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Novel porphyrin–quinazoline conjugates via the Diels–Alder reaction

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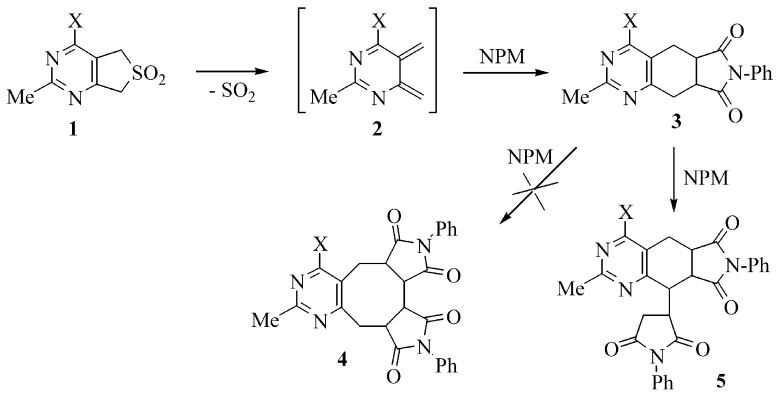
Abstract—Novel derivatives of *meso*-tetraphenylporphyrin with appended quinazoline moieties were synthesized, via the Diels–Alder reaction, between a 4-(porphyrinyl)pyrimidine *ortho*-quinodimethane and 1,4-benzoquinone, 1,4-naphthoquinone and *N*-(*p*-nitrophenyl)-maleimide. The structure of one bis adduct was established by X-ray crystallography and mass spectrometry. We have unequivocally confirmed that the 2:1 adducts obtained from the reaction of pyrimidine-fused 3-sulfolenes with *N*-arylmaleimides have an open-chain structure and not a cyclooctapyrimidine structure, as previously published.

1. Introduction

ortho-Benzoquinodimethanes, their heterocyclic analogues, and aza-*ortho*-quinodimethanes have been widely used in many synthetic routes leading to natural products or other interesting compounds. *ortho*-Quinodimethanes are transient and highly reactive dienes, which can be generated from a range of stable precursors and trapped in situ by dienophiles, yielding the corresponding Diels–Alder adducts. Several reviews on the generation and reactivity of *ortho*-quinodimethanes[1–3] and aza-*ortho*-quinodimethanes[4] are available.

A few years ago we reported the generation of pyrimidine *ortho*-quinodimethanes **2** by thermal extrusion of sulfur dioxide from pyrimidine-fused 3-sulfolenes **1** (Scheme 1).[5,6] We described then the interception of those dienes with dienophiles. In the presence of an excess of *N*-arylmaleimides, the resulting 1:1 adducts **3** are converted into a pair of diastereoisomeric 2:1 adducts. Based on the NMR spectra and in a plausible mechanistic interpretation, we proposed a cyclooctapyrimidine structure **4** for the 2:1 adducts. Later, similar 8-membered ring structures (**7** and **10**) were also proposed for the 2:1 adducts obtained in the reactions of other *ortho*-quinodimethanes with excess



Scheme 1.

Keywords: *ortho*-quinodimethanes; porphyrins; Diels–Alder reactions; X-ray crystallography.
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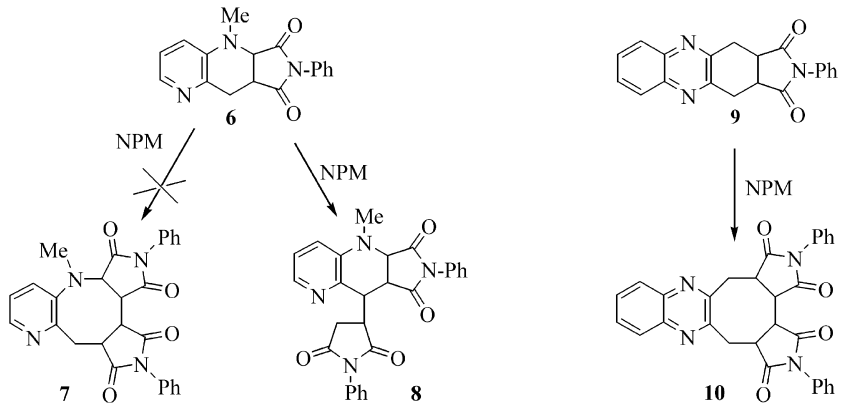


Scheme 2.

N-phenylmaleimide (Scheme 2).[7,8] In the meantime, Storr et al.[2] pointed out that our 2:1 adducts should have structure **5** and not structure **4**, and suggested that the 8-membered ring structures proposed by other groups should be reconsidered. In fact, structure **7** had already been withdrawn,[4,9] but structure **10** was confirmed.[10] Since the structural debate on these 8-membered ring structures was based on unpublished results,[11] we decided to look for solid evidence which would enable us to assign unequivocally the structures of the 2:1 adducts obtained from the pyrimidine *ortho*-quinodimethanes **2**. Based on the single-crystal X-ray diffraction of a 2:1 adduct, and the study of the mass spectra, we can now confirm that the 2:1 adducts have, in fact, structure **5**.

2. Results and discussion

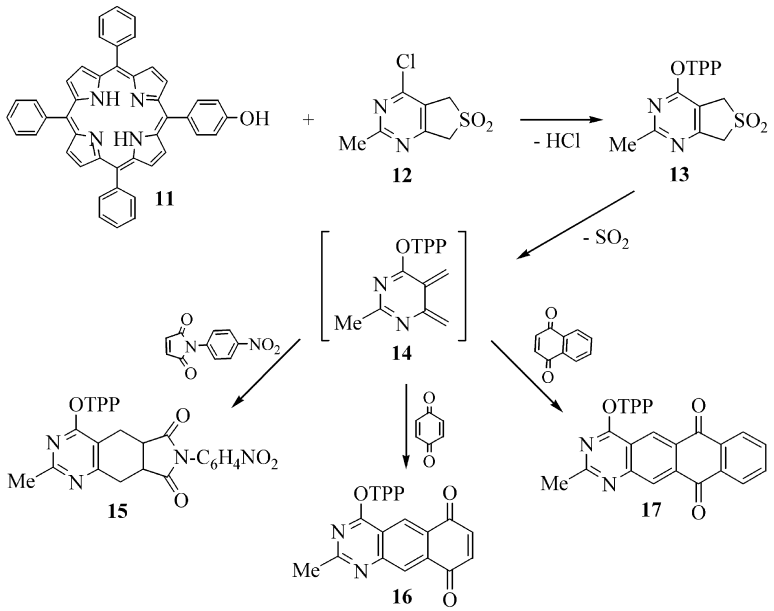
Tetrahydroquinazoline derivatives of *meso*-tetraphenylporphyrin were synthesized via the Diels–Alder reaction of quinones and maleimides with the 4-(tetraphenylporphyrinyloxy)pyrimidine *ortho*-quinodimethane **14** (Scheme 3).[12] In view of their ability to intercalate and cleave DNA,[13,14] porphyrins with planar polycyclic systems as substituents (such as **16** and **17**) are used as sensitizers in the photodynamic therapy of malignant tumours.

2.1. Synthesis of the 4-(porphyrinyloxy)pyrimidine fused 3-sulfolene 13

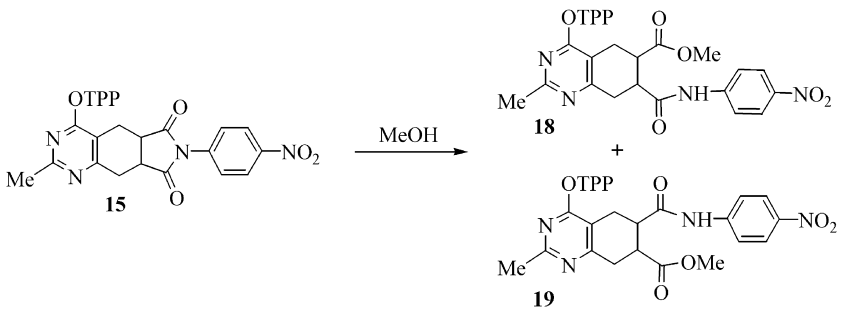
Our approach to the synthesis of sulfone **13** is based on the well-known displacement of the chlorine atom of 4-chloropyrimidines by nucleophiles.[6] In this case the nucleophile was the *meso*-(*p*-hydroxyphenyl)triphenylporphyrin (TPPOH, **11**).[15] The 4-chloropyrimidine **12** was prepared following our synthetic approach.[6] Compound **13** was obtained at 81% yield by treatment of a toluene solution of TPPOH with sodium hydride followed by addition of 4-chloropyrimidine **12**.

2.2. Thermal extrusion of sulfur dioxide from sulfone 13 in the presence of dienophiles

Pyrimidine-fused 3-sulfolenes extrude sulfur dioxide when heated in refluxing 1,2,4-trichlorobenzene, generating the corresponding pyrimidine *ortho*-quinodimethanes.[6]



Scheme 3.



Scheme 4.

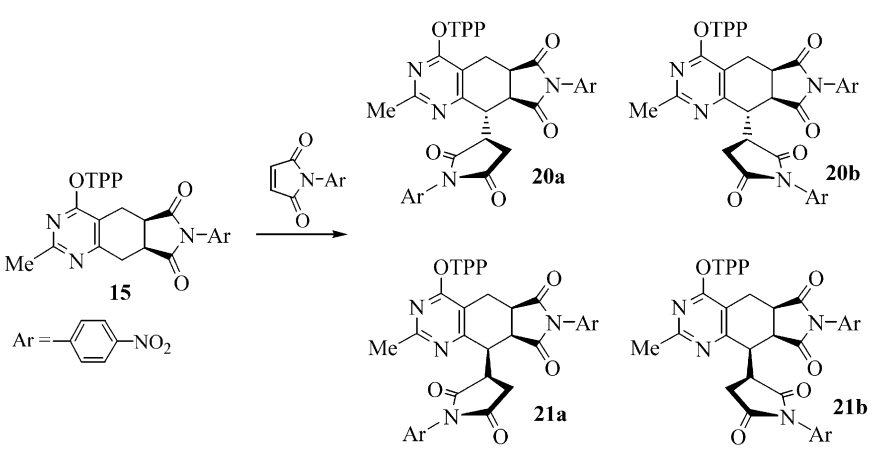
Thermolysis of sulfone **13** under these experimental conditions and in the presence of *N*-(*p*-nitrophenyl)maleimide (1.2 equiv.) afforded, after 3 h, the expected tetrahydroquinazoline **15** at 92% yield (Scheme 3). The structure of **15** was unambiguously established by ^{1}H and ^{13}C NMR and mass spectrometry.

When sulfone **13** was thermolised in the presence of 1,4-benzoquinone or 1,4-naphthoquinone the dehydrogenated compounds **16** and **17**, respectively, were obtained at high yields. The ^{1}H NMR and mass spectra of both compounds are typical of aromatic structures: the mass spectra (FAB^{+}) show parent ions at *m*/*z* 853 and 903, respectively, and, in both cases, only the singlet due to the methyl group is observed in the aliphatic region of the ^{1}H NMR spectra. Compound **16** shows an AB system at δ 6.83–6.85 ppm (J=6 Hz) due to the quinone protons; the resonances of the two protons in the quinazoline ring fall in the region of absorption of the porphyrinic protons. The ^{1}H NMR spectrum of compound **17** shows two singlets at δ 8.67 and δ 9.33 ppm due to the quinazoline protons; the signals corresponding to the other four protons appear at δ 7.73–7.79 ppm together with the resonances of the *m*- and *p*-protons of the porphyrin phenyl rings.

During an attempt to crystallize porphyrin **15** from methanol, we accidentally observed that the imide ring is easily opened by this solvent, affording a 1:1 mixture of the regioisomeric compounds **18** and **19** (Scheme 4). Both compounds show the same parent ion at *m*/*z*=999 in their mass spectra (FAB^{+}). Each ^{1}H NMR spectrum shows a singlet at ca. δ 2.6 ppm, due to the 2-methyl group, a multiplet corresponding to six protons at δ 3.00–3.60 ppm (or δ 3.06–3.63 ppm for the other isomer) due to the tetrahydroquinazoline protons, and a singlet at δ 3.82 ppm (δ 3.90 ppm for the other isomer) due to the methyl ester group.

2.3. Formation and characterization of 2:1 adducts

As discussed above, pyrimidine *ortho*-quinodimethanes give 2:1 adducts when generated in the presence of a large excess of an *N*-arylmaleimide. The question is whether these compounds have structures of type **4** or **5**. We tried unsuccessfully to obtain single-crystals of our 2:1 adducts[6] suitable for X-ray analysis but, using various 1D and 2D-NMR techniques, we have been able to establish the connectivities of all sp^3 carbons in the 2:1 adducts as $-CH_2-CHR-CHR-CHR-CHR-CH_2-$.[16] Since this sequence fits structure **4**, we originally assumed this to be the structure of the 2:1 adducts. Since questions have been raised about this assumption, we now realise that this sequence also fits structure **5**. NMR is thus unable to distinguish between these two structures, and an X-ray study is needed. Since porphyrin derivatives frequently gave crystals adequate for X-ray analysis, we decided to prepare 2:1 adducts from sulfone **13** and *N*-(*p*-nitrophenyl)maleimide hoping to obtain a suitable single-crystal. When we carried out the thermolysis of sulfone **13** in the presence of a large excess of *N*-(*p*-nitrophenyl)maleimide we obtained the 1:1 adduct **15** and two other new compounds, in the relative proportions of ca. 2:1, which were identified as 2:1 adducts **20/21** (Scheme 5). The same 2:1 adducts were also obtained from the reaction of **15** with the same maleimide in refluxing 1,2,4-trichlorobenzene. The two diastereoisomeric 2:1 adducts were separated from **15** by flash chromatography and then further purified by preparative TLC. The



Scheme 5.

Table 1. Crystal data and structure refinement information for the most abundant 2:1 adduct **20/21**

Formula	$C_{83}H_{69}Cl_9N_{10}O_9$
Formula weight	1669.53
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	19.4565(4)
b (Å)	31.9240(5)
c (Å)	13.1069(2)
β (°)	104.343(8)
Volume (Å^3)	7887.3(2)
Z	4
D_c (g cm^{-3})	1.406
μ(Mo Kα) (mm^{-1})	0.385
F(000)	3448
Crystal size (mm)	0.20×0.15×0.13
Crystal type	Dark-red blocks
θ range	3.55–22.52
Index ranges	$-20\leq h\leq 20$; $-34\leq k\leq 34$; $-13\leq l\leq 14$
Reflections collected	46850
Independent reflections	10222 (R_{int}=0.1030)
Final R indices [$I>2\sigma(I)$]	$R1$=0.1994; $wR2$=0.3543
Final R indices (all data)	$R1$=0.2528; $wR2$=0.3779
Largest diff. peak and hole	1.159 and −1.107 eÅ^3

most abundant 2:1 adduct gave adequate crystals when crystallised from a chloroform/cyclohexane mixture, which were analysed using single-crystal X-ray diffraction and formulated as [**20a**·$(CHCl_3)_3$·$(C_6H_{12})_{1.5}$] (Table 1). Interestingly, from the reaction we can expect the formation of four diastereoisomers (Scheme 5), but single-crystal data shows **20a** to be the most abundant one (Fig. 1).

Mass spectrometry studies on the same compound revealed that the product ion spectrum (Fig. 2) of the most abundant 2:1 adduct (MS/MS of $[M+H]^+$=m/z 1185) shows three structurally significant fragment ions (within the m/z range 850–1200). The most intense peak occurs at m/z 967 and is due to the loss of $C_{10}H_6N_2O_4$ (mass 218) from the precursor ion. There are also two peaks due to the loss of NO_2H (mass 47) from the precursor ion (m/z 1138) and after the loss of mass 218 (m/z 920). It is also assumed that m/z 1138 can also lose mass 218 to produce m/z 920—although there is no direct evidence for this. The loss of $C_{10}H_6N_2O_4$ can only be due to the **5** side group and would not occur from the **4** structure. This is strong evidence for the proposed structure and is in good agreement with the X-ray crystallography results.

3. Conclusion

We have unequivocally confirmed that the 2:1 adducts obtained from the reaction of pyrimidine-fused 3-sulfolenes with *N*-arylmaleimides have structures **5** and not **4**, as previously published. We have also shown that sulfone **13** can be used as a precursor for novel and interesting porphyrin–quinazoline dyads. Since other dienophiles can be used to trap the pyrimidine *ortho*-quinodimethane **14**, a range of other dyads of this type can also be prepared efficiently from a single key compound. It is expected that some of the compounds described in this paper (especially the more planar ones **16** and **17**) present some intercalating abilities, and thus, are potential candidates for DNA cleavage inducers.

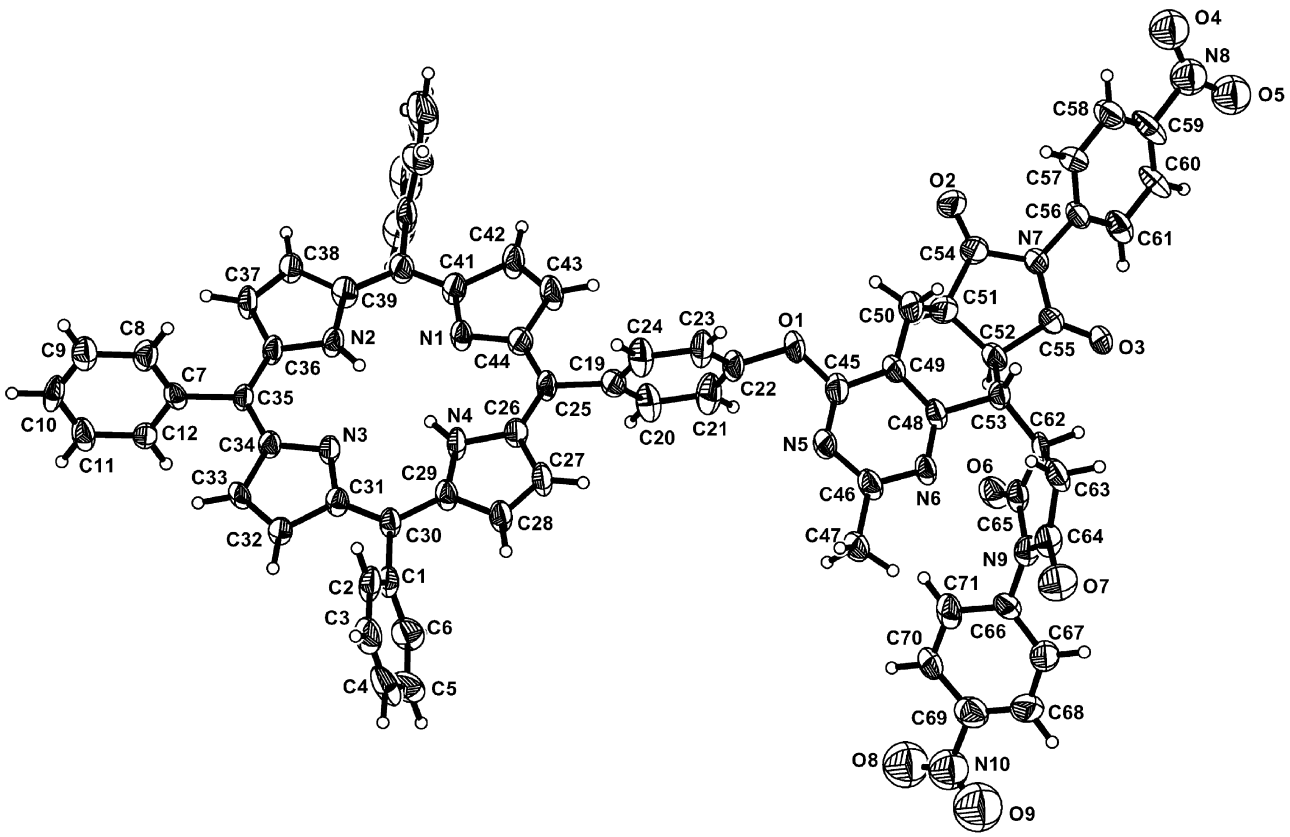


Figure 1. A view of **20a** showing the labelling scheme for all non-H atoms. Displacement ellipsoids are drawn at the 30% probability level and hydrogen atoms are shown as small spheres. Labels for the C13–C18 ring have been omitted because the atoms are eclipsed.

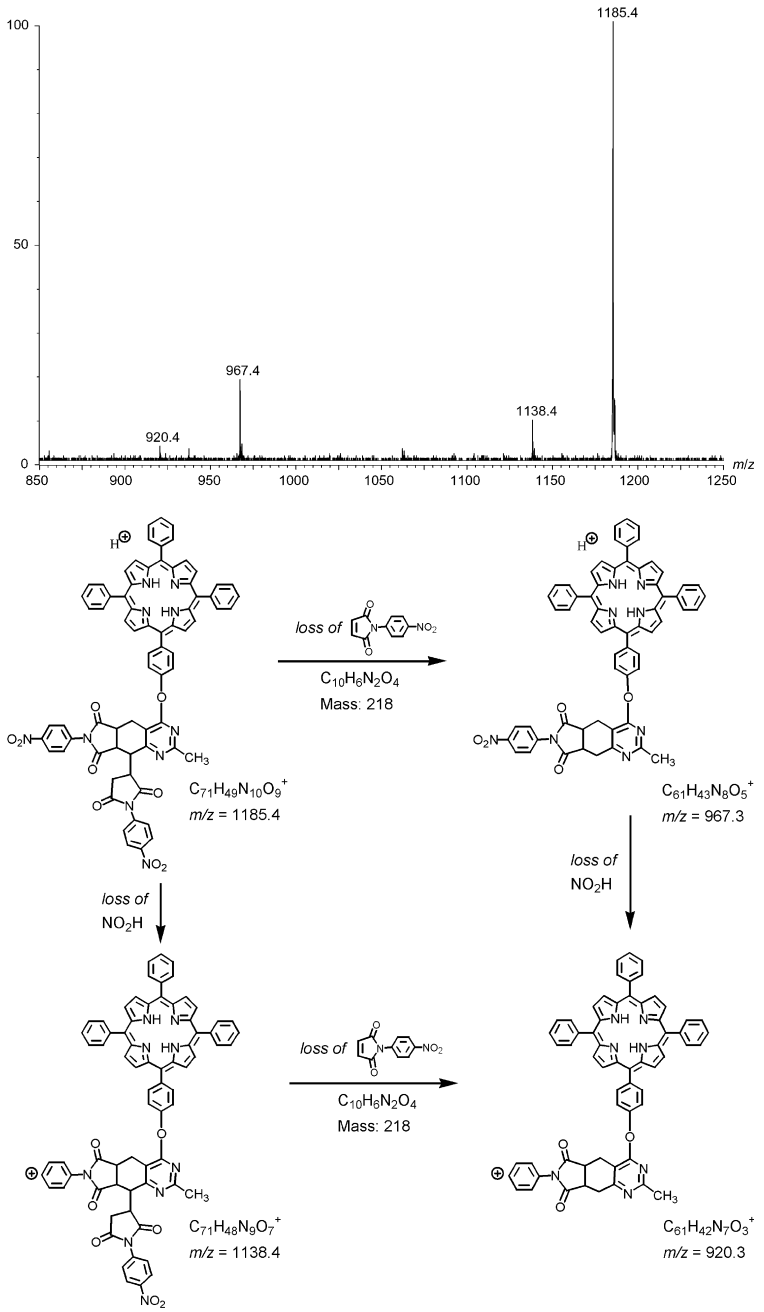


Figure 2. Portion of the MS–MS spectrum of $[M+H]^+$ (at *m/z* 1185.4) and proposed fragmentation route.

4. Experimental

The UV–Vis spectra were recorded in chloroform solution on a Kontron Instruments spectrophotometer. The NMR spectra were recorded on a Bruker AMX 300 spectrometer. Deuterated chloroform was used as solvent and TMS as internal reference. Coupling constants are in Hz. Mass spectra were recorded under FAB^+ on a VG AutoSpec-Q instrument. MS/MS analysis was performed on a Q-Tof (Micromass, Manchester, UK) using electrospray ionisation (ESI). The sample was dissolved in chloroform and infused into the ESI source at 10 μL/min from a syringe pump. Fragmentation was brought about by collision induced decomposition (CID) on the isolated parent ion (1 *m/z* isolation window) using He as the collision gas. The collision energy was tuned to produce a good product ion spectrum at the minimum energy to prevent high-energy processes from occurring. Melting points were measured on a Reichert Thermovar microscopic hot stage apparatus. Elemental analyses were performed in the microanalytical laboratory at the University of Coimbra. Preparative thin layer chromatography was carried out on 20×20 cm glass plates coated with silica gel. Reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Petroleum ether refers to the fraction boiling at 40–60°C.

4.1. Single-crystal X-ray crystallography

A suitable single-crystal of the 2:1 adduct **20/21** was manually selected and mounted on a glass fibre using perfluoropolyether oil.[17] Data were collected on a Nonius

Kappa CCD diffractometer with Mo Kα graphite-monochromated radiation (λ=0.7107 Å). The structure was solved by the direct methods of SHELXS 97,[18] and refined by full-matrix least squares on F^2 using SHELXL 97,[19] with, when possible, anisotropic displacement parameters for non-hydrogen atoms. Multi-scan absorption corrections were also applied.[20] Carbon atoms from the substituent benzyl groups attached to the porphyrin ring are characterized by large anisotropic displacement parameters, suggesting that they are affected by thermal disorder. The terminal $-NO_2$ groups from the *N*-(*p*-nitrophenyl)maleimide residues are also severely affected by thermal disorder, with the corresponding ellipsoids showing large tensors in more than one direction. Consequently, atoms from these two terminal groups have been treated with common isotropic parameters (one for the N-atoms and other for the O-atoms). All H-atoms have been placed in calculated positions, and refined using a riding model with an isotropic thermal displacement parameter, fixed at 1.2 times U_{eq} for the atom to which they are attached.

The crystal structure is perforated by channels, running parallel to the *c* direction, which account for more than one third of the total volume of the unit cell (PLATON routines indicate 2776.8 $Å^3$ as the potential solvent area volume, i.e. 35.2%). These channels contain a considerable diffuse electron density, which proved to be very difficult to resolve. Four and a half crystallographically unique solvent molecules (three molecules of $CHCl_3$, and one and a half molecule of C_6H_{12}) where successfully located from consecutive difference Fourier map syntheses, and refined with geometry heavily restrained [distances of 1.70(2) and 1.44(2) Å for the C–Cl and C–C bonds in $CHCl_3$ and C_6H_{12}, respectively]. SQUEEZE,[21] the disorder solvent area refinement tool which comes with the software package PLATON,[22] indicates that virtually all the electron density in the channels is described by the located solvent molecules. The last difference Fourier map synthesis showed a residual electron density with the highest peak (1.16 $eÅ^{-3}$) located at 0.48 Å from C76, and the deepest hole (−1.11 $eÅ^{-3}$) located at 0.51 Å from Cl8. Information concerning crystallographic data collection and structure refinement for the 2:1 adduct **20/21** is summarised in Table 1.

SQUEEZE[19] was used to completely remove the referred diffuse electron density from the existing channels in the structure. This refinement strategy only led to a small improvement in the *R*-factors [$I>2\sigma(I)$: *R1*=0.1148 and *wR1*=0.3103; all data: *R1*=0.1662 and *wR1*=0.3408], with the molecular geometry of the 2:1 adduct **20/21** remaining the same [highest peak (0.41 $eÅ^{-3}$) located at 0.82 Å from H63A, and the deepest hole (−0.38 $eÅ^{-3}$) located at 0.72 Å from O5].

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-212335. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 2EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

4.2. Synthesis of the 4-(porphyrinyloxy)pyrimidine-fused 3-sulfolene 13

Sodium hydride (19 mg, 0.80 mmol, 4 equiv.) was added to a solution of *meso*-(*p*-hydroxyphenyl)triphenylporphyrin **11** (126 mg, 0.200 mmol) in dry toluene (30 ml). After 5 min 4-chloropyrimidine fused 3-sulfolene **12** (61.2 mg, 0.280 mmol, 1.4 equiv.) was added and the mixture was stirred for 24 h at 70°C. The reaction was quenched by the addition of water and extracted exhaustively with dichloromethane. The combined organic phase was dried over anhydrous sodium sulphate, and concentrated under vacuum. The resulting solution was purified by flash chromatography (silica) using dichloromethane/acetone (95:5) as eluent. The porphyrin **13** (132 mg; 81%) was recrystallised from dichloromethane/petroleum ether. The spectroscopic data for compound **13** have already been published.[12] Anal.: found (%): C, 75.39; H, 5.05; N, 10.09; S, 4.22; calcd for $C_{51}H_{36}N_6O_3S$: C, 75.35; H, 4.46; N, 10.34; S, 3.94.

4.3. Generation and trapping of pyrimidine *ortho*-quinodimethane 14

General procedure. Sulfone **13** (0.04 mmol) and the dienophile (0.05 mmol, 1.3 equiv.; with 1,4-benzoquinone 15 equiv. were used instead), under a nitrogen atmosphere, were heated in refluxing 1,2,4-trichlorobenzene (3 ml) for 3 h. After cooling to rt, the mixture was applied to a silica column and the trichlorobenzene was eluted with petroleum ether: $CHCl_3$ (3:1). The adducts were then eluted with a more polar eluent ($CHCl_3$ or 95:5 $CHCl_3$/acetone). The main products were further purified by preparative TLC.

4.3.1. Compound 15. Obtained in 92% yield by reaction of porphyrin **13** with *N*-(*p*-nitrophenyl)maleimide. After purification by flash chromatography (silica gel, $CHCl_3$ as eluent), the adduct was crystallized from CH_2Cl_2/petroleum ether. The spectroscopic data for compound **15** have already been published.[12] Anal.: found (%): C, 76.10; H, 4.38; N, 11.53; calcd for $C_{61}H_{42}N_8O_5$: C, 75.76; H, 4.38; N, 11.59.

4.3.2. Compound 16. Obtained in 61% yield by reaction of sulfone **13** with 1,4-benzoquinone. This compound was purified by flash chromatography (silica gel, 95:5 $CHCl_3$: acetone as eluent). It was further purified by preparative TLC (silica gel, 95:5 chloroform/acetone) and recrystallised from $CHCl_3$/petroleum ether. Mp>300°C; ^{1}H NMR: δ −2.86 (s, 2H, NH), 2.86 (s, 3H, CH_3), 6.83–6.85 (AB, 2H, *J*=6 Hz, quinone-H), 7.69–7.80 (m, 11H, phenyl-*m*- and *p*-H), 8.24–8.38 (m, 9H, *phenyl-o*-H and quinazoline-H), 8.87–8.97 (m, 9H, porphyrin β-H and quinazoline-H); MS (FAB) 853 $(M+H)^+$; UV/Vis λ_{max} (log ε), 418 (5.65), 514 (4.26), 550 (3.90), 589 (3.74), 645 (3.60) nm.

4.3.3. Compound 17. Obtained in 66% yield by reaction of sulfone **13** with 1,4-naphthoquinone. The adduct was purified by preparative TLC (silica gel, $CHCl_3$ as eluent). It was recrystallized from $CHCl_3$/petroleum ether. Mp>300°C; ^{1}H NMR: δ −2.86 (s, 2H, NH), 2.89 (s, 3H, CH_3), 7.73–7.79 (m, 13H, phenyl-*m*- and *p*-H and naphtho-H), 8.19–8.25 (m, 8H, phenyl-*o*- and *m*-H), 8.37–8.40 (d, 2H, phenyl-*o*-H), 8.67 (s, 1H, quinazoline-H), 8.86–8.96

(m, 8H, porphyrin β-H), 9.33 (s, 1H, quinazoline-H); MS (FAB) 903 $(M+H)^+$; UV/Vis λ_{max} (log ε): 415 (5.38), 515 (4.26), 551 (3.91), 590 (3.74), 646 (3.63) nm; Anal.: found (%): C, 78.33; H, 4.25; N, 8.77; calcd For $C_{61}H_{38}N_6O_3 \cdot 2H_2O$: C, 78.02; H, 4.51; N, 8.95.

4.3.4. Compounds 18 and 19. These compounds were obtained by stirring a $CHCl_3$ solution of porphyrin **15** with MeOH at 60°C for 2 h. After removing the solvents under vacuum, the residue was redissolved in CH_2Cl_2 and the mixture was separated by preparative TLC (silica gel, 95:5 CH_2Cl_2/acetone as eluent). Three fractions were obtained: the less polar one corresponds to some unchanged porphyrin **15** and the others to compounds **18** and **19**. These compounds were recrystallized from CH_2Cl_2/petroleum ether.

Isomer with higher R_f: mp 289–291°C; ^{1}H NMR: δ −2.78 (s, 2H, NH), 2.65 (s, 3H, CH_3), 3.00–3.60 (m, 6H, CH_2, CH), 3.82 (s, 3H, OCH_3), 7.56–7.79 (m, 13H, phenyl-*m*- and *p*-H and $C_6H_4-NO_2$), 8.16–8.27 (m, 10H, phenyl-*o*-H and $C_6H_4-NO_2$), 8.71 (s, 1H, NH), 8.86–8.96 (m, 8H, porphyrin β-H); ^{13}C NMR: δ 24.1, 25.6, 31.8, 40.7, 41.3, 53.0, 111.9, 119.1, 119.8, 120.2, 120.3, 125.0, 126.7, 127.7, 131.2, 134.5, 135.4, 139.0, 142.1, 143.4, 143.5, 152.6, 163.6, 165.2, 166.8, 170.5, 174.5; MS (FAB) 999 $(M+H)^+$; UV–Vis λ_{max} (log ε): 416 (5.54), 514 (4.29), 549 (3.94), 590 (3.75), 646 (3.67) nm; Anal.: found (%): C, 73.92; H, 4.35; N, 10.83; calcd for $C_{62}H_{46}N_8O_6 \cdot 0.5H_2O$: C, 73.87; H, 4.70; N, 11.12.

Isomer with smaller R_f: mp 217–220°C; ^{1}H NMR: δ −2.78 (s, 2H, NH), 2.67 (s, 3H, CH_3), 3.06–3.63 (m, 6H, CH_2, CH), 3.90 (s, 3H, OCH_3), 7.54–7.79 (m, 13H, phenyl-*m*- and *p*-H and $C_6H_4-NO_2$), 8.18–8.27 (m, 10H, phenyl-*o*-H and $C_6H_4-NO_2$), 8.86–8.95 (m, 9H, porphyrin β-H and NH); ^{13}C NMR: δ 22.2, 25.7, 34.1, 40.7, 41.5, 53.0, 111.5, 119.1, 119.8, 120.2, 120.3, 125.1, 126.7, 127.7, 131.3, 134.5, 135.4, 139.0, 142.1, 143.5, 152.5, 164.1, 165.7, 166.4, 170.5, 174.9; MS (FAB) 999 $(M+H)^+$; UV–Vis λ_{max} (log ε): 417 (5.63), 514 (4.24), 549 (3.91), 590 (3.72), 645 (3.63) nm.

4.3.5. Synthesis of the 2:1 adducts 20/21. A solution of porphyrin **13** (100 mg, 0.123 mmol) and *N*-(*p*-nitrophenyl)-maleimide (250 mg, 1.15 mmol, 9.4 equiv.) in 1,2,4-trichlorobenzene, under a nitrogen atmosphere, was heated at reflux for 4 h. TLC analysis of the reaction mixture shows three main spots: one corresponding to porphyrin **15** and the other two to 2:1 adducts. The other very minor fractions were discharged. Porphyrin **15** (69%) was separated from the two less polar minor compounds **20/21** by flash chromatography (silica gel, $CHCl_3$ as eluent). These two diastereoisomers were then separated by preparative TLC (silica, $CHCl_3$ as eluent). The isomer with higher R_f was obtained at 13% yield and the isomer with smaller R_f was obtained at 7.4% yield. In order to obtain adequate crystals for X-ray crystallography from the main 2:1 adduct, this compound was recrystallised in several solvent mixtures; the best crystals were obtained from $CHCl_3$/cyclohexane. The spectroscopic data for compounds **20** and **21** have already been published.[12]

Acknowledgements

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