The Synthesis of Arylalkyne-Substituted Tetrapyrazinoporphyrazines and an Evaluation of Their Potential as Photosensitisers for Photodynamic Therapy

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New aryl-terminated octaalkynyl tetrapyrazinoporphyrazines were prepared in three steps starting from functionalised bisarylalkynyl 1,2-diones. While the *tert*-butylphenyl substituents were shown to aid solubility in organic solvents and to reduce chromophore aggregation efficiently, more hydrophilic tetrapyrazinoporphyrazines were obtained through the use of polyethylene glycol-substituted (PEG-substituted) phenyl groups. The absorption profiles and the singlet oxygen quantum yields of the acetylenic tetrapyrazinoporphyrazines were determined with a view to assess their suitability for PDT applications. In all cases the presence of the terminal aryl moieties resulted in noticeable bathochromic and hyperchromic shifts of the lowest-energy absorption maxima to 680 nm and of the extinction coefficients to beyond 320000. If magnesium is coordinated in the centre of the acetylenic tetrapyrazinoporphyrazines the compounds have singlet oxygen quantum yields of 0.40 in THF. With zinc as the central metal ion, the singlet oxygen quantum yields in the same solvent increase to 0.70. The absorption characteristics of the newly prepared chromophores, as well as their ability to generate singlet oxygen, suggest that these phthalocyanine analogues are interesting candidates as PDT-sensitisers.

Introduction

Photodynamic therapy (PDT) has received considerable attention in recent years, most notably as a valuable alternative to more conventional cancer treatments. The principle of PDT lies in the excitation of a photosensitiser embedded in the malignant tissue with external light of an appropriate wavelength. This will trigger the formation of highly reactive oxygen species, the most important being cytotoxic singlet oxygen.[1−9] Because of the enhanced light penetrability of biological tissues at longer wavelengths, an ideal PDT photosensitiser is characterised by intense absorptions at the far red end of the visible spectrum, or preferably in the near infrared (NIR). Beyond approximately 800 nm, though, the energy of the incident light becomes too low to generate singlet oxygen from ground state oxygen in a biological matrix.[1,2] Most clinical efforts are currently focused on porphyrin-based sensitisers such as haematoporphyrin (commercialised as a mixture of porphyrins under the brand name Photofrin™),[10] the haematoporphyrin prodrug 5-aminolaevulinic acid (e.g., Levulan™)[11,12] and 5,10,15,20-tetrakis(*m*-hydroxyphenyl)chlorin (Foscan™),[13−15] despite their low-intensity absorption maxima around 630 and 650 nm. To tackle this problem, more strongly absorbant phthalocyanines,[9] porphyrin isomers such as porphycenes[16−18] and expanded porphyrins such as texaphyrins[19−21] have been proposed and are currently being tested in PDT applications.

Our efforts in developing short and flexible routes to chromophores with intense absorptions in the biologically relevant window between 650 and 800 nm[22] had previously resulted in the synthesis of octaalkynyl phthalocyanines[23] and tetrapyrazino-[24] and tetraquinoxalinoporphyrazines.[25,26] The building blocks common to all of these chromophores, the readily available dialkynyl 1,2-diones **1**[27] (Figure 1), ensure that the macrocycles benefit from extended π-systems and, in comparison to non-alkynylated congeners, from the associated batho- and hyperchromically shifted absorption profiles. In addition, acetylene substitution provides a convenient synthetic handle with which to modulate the solubility properties of the chromophores by varying the terminal alkyne substituents. Capitalising on these advantages, we have developed functionalised octaalkynyl tetra[6,7]quinoxalinoporphyrazines into efficient photosensitisers and hence into promising candidates for PDT

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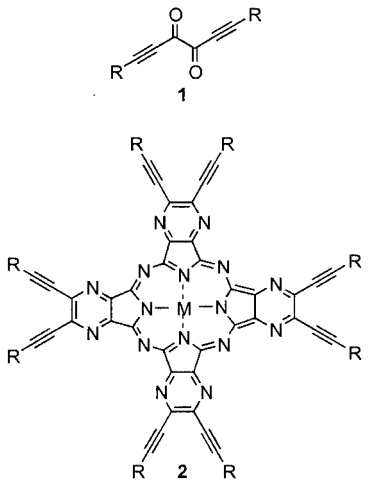
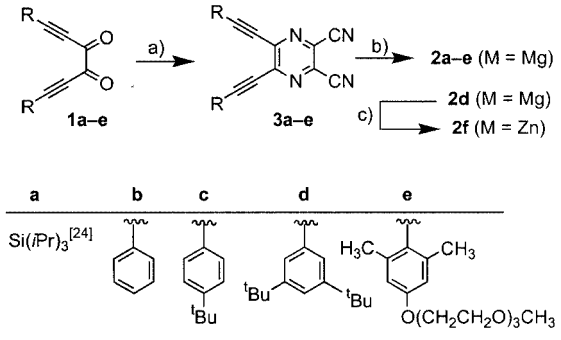


Figure 1. Dialkynyl 1,2-diones **1** and octaethynyltetrapyrazinoporphyrazines **2**

applications.[25,26] Here we report an extension of this concept to the formation of octaalkynyl tetrapyrazinoporphyrazines **2** (Figure 1).[28] As the only structural precedent for compound **2** exists in the form of lipophilic derivatives [e.g., **2a**, with R = Si(*i*Pr)$_3$, M = Mg],[24] we initially sought to implement synthetically flexible arylethynyl substituents at the peripheries of the chromophores. Subsequently, more hydrophilic derivatives of **2** were investigated and their photophysical and -chemical properties with relevance to PDT were assessed.

Results and Discussion

Synthesis of Octakis(arylethynyl)tetrapyrazinoporphyrazines: The backbone of the tetrapyrazinoporphyrazines **2** is conveniently assembled by a base-induced cyclotetramerisation of dicyanopyrazines **3**, which in turn are obtained by condensation of diaminomaleonitrile with acetylenic 1,2-diones **1** (Scheme 1).[24] We had previously developed the copper-mediated, twofold alkynylation of oxalyl chloride[27] and prepared diones **1a**−**e**.[23,26,27] Gratifyingly, problems previously encountered in the reaction between the phenyl-substituted dione **1b** and diaminomaleonitrile[27] have now been resolved, and the dicyanopyrazines **3b**−**d** were easily obtained during the course of the current study by condensation of diaminomaleonitrile with the appropriate dione **1** in acetic acid (Scheme 1). The crude products can be purified by recrystallisation and are obtained as bright golden flakes (**3b**), fine yellow needles (**3c**) or fine pale yellow needles (**3d**). The compounds are air-stable and easy to handle. The cyclotetramerisation reaction to obtain the tetrapyrazinoporphyrazine framework could be performed by heating the corresponding 2,3-dicyanopyrazines **3b**−**3d** at reflux in freshly prepared solutions of magnesium butoxide in butanol[24] to afford the magnesium complexes **2b**−**d** (Scheme 1). After removal of the solvent, the crude products are obtained as dark green solids.



Scheme 1. Synthesis of the acetylenic tetrapyrazinoporphyrazines **2b**−**e**; a) diaminomaleonitrile, AcOH, room temp., 20 min, **3b**: 76%, **3c**: 93%, **3d**: 89%, **3e**: 85%; b) Mg(OBu)$_2$, BuOH, reflux 30 min, **2d**: 42%, **2f**: 46%; c) i. 4-TosOH, THF, room temp. 30 min; ii. Zn(OAc)$_2$, THF, room temp., 10 min, 100%

The tetrapyrazinoporphyrazine **2b** is (at best) sparingly soluble in most common organic solvents such as benzene, toluene, ethyl acetate, diethyl ether, THF, methanol, acetone, hexane and DMSO. It is soluble in dichloromethane and chloroform. Even in these solvents, however, the compound aggregates significantly, a fact that prevented the acquisition of NMR data for **2b**. It also shows an extremely high affinity for silica gel and aluminium oxide and could not be eluted with any of the solvents listed above when subjected to column chromatography. As a result, we refrained from further attempts to obtain this compound in pure form, so **2b** has been characterised only by mass spectrometry and qualitative UV/Vis spectroscopy. Although the 4-*tert*-butyl-substituted derivative **2c** is somewhat more soluble in organic solvents, the problem still persists and **2c** likewise could only be characterised by mass spectrometry and qualitative UV/Vis spectroscopy.

The more extensively *tert*-butyl-substituted derivative **2d**, on the other hand, displays good solubility in organic solvents, dissolving readily in solvents such as THF, diethyl ether, ethyl acetate, acetone, dichloromethane and chloroform. We anticipate that this is due not only to the lipophilicity of the *tert*-butyl groups, but also to their steric demand, which forces the phenyl termini out of the plane of the central core, thereby preventing π-stacking and reducing chromophore aggregation.[29] Compound **2d** could be purified by flash column chromatography on silica gel, followed by gel permeation chromatography on a polystyrene resin cross-linked with divinylbenzene. No NMR data could be obtained for **2d** in deuterated chloroform due to aggregation. However, THF is known to minimise aggregation of phthalocyanines, presumably through coordination of two THF molecules to the central metal through their oxygen atoms. ^{1}H and ^{13}C NMR spectra of **2d** in THF solution could indeed be recorded, with addition of a trace of $CDCl_3$ to obtain a lock signal. The ^{13}C NMR spectrum of **2d** features, as would be expected, seven signals in the aromatic region (δ_C = 151.0, 150.1, 148.1, 141.8, 126.5, 124.1, 121.3 ppm), two acetylenic signals (δ_C = 98.6, 86.9 ppm) and two signals for the *tert*-butyl groups (δ_C = 34.5, 30.8 ppm), confirming the highly symmetric structure of **2d**. The MALDI-TOF mass spectrum of **2d** displays an isotopic cluster peaking at *m*/*z* = 2243 as the most intense signal, corresponding to the M^+ − ion.

While the above procedure allows the efficient synthesis of Mg-tetrapyrazinoporphyrazines **2**, it was deemed beneficial with regard to PDT applications to explore the incorporation of other metal ions in the central cavities of the novel dyes. In this respect, Zn^{2+} is particularly interesting, as Zn-phthalocyanines are known to have both high triplet quantum yields and long triplet lifetimes,[9] and hence display efficient singlet oxygen generation. Several attempts to convert the pyrazines **3b**−**d** into the corresponding Zn-tetrapyrazinoporphyrazines by using either urea, quinoline and $Zn(OAc)_2$,[24] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), hexanol and $Zn(OAc)_2$,[30,31] lithium pentoxide, pentanol and $Zn(OAc)_2$ [32] or *N*,*N*-dimethylethanolamine (DMAE) and $Zn(OAc)_2$ [33] did not result in the formation of the desired product. A more successful approach to the incorporation of other metal ions into the tetrapyrazinoporphyrazines was the transmetallation of the magnesium complex **2d**. Stirring a solution of **2d** in THF with an excess of 4-toluenesulfonic acid furnishes the corresponding metal-free tetrapyrazinoporphyrazine,[24] which was converted without isolation quantitatively to its zinc complex **2f** by the addition of $Zn(OAc)_2$ (Scheme 1). The ease and excellent yield of this reaction should also allow access to numerous other metal tetrapyrazinoporphyrazinato complexes.

Since hydrophilic sensitisers might be better suited than lipophilic derivatives[1,2] for PDT applications, we ventured into the synthesis of more hydrophilic tetrapyrazinoporphyrazines **2**. To this end, a structural amendment that we[26] and others[19−21] have previously implemented lies in the attachment of polyethylene glycol (PEG) chains into the *para*-positions of the peripheral phenylacetylene moieties of **2b** to confer hydrophilicity. In addition, the presence of methyl groups on the aryl rings flanking the CC triple bonds should reduce the tendency towards aggregation. Although methyl groups are smaller than the *tert*-butyl groups used to minimise aggregation in **2d**, they enforce the non-coplanarity of aryl rings and porphyrazine.

The PEGylated tetrapyrazinoporphyrazine **2e** was prepared by condensation of the acetylenic 1,2-dione **1e**[26] with diaminomaleonitrile to give the dicyanopyrazine **3e**, followed by cyclotetramerisation with magnesium butoxide in butanol (Scheme 1) to afford the desired dye **2e** as a dark green, waxy solid after purification by flash chromatography and gel permeation chromatography. PEG-substituted **2e** is soluble in organic solvents such as dichloromethane, chloroform and THF, but is not soluble in water. Unlike the purely lipophilic derivative **2d**, **2e** displays good solubility in the polar protic solvents methanol and ethanol and is suitably soluble in DMSO. No NMR data for **2e** could be obtained, due to aggregation in $CHCl_3$ and THF at higher concentrations, but the constitution and the homogeneity of this compound were unambiguously confirmed by its MALDI-TOF mass spectrum, featuring an isotopic cluster peaking at *m*/*z* = 2869 corresponding to the respective M^+ − ion, and by microanalysis.

Electronic Absorption Spectra: The electronic absorption spectra of the novel acetylenic chromophores are dominated by the two transitions typical for this class of compounds:[7] the higher-energy *B*-band absorption maximum around 400 nm and the lower-energy *Q*-band absorption maximum at approximately 670 nm (Table 1).

Table 1. *B*- and *Q*-band absorption maxima of selected acetylenic tetrapyrazinoporphyrazines

Compound	Solvent	*B*-band[a]	*Q*-band[a]
2b	THF	362	679
2c	THF	389	676
2d	THF	394 (205000)	676 (338000)
2e	THF	405 (194000)	677 (157000)
2e	DMSO	413 (189000)	684 (320000)
2f	THF	387 (211000)	673 (323000)

[a] $\lambda_{max.}$ (nm) (ε, $M^{-1}\cdot cm^{-1}$).

In the case of **2d**, the *B*-band peaks at 394 nm (ε = 205000 $M^{-1}\cdot cm^{-1}$) whereas the *Q*-band of **2d** at the far red end of the visible spectrum in THF solution (Figure 2) appears as an intense, sharp absorption peaking at 676 nm (ε = 338000 $M^{-1}\cdot cm^{-1}$). The shapes and the intensities of the absorption bands indicate that the molecules are not aggregated under these conditions. This is an important aspect with regard to PDT applications, since highly aggregated chromophores tend to be less efficient sensitisers, as aggregation shortens the triplet state lifetime and reduces the singlet oxygen quantum yield by dissipating the energy through internal conversion.[8] Comparison of the absorption spectrum of **2d** to that of the octakis(triisopropylsilyl) derivative **2a**[24] reveals that the presence of the additional eight peripheral phenyl substituents produces bathochromic shifts both of the *B*-band and of the *Q*-band absorption maxima, of about 10 nm (Figure 2). Although these bathochromic shifts are only marginal, they may be utilised to fine-tune the absorption properties of these chromophores. The electronic absorption spectrum of **2f** is similar to that of **2d** (Table 1) and is not explicitly shown here.

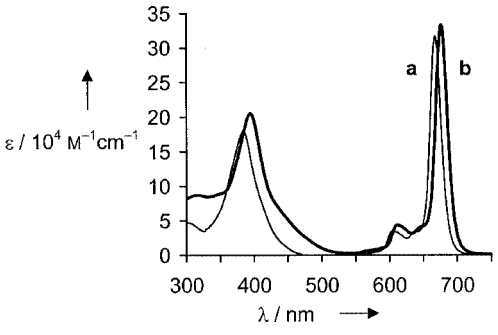


Figure 2. Electronic absorption spectra of **2a** (thin trace, a) and **2d** (thick trace, b) in THF at 298 K

The PEGylated tetrapyrazinoporphyrazine **2e** displays rather delicate aggregation behaviour. Its electronic absorp-

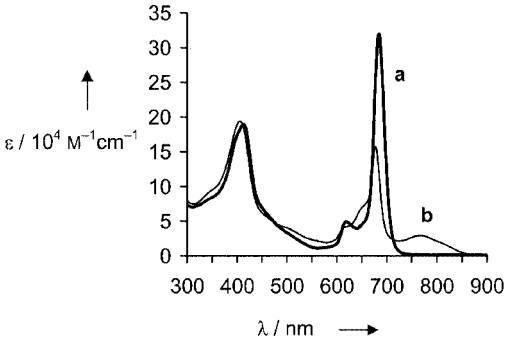


Figure 3. Electronic absorption spectra of **2e** in TFH (thin trace, a) and DMSO (thick trace, b) at 298 K, $c = 0.15 \times 10^{-1}$ M

tion spectrum in THF (depicted in Figure 3) indicates that the molecules are aggregated to a certain extent at this concentration despite the coordinating ability of THF to the central metal. This can be deduced from the comparatively low and broad absorption maxima. In the more polar (and more strongly coordinating) solvent DMSO, aggregation of **2e** is clearly averted and the shape of the absorption spectrum is similar to that of **2d**.

Singlet Oxygen Generation: The potential of the novel acetylenic tetrapyrazinoporphyrazines to act as PDT-photosensitisers was first established qualitatively through the use of 1,3-diphenylisobenzofuran (DPBF) as a singlet oxygen quencher. DPBF reacts with singlet oxygen to form an endoperoxide, which, under protic conditions, converts swiftly into 1,2-dibenzoylbenzene.[34–39] DPBF has an absorption maximum at 413 nm, whereas the photooxygenation product does not absorb light in this region. Thus, the photoinduced decay of DPBF can be conveniently followed by monitoring the absorption at 413 nm. The outcome of two such experiments is illustrated in Figure 4. Solutions of DPBF and the photosensitiser in hexan-1-ol were prepared such that the absorption at 413 nm was approximately $A = 1$. The concentrations of the photosensitiser were [PS] = 5.0×10^{-7} M in each experiment. The solutions were irradiated in quartz cuvettes at room temperature with the aid of a slide-projector halogen lamp (24 V, 250 W) with a fluence rate of 50 mW·cm^{-1}. All high-energy wavelengths (< 550 nm) were filtered out by passing the incident beam through an appropriate cut-off filter.

In order to confirm a ternary mechanism for the photodegradation (i.e., the presence of molecular oxygen, the photosensitiser and light), control experiments were carried out, in which the samples either were deoxygenated, were lacking the photosensitiser or were kept in the dark while the time-dependent absorption of DPBF was followed. As Figure 4 reveals, the DPBF absorption maximum at 413 nm decays exponentially in the presence of **2d** or **2e**, air and light. The control experiments reveal that the presence of the tetrapyrazinoporphyrazine sensitisers **2**, light and oxygen are essential for an oxidative DBPF degradation. However, some degree of photobleaching (i.e., a DBPF decay in the absence of oxygen) is observed in the case of **2d**. Profiles similar to that of **2d** were obtained for the silyl-substituted derivative **2a** and the zinc complex **2f**, with the decay in the

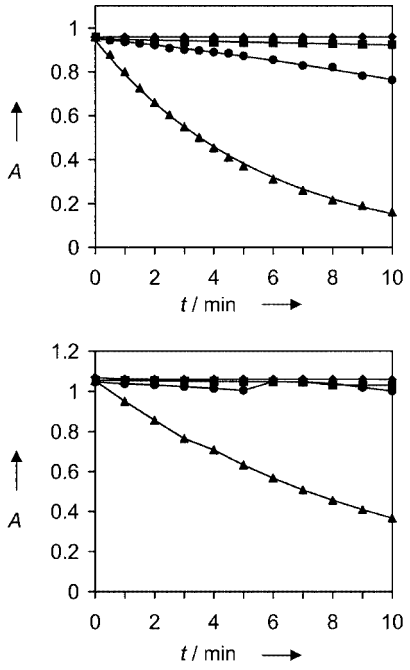


Figure 4. Photooxidation of 1,3-diphenylisobenzofuran (DPBF) with **2d** (top) and **2e** (bottom) in aerated hexan-1-ol at 298 K; c_o (DPBF) = 4.5×10^{-5} M; c_o (**2d**, **2e**) = 5.0×10^{-7} M; light source: slide projector lamp (24 V, 250 W), cut-off filter for wavelengths below 550 nm; the absorption at 413 nm was monitored (▲); in the absence of light (◆); in the absence of **2d** and **e** (■); in the absence of oxygen (●)

presence of **2f** being significantly faster. The somewhat slower DPBF-decay rate in the presence of **2e** in relation to that of **2d** is explained by the fact that **2e** is aggregated in hexanol.

The efficiency with which the acetylenic tetrapyrazinoporphyrazines can generate singlet oxygen was quantified by determination of their singlet oxygen quantum yields through $^1O_2$-phosphorescence measurements in THF (Table 2). Both the lipophilic and the more hydrophilic magnesium tetrapyrazinoporphyrazines **2d** and **2e** have very satisfactory singlet oxygen quantum yields of approximately 0.4. However, the value obtained for **2e** should be treated with some caution, since this sensitiser aggregates in THF, which will reduce its efficiency as a singlet oxygen producer. The values obtained for **2d** and **2e** compare favourably with

Table 2. Fluorescence lifetimes τ_f, fluorescence quantum yields Φ_f and singlet oxygen quantum yields Φ_Δ of selected octakis(arylalkynyl)tetrapyrazinoporphyrazines

Compound[a]	τ_f/ns	Φ_f[b]	Φ_Δ [c]
2d	4.5±0.1	0.65	0.38
2e	4.1±0.1	0.47	0.43
2f	2.0±0.1	0.31	0.70

[a] All measurements were performed in aerated THF at 298 K. [b] Absolute values (±10%) relative to cresyl violet in MeOH (Φ_f = 0.54) and disulfonated aluminium phthalocyanines in H_2O (Φ_f = 0.40). [c] Obtained by time-resolved phosphorescence measurements with excitation at λ_{ex} = 355 nm. Values are relative to perinaphthenone (Φ_Δ = 0.97) and have an error of ±10%.

that obtained for sulfonated aluminium phthalocyanine (Φ_Δ = 0.36 in MeOD),[2] a sensitiser currently in clinical trials for use as a PDT agent. The singlet oxygen quantum yield obtained for the zinc tetrapyrazinoporphyrazine **2f** (Φ_Δ = 0.70) is remarkable and considerably exceeds that of sulfonated aluminium phthalocyanine. The singlet oxygen quantum yield of **2f** is also higher than that of the approved PDT-sensitisers Photofrin™ **1** (Φ_Δ = 0.57 in benzene)[2] and Foscan™ **2** (Φ_Δ = 0.46 in methanol).[40] Compound **2f** is also superior to sulfonated zinc phthalocyanine (Φ_Δ = 0.43 in methanol),[2] a compound structurally related to **2f** that is being considered as a PDT dye. These results suggest that the tetrapyrazinoporphyrazine photosensitisers presented here are interesting candidates as PDT agents and encourage further studies about their suitability for PDT. It is noteworthy that the somewhat lower singlet oxygen quantum yields of the magnesium complexes **2a**−**e** are combined with good fluorescence quantum yields, a finding that suggests that these dyes could find use as diagnostics in fluorescence imaging.

Conclusions

The dialkynyl 1,2-diones **1** represent a flexible synthetic building block for the preparation of octakis(arylethynyl)tetrapyrazinoporphyrazines. It has been shown that the solubility and the aggregation behaviour of the novel chromophores can be modified by alteration of the substitution pattern of the peripheral phenyl groups and that both lipophilic and more hydrophilic derivatives can be conveniently prepared by this synthetic methodology. In the corresponding UV/Vis spectra, the *Q*-bands of aryl-substituted tetrapyrinoporphyrazines appear as sharp, intense absorptions, with absorption maxima bathochromically shifted by approximately 10 nm relative to that of the previously reported corresponding silyl-substituted derivative **2a** and by 40 nm relative to those of non-acetylenic tetrapyrazinoporphyrazines. Qualitative and quantitative measurements confirm that the tetrapyrazinoporphyrazines **2** are efficient singlet oxygen generators.

Overall, the flexible synthesis, the adjustable solubility, the intensive absorption in the far red region of the visible and their good singlet oxygen quantum yields make such tetrapyrazinoporphyrazines interesting candidates as photosensitisers in PDT and suggest a more detailed investigation for their suitability as PDT agents. Work in this direction is currently underway in our laboratory.

Experimental Section

General: All reactions were conducted in oven-dried glassware under argon. Unless otherwise indicated, all reagents were purchased from commercial suppliers and were used as received. Known starting materials that were not commercially available were prepared according to literature procedures, cited in the text. Solvents were purified and dried by customary procedures:[41] THF was distilled from sodium/benzophenone under nitrogen; butanol was heated at reflux with iodine-activated magnesium, distilled and stored under argon over molecular sieves (4 Å). Analytical thin-layer chromatography was carried out on precoated, aluminium-backed, silica 60 F_{254} plates (E. Merck + Co.) and the spots were viewed under UV light. Flash column chromatography was performed under positive pressure from a compressed air line on silica 60, supplied by BDH (230−400 mesh). Gel permeation chromatography was performed with a polystyrene resin cross-linked with divinylbenzene (Bio-beads 1-SX®, Bio-Rad, Munich), pre-swollen in THF. Melting points were determined with a Reichert hot-stage and are uncorrected. ^{1}H NMR spectra were recorded with Bruker AMX 300, Bruker AMX 400 and Bruker DRX 500 instruments in $CDCl_3$, [D_6]acetone or THF/$CDCl_3$. Residual protic solvent $CHCl_3$ (δ_H = 7.24 ppm) or $CD_3C(O)CD_2H$ (δ_H = 2.04 ppm) was used as internal reference. ^{13}C NMR spectra were recorded with the two more powerful instruments, operating at frequencies of 100.5 MHz and 125.6 MHz, respectively, with use of the central signals of $CDCl_3$ (δ = 77.0 ppm) or [D_6]acetone (δ = 29.8 ppm) as reference signals. IR spectra were taken on Perkin−Elmer 1600 FT-IR and Shimadzu FTIR-8700 spectrometers either as KBr discs or in chloroform solution. UV/Vis spectra were taken with a Perkin−Elmer Lambda 40 instrument; absorption maxima ($\lambda_{max.}$) in nm; extinction coefficients ε in $M^{-1}\cdot cm^{-1}$. Mass spectra were recorded with a VG ZAB SE instrument (EI and FAB ionisation). MALDI-TOF mass spectrometry was carried out with a Fisons VG TOF Spec or a Bruker Biflex III Reflectron MALDI-TOF mass spectrometer with *trans*-3-indolylacrylic acid as matrix. Microanalyses were carried out with a Perkin−Elmer 2400 CHN machine.

Fluorescence spectra were recorded with a Jobin−Yvon Fluorolog FL3−22 spectrofluorimeter. Fluorescence quantum yields were determined from the integrated emission spectra relative to cresyl violet in methanol (Φ_f = 0.54)[42] and disulfonated aluminium phthalocyanine in water (Φ_f = 0.40).[43] Fluorescence lifetimes were recorded by time-correlated single photon counting with a pulsed 635 nm laser as the excitation source. The equipment used for this measurement has been fully described elsewhere.[44] Singlet oxygen quantum yields were recorded by time-resolved phosphorescence measurements by use of the method described by Nonell and Braslavsky[45] with 355 nm excitation and perinaphthenone as a standard (Φ_Δ = 0.97).[46]

[2,3,9,10,16,17,23,24-Octakis(phenylethynyl)tetrapyrazinoporphyrazinato]magnesium(II) (2b): A suspension of Mg turnings (49 mg, 2.0 mmol), one small crystal of iodine and butanol (5 mL) was heated at reflux for 4 h. The reaction mixture was then cooled to room temperature, and dicyanopyrazine **3b** (165 mg, 0.5 mmol) was added in one portion. The reaction mixture was quickly reheated to reflux for 30 min. After approximately 5 min, the reaction mixture had become dark green. The mixture was cooled and the solvent was removed in vacuo (Kugelrohr), yielding the crude product as a dark green solid. Because of its poor solubility, this compound could not be further purified. UV/Vis (THF): $\lambda_{max.}$ = 362, 679 nm. FAB-MS: *m*/*z* (%) = 1347 (4.8) $[MH]^+$. MALDI-TOF-MS isotopic cluster peaking at *m*/*z* = 1346 $[M]^+$.

[2,3,9,10,16,17,23,24-Octakis(4-*tert*-butylphenylethynyl)tetrapyrazinoporphyrazinato]magnesium(II) (2c): The tetrapyrazinoporphyrazine **2c** was prepared from the dicyanopyrazine **3c** (221 mg, 0.5 mmol) analogously to **2b**, yielding the crude product as a dark green solid. Because of its poor solubility, **2c** could not be purified. UV (THF): $\lambda_{max.}$ = 389, 676 nm. MALDI-TOF-MS: isotopic cluster peaking at *m*/*z* = 1796 $[M]^+$.

[2,3,9,10,16,17,23,24-Octakis{3,5-di(*tert*-butyl)phenylethynyl}tetrapyrazinoporphyrazinato]magnesium(II) (2d): The tetrapyrazinopor-

phyrazine **2d** was prepared from the dicyanopyrazine **3d** (277 mg, 0.5 mmol) analogously to **2b**. The crude product was purified by flash chromatography (CH_2Cl_2 → 20% Et_2O in CH_2Cl_2), followed by gel permeation chromatography, with THF, yielding the product as dark green solid (117 mg, 52 μmol, 42%). M.p. > 300 °C. UV (THF): $\lambda_{max.}$ (ε) = 317 (87000), 394 (205000), 612 (44000), 676 nm (338000). IR (KBr): $\tilde{\nu}_{max.}$ = 2956 (CH), 2202 (C≡C) cm^{-1}. ^1H NMR (400 MHz, THF/$CDCl_3$): δ = 1.43 [s, 144 H, $C(CH_3)_3$], 7.64 (s, 8 H, CH), 7.79 (s, 16 H, CH) ppm. ^{13}C NMR (100.5 MHz, THF/$CDCl_3$): δ = 30.8, 34.5, 86.9, 98.6, 121.3, 124.1, 126.5, 141.8, 148.1, 150.1, 151.0 ppm. MS (MALDI-TOF) isotopic cluster peaking at *m/z* = 2243 $[M]^+$. $C_{152}H_{168}MgN_{16}\cdot 2H_2O$: calcd. C 80.1, H 7.6, N 9.8; found C 79.6, H 7.7, N 9.4.

[2,3,9,10,16,17,23,24-Octakis{4-{[(methoxyethoxy)ethoxy]ethoxy}-2,6-dimethylphenylethynyl}tetrapyrazinoporphyrazinato]-magnesium(II) (2e): Tetrapyrazinoporphyrazine **2e** was prepared from dicyanopyrazine **3e** (200 mg, 0.28 mmol) analogously to **2b**. The crude product was purified by flash chromatography, impurities first being eluted with THF/CH_2Cl_2 (3:1), the dark green band then being eluted with THF/MeOH (4:1); dark green, waxy solid (93 mg, 32 μmol, 46%). An analytically pure sample was obtained by gel permeation chromatography (THF). UV (DMSO) $\lambda_{max.}$ (ε) = 413 (189000), 618 (49000), 684 nm (320000). IR (KBr): $\tilde{\nu}_{max.}$ = 2870 (CH), 2187 (C≡C), 1107 (C−O) cm^{-1}. MS (MALDI-TOF): isotopic cluster peaking at *m/z* = 2869 $[M]^+$. $C_{160}H_{184}N_{16}O_{32}Mg\cdot 2H_2O$: calcd. C 66.2, H 6.55, N 7.7; found C 66.5, H 6.6, N 7.8.

[2,3,9,10,16,17,23,24-Octakis{3,5-di(*tert*-butyl)phenylethynyl}-tetrapyrazinoporphyrazinato]zinc(II) (2f): *p*-Toluenesulfonic acid (285 mg, 1.5 mmol) was added to a solution of the Mg-tetrapyrazinoporphyrazine **2d** (70 mg, 31 μmol) in THF (15 mL) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then poured into a suspension of $Zn(OAc)_2$ (283 mg, 1.5 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 10 min. The solvent was evaporated in vacuo and the residue was subjected to flash chromatography (20% Et_2O in CH_2Cl_2), yielding the product as a dark green solid (71 mg, 31 μmol, 100%). M.p. > 300 °C. UV (THF) $\lambda_{max.}$ (ε) = 289 (40000), 387 (211000), 611 (44000), 673 nm (323000). IR (KBr): $\tilde{\nu}_{max.}$ = 2958 (CH), 2201 (C≡C) cm^{-1}. ^1H NMR (400 MHz, THF/$CDCl_3$): δ = 1.37 [s, 144 H, $C(CH_3)_3$], 7.59 (s, 8 H, CH), 7.74 (s, 16 H, CH) ppm. ^{13}C NMR (100.5 MHz, THF/$CDCl_3$): δ = 29.7, 33.5, 85.6, 97.3, 120.1, 123.0, 125.4, 140.7, 146.5, 149.7, 149.9 ppm. MS (MALDI-TOF): isotopic cluster peaking at *m/z* = 2284 $[M]^+$. $C_{152}H_{168}N_{16}Zn\cdot 2H_2O$: calcd. C 78.65, H 7.45, N 9.65; found C 78.1, H 7.45, N 9.15.

5,6-Bis(phenylethynyl)pyrazine-2,3-dicarbonitrile (3b): Diaminomaleonitrile (110 mg, 1.0 mmol) was added in one portion at room temperature to a solution of dione **1b**[27] (330 mg, 1.0 mmol) in AcOH (20 mL). The reaction mixture was stirred for 20 min, during which a yellowish precipitate formed. The solvent was removed in vacuo to give the crude product as a brownish solid. Recrystallisation from MeCN afforded the pure product as bright golden flakes (251 mg, 0.76 mmol, 76%). M.p. 212−213 °C (decomp.). UV (CH_2Cl_2): $\lambda_{max.}$ (ε) = 241 (20800), 280 (15600), 324 (24100, 378 nm (29400). IR ($CHCl_3$): $\tilde{\nu}_{max.}$ = 3026 (CH), 2256 (C≡C), 2209 (C≡N) cm^{-1}. ^1H NMR (300 MHz, [D_6]acetone): δ = 7.51−7.79 (m, 10 H, CH) ppm. ^{13}C NMR (125.6 MHz, [D_6]acetone): δ = 85.3, 102.1, 113.8, 120.5, 129.6, 131.1, 131.8, 133.0, 143.6 ppm. EI-MS (70 eV): *m/z* (%) = 330 (100, $[M]^+$). $C_{22}H_{10}N_4$ (330.3): calcd. C 80.0, H 3.05, N 16.95; found C 80.25, H 2.75 N 16.9.

5,6-Bis(4-*tert*-butylphenylethynyl)pyrazine-2,3-dicarbonitrile (3c): The pyrazine **3c** was prepared analogously to the pyrazine **3b** from the dione **1c**[23] (370 mg, 1.0 mmol), by addition of THF (5 mL) to the reaction mixture in order to dissolve the starting dione. The crude product was recrystallised from *i*PrOH, affording the title compound in pure form as yellow needles (409 mg, 0.93 mmol, 93%). M.p. 192 °C. UV (CH_2Cl_2): $\lambda_{max.}$ (ε) = 246 (26800), 283 (15400), 340 (31800), 393 nm (36400). IR $_{max.}$ ($CHCl_3$): $\tilde{\nu}_{max.}$ = 3017 (CH), 2971 (CH), 2203 (C≡N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 18 H, CH_3), 7.45 (d, *J* = 8.4 Hz, 4 H, CH), 7.61 (d, *J* = 8.4 Hz, 4 H, CH) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 31.0, 35.2, 85.1, 104.3, 112.7, 117.1, 126.0, 129.5, 132.7, 143.8, 1553 ppm. EI-MS (70 eV): *m/z* (%) = 442 (56.2) $[M^+]$, 427 (100) $[M - CH_3]^+$. $C_{30}H_{26}N_4$ (442.6): calcd. C 81.4, H 5.9, N 12.6; found C 81.35, H 5.7, N 12.65.

5,6-Bis[3,5-di(*tert*-butyl)phenylethynyl]pyrazine-2,3-dicarbonitrile (3d): The pyrazine **3d** was prepared analogously to the pyrazine **3b** from the dione **1d**[23] (482 mg, 1.0 mmol), by addition of THF (5 mL) to the reaction mixture and warming gently in order to dissolve the starting dione. The crude product was recrystallised from *i*PrOH, affording the pure product as pale yellow needles (493 mg, 0.89 mmol, 89%). M.p. 243−246 °C (dec.). UV (CH_2Cl_2): $\lambda_{max.}$ (ε) = 245 (24900), 280 (15600), 340 (31800), 387 nm (29800). $IR_{max.}$ ($CHCl_3$): $\tilde{\nu}_{max.}$ = 3032 (CH), 2971 (CH), 2210 (C≡N). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 36 H, CH_3), 7.47 (d, *J* = 1.9 Hz, 4 H, CH), 7.55 (t, *J* = 1.9 Hz, 2 H, CH) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 31.2, 34.9, 84.1, 105.5, 112.7, 119.2, 126.0, 126.8, 129.6, 143.9, 151.6 ppm. EI-MS (70 eV): *m/z* (%) = 554 (52.6) $[M]^+$, 483 (100) $[M - CH_3 - C(CH_3)_3 + H]^+$. $C_{38}H_{42}N_4$ (554.8): calcd. C 82.25, H 7.65, N 10.1; found C 82.35, H 7.7, N 10.0.

5,6-Bis[4-{[(methoxyethoxy)ethoxy]ethoxy}-2,6-dimethylphenylethynyl]pyrazine-2,3-dicarbonitrile (3e): Diaminomaleonitrile (55 mg, 0.5 mmol) was added to a solution of the dione **1e**[26] (319 mg, 0.5 mmol) in AcOH (10 mL) and the reaction mixture was stirred at room temperature for 20 min. Removal of the solvent in vacuo left a brown oil, which was subjected to flash chromatography (CH_2Cl_2/EtOAc 2:1 → 1:2), yielding the title compound as a waxy, yellow solid (302 mg, 0.43 mmol, 85%). An analytically pure sample was obtained by recrystallisation from EtOH. M.p. 78−80 °C. UV (CH_2Cl_2): $\lambda_{max.}$ (ε) = 259 (40700), 423 nm (38000). IR (KBr): $\tilde{\nu}_{max.}$ = 2883 (CH), 2185 (C≡N), 1148 (C−O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 12 H, CH_3), 3.36 (s, 6 H, CH_3), 3.53 (m, 4 H, OCH_2), 3.65 (m, 8 H, OCH_2), 3.71 (m, 4 H, OCH_2), 3.83 (t, *J* = 4.8 Hz, 4 H, OCH_2), 4.12 (t, 4 H, t, *J* = 4.8, OCH_2), 6.61 (s, 4 H, CH) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.2, 59.0, 67.4, 69.5, 70.5, 70.6, 70.8, 71.9, 92.4, 102.4, 112.5, 112.9, 113.5, 129.2, 143.5, 144.2, 160.6 ppm. EI-MS (70 eV): *m/z* (%) = 710 (4.3) $[M]^+$, 59 (65.0) $[CH_3OCH_2CH_2]^+$, 28 (100) $[CH_2CH_2]^+$. $C_{40}H_{46}N_4O_8$: calcd. C 67.6, H 6.5, N 7.9; found C 67.4, H 6.6, N 7.9.

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