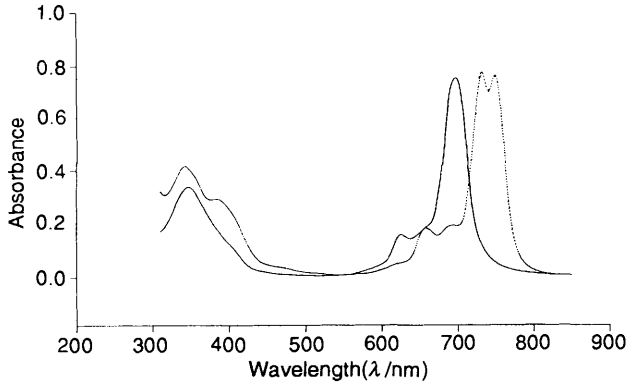


Fig. 2 UV–VIS spectra of monosulfobenzonaphthoporphyrazines in DMF, **10** (---) and **15** (—)

maximum is observed around 690 nm. This band is red-shifted relative to that of the corresponding zinc phthalocyanine (Fig. 2, Table 2). The presence of a symmetric, single absorption maximum suggests that both the molecular asymmetry and the substituents exert a synergistic effect on the absorption properties of the phthalocyanine derivatives. Similarly, the benzonaphthoporphyrazine **10**, featuring three naphtho groups and one sulfobenzo group, would be expected to have spectral properties resembling those of the corresponding zinc naphthalocyanine. Instead, we observed two bands in the naphthalocyanine absorption region (Fig. 2, Table 2). This observation is, however, in agreement with the two-fold orbital degeneracy of the excited electronic state of the metallophthalocyanines when the group of symmetry of the molecule varies from D_{4h} (zinc naphthalocyanine) to C_{2v} (*i.e.*, as in compound **10**).[10] Our spectral data for the monosulfonate **10** are similar to those reported by Margaron *et al.*[3b] for the analogous, unsubstituted aluminium monosulfobenzotrinaphthoporphyrazine.

Experimental

Materials and Methods.—FAB–MS were obtained on an LG Autospec Q mass spectrometer from the Department of Chemistry, University of Montreal. High-resolution DIP mass spectra (HR–MS) were obtained on a V9 Micro-mass Model ZAB-1F apparatus at 70 eV ionization voltage. ^1H NMR spectra were taken on a Bruker AC-300 (300 MHz) spectrometer. UV–VIS spectra were recorded with a Hitachi U-2000 spectrophotometer.

Preparative chromatography was done on 70–230 mesh silica gel (Aldrich). TLC was performed on 0.25 mm thick POLYGRAM SIL G/UV_{254} plates (Macherey-Nagel, Germany). Analytical HPLC was conducted on a 0.94 × 25 cm column (CSC, Montreal) packed with ODS-2, C-18 reversed-phase particles and operated with a linear gradient from 100% aq. sodium phosphate buffer (pH 7) to 100% methanol over a period of 25 min, followed by isocratic elution with 100% methanol for 10 min, at 1.5 $cm^3/min.^{-1}$ Eluted phthalocyanines (Pcs) and benzonaphthoporphyrazines (BNPs) were detected by their absorbance at 670–700 nm, porphyrins at 410 nm.

The following materials were obtained from a commercial source: 4-(*tert*-butyl)phthalonitrile and 4-nitrophthalonitrile (TCI America), tetrafluorophthalodinitrile, 4-(*tert*)-butyl-*o*-xylene, fumarodinitrile, *o*-, *m*- and *p*-nitrobenzaldehyde and pyrrole (Aldrich). All solvents were HPLC-grade and were used without further purification unless otherwise noted. Anhydrous-grade sulfur dioxide was purchased from Canadian Liquid Air Ltd and was used as supplied.

The following products were prepared by published methods. 3-Nitrophthalodinitrile,[11] by dehydration of the appropriate nitrobenzenedicarboxamide. 2,3-Dicyano-5-nitronaphthalene,[12] by nitration of 2,3-dicyanonaphthalene with a mixture of KNO_3 and H_2SO_4 at −10 °C. 4-Aminophthalodinitrile,[13] by hydrogenation of 4-nitrophthalodinitrile with 10% palladium on charcoal in 95% aq. ethanol. 4-Acetamidophthalodinitrile,[14] by acetylation of 4-aminophthalodinitrile with acetyl chloride in pyridine. 6-(*tert*-Butyl)-2,3-dicyanonaphthalene,[15] by condensation of α,α,α′,α′-tetrabromo-4-(*tert*-butyl)-*o*-xylene with fumarodinitrile in DMF containing sodium iodide. 5-(3-Nitrophenyl)-10,15,20-triphenylporphyrin (mono-*m*-nitroTPP),[16] 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (mono-*p*-nitroTPP),[17] and 5-(2-nitrophenyl)-10,15,20-triphenylporphyrin (mono-*o*-nitroTPP),[18] by mixed condensation of benzaldehyde, the appropriate nitrobenzaldehyde (in molar ratio 2:1) and pyrrole in glacial acetic acid, followed by chromatographic purification of the desired product. 5-(3-Aminophenyl)-10,15,20-triphenylporphyrin (mono-*m*-aminoTPP),[16] 5-(4-aminophenyl)-10,15,20-triphenylporphyrin (mono-*p*-aminoTPP),[19] and 5-(2-aminophenyl)-10,15,20-triphenylporphyrin (mono-*o*-aminoTPP),[18] by reduction of the corresponding mononitroTPP with tin(II) chloride dihydrate in conc. hydrochloric acid.

Zinc Tri(tert-*butyl*)-4-*nitrophthalocyanine* **3a**.—A mixture of 4-nitrophthalodinitrile **1a** (0.519 g, 3 mmol), the dinitrile **2** (1.656 g, 9 mmol) and zinc acetate dihydrate (2.34 g, 12 mmol) was heated at 160 °C for 3 h. Chromatography of the acetone extract

Table 2 Monosulphophthalocyanines and 10,15,20-triphenyl-5-sulphophenylporphyrins (sodium salts)

No.	Yield (%)	HPLC analysis (t_R/min)	Found[a] (Calc.)	Molecular formula	FAB–MS, m/z	λ_{max} nm (log ε) [solvent]	^{1}H NMR δ [solvent][b]
5a	55	30.8	C, 57.1; H, 4.9; S, 3.5/for M·4H_2O: (C, 57.42; H, 5.15; S, 3.48%)	$C_{44}H_{39}N_8NaO_3SZn$	848 (M^+)	674 (5.5), 607 (4.8), 347 (5.16) [MeOH]	9.63 (s, 3-sulfobenzo), 9.45–9.2 (m, 3,5-Bu^t-benzo, 5-sulfobenzo), 8.46 (d, 6-sulfobenzo), 8.36–8.26 (m, 6-Bu^t-benzo), 1.75 (s, Bu^t) [$(CD_3)_2SO$]
5b	37	30.7	C, 56.3; H, 4.8; N, 11.4; S, 3.2/for M·5H_2O:(C,56.32;H,5.26;N,11.94; S, 3.42%)	$C_{44}H_{39}N_8NaO_3SZn$	848 (M^+)	676 (5.48), 608 (4.79), 345 (5.14) [DMF]; 675 (5.36), 345 (5.03) [MeOH]	9.75 (br, 4-sulfobenzo), 9.55–9.2 (m, 5-sulfobenzo, 3,5-Bu^t-benzo), 8.6 (d, 6-sulfobenzo), 8.35–8.25 (m, 6-Bu^t-benzo), 1.75 (s, Bu^t) [$(CD_3)_2SO$]
5c	60	29.2	C, 56.5, H, 4.9; N, 11.4; S, 3.4/for M·5H_2O: (C, 56.43; H, 5.27; N, 11.96; S, 3.42%)	$C_{44}H_{39}CuN_8NaO_3S$	846 (M^+)	675 (5.56), 608 (4.82), 346 (5.11) [DMF]	
10	42	31.2	C, 65.0; H, 4.1; S, 3.62/for M·2H_2O: (C, 65.02; H, 4.77; S, 3.10%)	$C_{56}H_{45}N_8NaO_3SZn$	998 (M^+)	751 (5.20), 733 (5.21), 658 (4.56), 343 (4.92) [DMF]	9.8 (br, 3,5-sulfobenzo), 8.4 (m, 6-sulfobenzo), 8.2 (m, 6-Bu^t-naphtho), 8.0 (br, 4,7-Bu^t-naphtho), 7.85 (m, 3,8-Bu^t-naphtho), 1.8 (s, Bu^t) [$(CD_3)_2SO$]
15	52	30.6	C, 59.5; H, 4.9; S, 3.38/for M·4H_2O: (C, 59.49; H, 5.10; S, 3.30%)	$C_{48}H_{41}N_8NaO_3SZn$	897 (M^+)	698 (5.48), 628 (4.8), 348 (5.12) [DMF] 693 (5.45), 343 (5.23) [MeOH]	10.89 (d, 5-sulfonaphtho), 10.05–9.95 (dd, 6,7-sulfonaphtho), 9.5–9.25 (m, 3,5-Bu^t-benzo), 8.7 (m, 3-sulfonaphtho), 8.4–8.25 (m, 6-Bu^t-benzo), 7.8 (m, 8-sulfonaphtho), 1.75 (s, Bu^t) [$(CD_3)_2SO$]
21	45	30.4	C, 42.8; H, 1.0; N, 12.5; S, 3.0 (C, 42.96; H, 0.34; N, 12.53; S, 3.74%)	$C_{32}H_3F_{12}N_8NaO_3SZn$	874 (M^+)[c]	633, 344 (1:1) [MeOH]; 675 (5.10), 356 (4.92) [DMF]	
24a	60	29.1	C, 64.35; H, 4.0; N, 7.3; S, 3.7/for M·6H_2O: (C, 64.07; H, 5.01; N, 6.79; S, 3.89)	$C_{44}H_{29}N_4NaO_3S$	717 (M^+)	645 (3.52), 588 (3.56), 542 (3.85), 512 (4.11), 412 (5.44), 304 (4.11) (MeOH)	8.54–8.84 (8 H, m, β-pyrrole), 8.19–8.30 (6 H, m, H^o-triphenyl), 7.66–7.85 (9 H, m, H^m, H^p-triphenyl), 7.45–7.55 (4 H, m, 2 H^o, H^m, H^p-sulfophenyl) [CD_3OD]
24b	38	30.6–29.1	C, 60.45; H, 4.5; N, 6.4/for M·8H_2O: (C, 61.39; H, 5.27; N, 6.51%)	$C_{44}H_{29}N_4NaO_3S$	717 (M^+)	648 (3.64), 589 (3.66), 542 (3.93), 512 (4.06), 413 (5.43), 306 (4.22) [MeOH]	8.7–9.0 (8 H, m, β-pyrrole), 8.19–8.27 (8 H, m, 6 H^o-triphenyl + 2 H-sulfophenyl), 7.77–7.82 (11 H, m; 9 H; H^m, H^p-triphenyl + 2 H-sulfophenyl) [CD_3OD]
24c	69	29.1	C, 62.4; H, 4.8; N, 7.3; S, 3.7/for M·7H_2O: (C, 62.7; H, 5.14; N, 6.65; S, 3.80%)	$C_{44}H_{29}N_4NaO_3S$	717 (M^+)	644 (3.53), 588 (3.68), 545 (3.84), 511 (4.13), 413 (5.48) [MeOH]	8.62–8.76 (8 H, m, β-pyrrole), 8.45 (2 H, d, 4-sulfophenyl), 8.12–8.25 (6 H, m, H^o-triphenyl), 7.49–7.99 (9 H, d + m, H^m, H^p-triphenyl + 2 H, d, 4-sulfophenyl) [CD_3OD]

[a] Samples were dried at 100 °C, at 10 mmHg, for 6 h prior to analysis. [b] Explanation: *e.g.*, 3-sulfobenzo means the 3-H atom in the sulfobenzo ring. [c] For the corresponding free acid.

Table 3 Monochlorophthalocyanines and 5-(chlorophenyl)-10,15,20-triphenylporphyrins

No.	Yield (%)	R_f [toluene–ethyl acetate (9:1)]	Found (Calc.)	Molecular formula	FAB–MS [HR–MS], *m/z*
6a	25	0.75	C, 67.35; H, 5.4; N, 14.22 (C, 67.70; H, 5.04; N, 14.35%)	$C_{44}H_{39}ClN_8Zn$	779 (10%, M^+), 764 (30, $M^+ - CH_3$), 749 (10, $M^+ - 2\,CH_3$), 734 (20, $M^+ - 3\,CH_3$), 722 (100, $M^+ - C_4H_9$)
6b	33	0.75	C, 67.5; H, 5.9; N, 14.5 (C, 67.70; H, 5.0; N, 14.35%)	$C_{44}H_{39}ClN_8Zn$	779 (10%, M^+), 734 (20, $M^+ - 3\,CH_3$), 722 (100, $M^+ - C_4H_9$), 703 (35, $M^+ - C_4H_9 - CH_3$)
6c	38	0.68	C, 67.9; H, 5.35; N, 15.50 (C, 67.85; H, 5.05; N, 14.39%)	$C_{44}H_{39}ClCuN_8$	778 (15%, M^+), 721 (100, $M^+ - C_4H_9$)
11	18	0.42[a]	C, 72.9; H, 5.6 (C, 72.2; H, 4.87%)	$C_{56}H_{45}ClN_8Zn$	929 (M^+)
16	28	0.72	C, 69.3; H, 5.7; N, 12.8 (C, 69.54; H, 4.99; N, 13.53%)	$C_{48}H_{41}ClN_8Zn$	829 (M^+)
22	25	0.25	C, 47.3; H, 1.1; N, 13.4 (C, 46.49; H, 0.37; N, 13.56%)	$C_{32}H_3ClF_{12}N_8Zn$	827 (M^+)
25a	30	0.8		$C_{44}H_{29}ClN_4$	[648.2073 ± 0.0019. Calc. M, 648.2081]
25b	45	0.8		$C_{44}H_{29}ClN_4$	[648.2067 ± 0.0019. Calc. M, 648.2081]
25c	15	0.8		$C_{44}H_{29}ClN_4$	[648.2073 ± 0.0019. Calc. M, 648.2081]

[a] Toluene–pyridine 20:1.

on silica gel in toluene–ethyl acetate (9:1) furnished compound **3a** as a dark-blue solid (0.242 g, 10.2% based on **1a**): R_f 0.84; FAB–MS *m/z* 790 (82%, M^+, ^{64}Zn), 792 (100, M^+, ^{66}Zn) and 794 (64, M^+, ^{68}Zn); λ_{max}(DMF)/nm (log ε) 705 (4.64), 672 (4.89), 609 (4.3) and 349 (4.56).

Monoaminophthalocyanines **4a–c** *and Monoaminobenzonaphthoporphyrazines* **9** *and* **14** *obtained by Reduction of Mononitro Derivatives.*—In a typical reaction, a powdered mixture of *tert*-butyl-substituted naphthalenedicarbonitrile or phthalodinitrile **2** or **7** (3 mmol), a nitro derivative **1a**, **1b** or **12** (1 mmol) and metal salt (4 mmol) was heated for 3–4 h at 160–190 °C. All soluble components were extracted from the reaction mixture with chloroform–acetone and, after evaporation of the solvent, the crude mixture of mono- and poly-nitrophthalocyanines was reduced with a 3-fold excess of $Na_2S{\cdot}9H_2O$ in DMF–tetrahydrofuran (THF) at 60 °C. The reaction mixture was diluted with water, and the solids were filtered off, washed with water, air-dried, redissolved in acetone, and chromatographed on silica gel, with different solvents (Table 1), to yield the monoaminophthalocyanines **4a–c** (dark-blue crystals) and monoaminobenzonaphthoporphyrazines **9** (greenish blue crystals) and **14** (dark-green crystalline solid) (Table 1).

Zinc 2-Acetamidodecafluorophthalocyanine **19**.—A mixture of the acetamide **17** (200 mg, 1.1 mmol) dinitrile **18** (650 mg, 3.3 mmol) and zinc acetate dihydrate (858 mg, 4.4 mmol) was heated to 200–220 °C for 4 h. All soluble components were extracted from the reaction mixture with acetone. The solvent was evaporated off and the residue was chromatographed on silica gel in toluene–ethyl acetate–pyridine (1:1:0.1) to yield compound **19** as red-blue crystals (17%); R_f 0.36; FAB–MS *m/z* 850 (100%, M^+); λ_{max}(DMF)/nm (log ε) 681 (4.92) and 358 (4.54).

Zinc 2-Aminododecafluorophthalocyanine **20**.—A suspension of compound **19** in 5 mol dm^{-3} hydrochloric acid was refluxed for 12 h. The precipitate was collected by filtration, washed successively with 0.1 mol dm^{-3} aq. NaOH and water, and air-dried. The crude product was chromatographed on silica gel. Elution with ethyl acetate gave compound **20** (dark-blue powder) (R_f 0.26) (in 86% yield) (Found: C, 47.6; H, 1.3. Calc. for $C_{32}H_5F_{12}N_9Zn$: C, 47.52; H, 0.62%) FAB–MS *m/z* 807 (M^+); λ_{max}(DMF)/nm (log ε) 682 (4.90) and 358 (4.68).

Sodium Salts of Monosulfophthalocyanines, Monosulfobenzonaphthoporphyrazines and 10,15,20-*Triphenyl*-5-*sulfophenylporphyrins* (*Table* 2), *and the Corresponding Monochloro and Chlorophenyl Derivatives* (*Table* 3).—In a typical experiment, a suspension of monoamino compound (0.5 mmol) in conc. hydrochloric acid (20 cm^3) containing acetone (1 cm^3) was cooled to 0–5 °C. Aq. sodium nitrite (38 mg, 0.55 mmol in 1–2 cm^3) was added dropwise to the stirred mixture, while the temperature of the mixture was kept at 0 °C. The mixture was stirred at 0 °C for 45 min to complete the reaction. To the resulting monodiazonium salt suspension were simultaneously added, with vigorous stirring, (i) aq. copper(II) chloride dihydrate (30 mg in 1 cm^3) and (ii) glacial acetic acid (2 cm^3) saturated with sulfur dioxide (0 °C). After evolution of nitrogen had ceased, the mixture was maintained at 0 °C for an additional 15 min, diluted with water, whereafter the precipitate was collected by suction-filtration, washed with cold water, and suspended in 1 mol dm^{-3} aq. NaOH (20 cm^3). This suspension was stirred at 60 °C for 1 h, allowed to cool, and filtered to yield a solid, which was repeatedly washed with water, air-dried, and chromatographed on silica gel. Elution with toluene–ethyl acetate (5:1) gave the monochloro compounds **6a–c**, **22** (dark-blue solid), **11** (dark-green solid), **16** (dark-greenish blue powder) and **25a–c** (purple powder), whereas subsequent elution with methanol gave the pure monosulfonates **5a–c**, **21** (dark-blue crystals), **10** (dark-green crystals), **15** (dark greenish blue crystals) and **24a–c** (purple crystalline solid). Reversed-phase HPLC analysis of the latter compounds revealed a single peak in each case.

Zinc 5,10,15-*Triphenyl*-20-(3-*sulfophenyl*)*porphyrin* **26**.—A solution of compound **24a** in methanol was refluxed with an excess of zinc acetate dihydrate for 0.5 h. The solvent was evaporated off and the residue was chromatographed on silica gel. Elution with methanol gave compound **26** as purple crystals (98%) (R_f 0.88) (Found: C, 61.35; H, 3.9; N, 7.4; S, 3.6. Calc. for $C_{44}H_{37}N_4NaO_7SZn{\cdot}4H_2O$: C, 61.87; H, 4.37; N, 6.56; S, 3.75. FAB–MS *m/z* 781 (M^+); λ_{max}(MeOH)/nm (log ε) 596 (2.84), 556 (3.32), 421 (4.78), 310 (3.35) and 230 (3.0).

Acknowledgements

This work was supported by the Medical Research Council of Canada.

References

1 B. W. Henderson, J. E. van Lier, B. D. Wilson, S. L. Marcus and T. J. Dougherty, in *Cancer Therapy into the Twenty-First Century*, ed. B. S. Huber, Burroughs Wellcome Co., in the press.

2 J. E. van Lier, in *Photodynamic Therapy of Neoplastic Disease*, ed. D. Kessel, CRC Press, Boca Raton, 1990, vol. 1, pp. 279–291.
3 (*a*) S. Gaspard, P. Margaron, C. Tempête and T. H. Tran-Thi, *J. Photochem. Photobiol., B: Biology*, 1990, **4**, 419; (*b*) P. Margaron, R. Langlois, J. E. van Lier and S. Gaspard, *J. Photochem. Photobiol., B: Biology*, 1992, **14**, 187; (*c*) B. Paquette, H. Ali and J. E. van Lier, *J. Chim. Phys.*, 1991, **88**, 1113.
4 H. Ali, R. Langlois, J. R. Wagner, N. Brasseur, B. Paquette and J. E. van Lier, *Photochem. Photobiol.*, 1988, **47**, 713.
5 E. E. Gilbert, *Synthesis*, 1969, 1.
6 B. N. Achar, G. M. Fohlen, J. A. Parker and J. Keshavaya, *Polyhedron*, 1987, **6**, 1463.
7 J. M. Birchall, R. N. Haszeldine and J. O. Morley, *J. Chem. Soc. C*, 1970, 456.
8 S. A. Mikhalenko, L. I. Solov'eva, T. M. Ivanova and E. A. Luk'yanets, *Zh. Obshch. Khim.*, 1985, **55**, 1106.
9 E. E. Gilbert, *Sulphonation and Related Reactions*, Interscience, New York, 1965, p. 171.
10 S. Gaspard, M. Verdaguer and R. Viovy, *C. R. Hebd. Seanes Acad. Sci. Ser. C, 1973,* **277**, 821; K. N. Solov'ev, V. A. Mashenkov and T. F. Tachura, *Opt. Spectrosk.*, 1969, **27**, 50.
11 J. Griffiths and B. Roozpeikar, *J. Chem. Soc., Perkin Trans. 1*, 1976, 42.
12 E. I. Kovshev and E. A. Luk'yanets, *Zh. Obshch. Khim.*, 1972, **42**, 1593.
13 C. R. Rasmussen, J. F. Gardecki, J. N. Plampin, B. L. Twardzik, B. E. Reynolds, A. J. Molinari, N. Schwartz, W. W. Bennettz, B. E. Price and J. J. Markowski, *J. Med. Chem.*, 1978, **21**, 1044.
14 P. J. Brach, S. J. Grammatica, O. A. Osanna and L. Weinberger, *J. Heterocycl. Chem.*, 1970, **7**, 1403.
15 E. I. Kovshev, V. A. Puchnova and E. A. Luk'yanets, *J. Org. Chem. USSR* (*Engl. Transl.*), 1971, **7**, 364.
16 Y. Sun, A. Martell and M. Tsutsui, *J. Heterocycl. Chem.*, 1986, **23**, 561.
17 K. Arishima, T. Matsuura, H. Tsuchida and J. Shigevara, *Jap. Pat.*, 60 188 405, 1984 (*Chem. Abstr.*, 1986, **105**, 43583w.
18 J. P. Collman, J. I. Braumann, K. M. Doxsee, T. R. Halbert, E. Bunnenberg, R. E. Linder, G. E. La Mar, J. Del Gaudio, G. Lang and K. Spartalian, *J. Am. Chem. Soc.*, 1980, **102**, 4182.
19 W. J. Kruper, Jr., T. A. Chamberlin and M. Kochanny, *J. Org. Chem.*, 1989, **54**, 2753.

Paper 4/02683G
Received 5*th May* 1994
Accepted 6*th June* 1994