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Zinc azaphthalocyanines with thiophen-2-yl, 5-methylthiophen-2-yl and pyridin-3-yl peripheral substituents: Additive substituent contributions to singlet oxygen production

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ABSTRACT

The syntheses of five pyrazine-2,3-dicarbonitriles, substituted with combinations of electron donating substituents, namely 5-methylthiophen-2-yl or thiophen-2-yl and the electron withdrawing substituent pyridin-3-yl, are reported. The compounds were obtained from the condensation of diaminomaleonitrile and vicinal dicarbonyl compounds. Cyclotetramerizations of the monomers with both $Zn(OAc)_2$ and $Zn(quinoline)_2Cl_2$, realised substituted zinc azaphthalocyanines (ZnAzaPcs). The UV–vis spectra of these macrocycles revealed that thiophene and methylthiophene peripheral substituents induce substantial, red shifted Q-band absorptions from 636 nm for unsubstituted ZnAzaPc to 679 nm for octa(5-methylthiophen-2-yl)ZnAzaPc. This effect is substituent-specific and additive since the observed red shift for the Q-band of tetra(5-methylthiophen-2-yl)-tetra(pyridin-3-yl)ZnAzaPc is close to the calculated contribution from each substituent. Singlet oxygen quantum yields (Φ_Δ) varied according to the peripheral substituent on ZnAzaPc and was also substituent-specific and additive. Whereas singlet oxygen production increased, the fluorescence quantum yield decreased with increasing number of substituents on ZnAzaPc; however, no quantitative relationship was found for Φ_F and substitution patterns for the zinc complexes. Improved solubility was observed for unsymmetrical ZnAzaPcs, substituted with push–pull peripheral substituents.

1. Introduction

Efficient photodynamic therapy (PDT) requires sensitizers with good solubility in organic solvents, strong UV–vis absorption in the vicinity of 700 nm, and the ability to induce significant production of singlet oxygen. Dyes of various kinds have shown promise as sensitizers for PDT [1–3]. Some of our recent studies have shown that tetrapyrazinoporphyrazines, a class of azaphthalocyanines (AzaPcs), have several of the above mentioned properties, and consequently might be of use in PDT. AzaPcs are derivatives of porphyrazine [4]; formally obtained from a condensation of the porphyrazine skeleton with various azaheterocycles. AzaPcs are closely related to phthalocyanines (Pc) as well; some of the benzene carbon atoms of the Pc macrocycle have been replaced by nitrogen atoms [5]. Generally, this interesting class of dyes has found use in several applications, due to non-linear optical behaviour [6], metal binding [7] or catalytic properties [8].

Octasubstituted zinc azaphthalocyanines (ZnAzaPcs) with peripheral thiophen-2-yl and alkylsulfanyl groups have qualities which are promising for their potential use in PDT [9,10]. Thiophene and alkylsulfanyl substituents on ZnAzaPc induce red shifted Q-bands, *i.e.* from 635 nm for unsubstituted ZnAzaPc to ca. 670 nm. However, alkylsulfanyl substituents are somewhat labile under certain conditions for syntheses of these macrocycles [11], whereas thiophene is not, due to the carbon–carbon bond between substituent and macrocycle. The Q-band of octa(pyridin-2-yl) substituted ZnAzaPc is found at 657 nm [10], *i.e.* pyridine induces a substantially less red shifted Q-band than thiophene. Singlet oxygen quantum yields show significant dependence on peripheral heterocyclic substituents as well.

These results, and other studies [12,13] strongly indicate that substituent effects, such as Q-band positions and singlet oxygen quantum yields, may be additive functions of the peripheral substituents on AzaPc. Therefore, in this work, we have

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investigated ZnAzaPc with thiophen-2-yl, 5-methylthiophen-2-yl and pyridin-3-yl substituents and tried to reveal the relationships that may influence the photophysical properties of AzaPcs. The solubility of ZnAzaPc in most organic solvents is significantly enhanced by alkylsulfanyl, and in particular *tert*-butylsulfanyl substituents. Methylthiophene substituted macrocycles are therefore expected to be more soluble than thiophene substituted analogues as well. Zinc chelated to the centre of the AzaPc macrocycle lengthens the triplet state lifetime and therefore significantly increases the singlet oxygen quantum yields. Therefore, zinc was chosen, both in order to find a wider spread in singlet oxygen quantum yields, and to find the most promising compound for PDT application.

2. Experimental

2.1. Materials and methods

Electron impact (EI) mass spectra, or electron spray ionisation (ESI) mass spectra were obtained for compounds **1**–**7** on a Finnigan MAT 95XL spectrometer, at 70 eV electron energy and 1.0 mA electron current for EI, and in positive mode for ESI, with MeOH + H_2O + AcOH/cap230 °C/3 kV. MALDI-TOF mass spectra of compounds **8**–**10** were recorded in negative reflectron mode on a mass spectrometer Voyager-DE STR (Applied Biosystems, Framingham, MA, USA). For each sample, 0.5 μl of the mixture was spotted onto the target plate, air-dried and covered with 0.5 μl of matrix solution consisting of 10 mg of α-cyano-4-hydroxycinnamic acid in 100 μl of 50% ACN in 0.1% TFA. The instrument was calibrated externally with a five-point calibration using Peptide Calibration Mix1 (LaserBio Labs, Sophia-Antipolis, France). IR spectra were obtained on a Nicolet 20-SXC FT IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 400 NMR spectrometer or on a Bruker Avance Digital 600 NMR spectrometer at 100.4 MHz, 399.65 MHz or 600.18 MHz, respectively. Chemical shifts are given relative to internal tetramethyl silane (TMS). UV–vis spectra were recorded on a Cary 50 UV–vis spectrophotometer or a UV-2401PC spectrophotometer from Shimadzu. Fluorescence data were obtained on an AMINCO-Bowman Series 2 luminescence spectrometer. Melting points were obtained on a Büchi 530 melting point apparatus and are uncorrected. Merck Kieselgel 60F 254 was used for thin layer chromatography (TLC) and Merck silica 63–200 μm was used for column chromatography. Basic alumina 5016 A from Fluka was used for oxidation of 2-hydroxy-[di(pyridin-3-yl)]ethane-1-one. 1,3-Diphenyl-isobenzofuran (DPBF), 5-methylthiophene-2-carboxaldehyde and 2-methylthiophene were obtained from Aldrich, thiophene-2-carboxaldehyde, 2-acetylthiophene and pyridine-3-carboxaldehyde were obtained from Acros Organics. Pyrazine-2,3-dicarbonitrile was prepared as in [14], m.p. 132–133 °C, lit. [14] m.p. 132 °C, and zinc tetrapyrazinoporphyrazine, ZnAzaPc [15] was prepared by reaction of pyrazine-2,3-dicarbonitrile with Zn(quinoline)$_2$Cl$_2$ dissolved in quinoline. UV–vis (pyridine): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 636 (78 000), 580 (15 200), 320 (56 000).

2.2. Synthesis

2.2.1. Ethane-1,2-diones ***1a*–*b***

*2.2.1.1. Di(5-methylthiophen-2-yl)ethanedione (**1a**).* M.p. 80–85 °C, was synthesized according to published procedures; lit. [16] m.p. 86–87 °C, lit. [17] m.p. 80–82 °C, lit. [18] m.p. 83–84 °C.

*2.2.1.2. Di(pyridin-3-yl)ethanedione (**1b**). Method A*. The published procedure [19] was modified as follows: aniline (10.5 mmol, 0.98 g) was added dropwise to pyridine-3-carboxaldehyde (10 mmol, 1.07 g) with stirring. The solution was heated in an open flask at 100 °C for 0.5 h with evaporation of some water from the reaction mixture. Sodium cyanide (4 mmol, 0.2 g; ed note: poison – may be fatal if inhaled or swallowed; contact with acid releases highly poisonous gas; low LD50; causes burns; skin and eye irritant) and DMSO (4 ml) were added to the crude *N*-(pyridin-3-yl-methylene)benzenamine, and the solution was stirred at ambient temperature for 15 h. A yellow precipitate appeared during the reaction. Ice (approx. 40 g) was added, and the yellow solid was isolated by filtration. Acetone (20 ml) was added to the solid, and the mixture was heated under reflux for 0.5 h. The solvent was removed under reduced pressure, diethyl ether (ca. 5 ml) was added, and a yellow powder was obtained. Yield of *N*,*N*-(di-pyridin-3-yl-ethanediylidene)dianiline 1.3 g (72%), R_f (acetone) = 0.73, m.p. 141–142 °C decomp, lit. [19] m.p. 138–139 °C. The NMR pulse techniques COSY, NOESY, HSQC and HMBC were used to correlate ^{1}H and ^{13}C NMR signals. ^{1}H/^{13}C NMR ($CDCl_3$): δ, ppm Pyridine: *H*2/*C*2, 9.07 (1H, d, $J_{2,4}$ = 1.8 Hz)/147.9; *C*3, 130.8; *H*4/*C*4, 8.19 (1H, app. dt, $J_{4,5}$ = 7.9 Hz, $J_{4,2}$ = 2.0 Hz), 135.4; *H*5/*C*5, 7.41 (1H, ddd, $J_{5,4}$ = 7.9 Hz, $J_{5,6}$ = 4.9 Hz, $J_{5,2}$ = 0.8 Hz), 123.7; *H*6/*C*6, 8.74 (1H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,4}$ = 1.6 Hz)/152.5. Phenyl: *C*1, 137.5; *H*2,6/*C*2,6, 7.64 (1H, d, J = 7.8 Hz)/120.5; *H*3,5/*C*3,5, 7.37 (1H, app. t, J = 7.5 Hz)/129.2; *H*4/*C*4, 7.18 (1H, tt, J = 7.4 Hz, J = 1.1 Hz)/125.1; *C* imine, 164.0.

A solution of *N*,*N*-(di-pyridin-3-yl-ethanediylidene)dianiline (3 mmol, 1.1 g) in 1 M hydrochloric acid (60 mmol, 60 ml) was stirred in an open beaker for 48 h, then left for slow evaporation. The pale yellow residue was mixed with $NaHCO_3$ (13 mmol, 1.1 g) and 3 ml water, stirred until gas evolution had stopped, and then extracted with DCM. The DCM extract was chromatographed on silica. DCM eluted a small amount of aniline, and a (1:1) mixture of DCM and acetone eluted compound **1b**. Yield 0.4 g (63%), R_f (acetone) = 0.68, m.p. 77–78 °C, lit. [19] m.p. 82 °C, lit. [20] m.p. 80–82 °C.

Method B. a) Benzoin condensation of pyridine-3-carboxaldehyde. A solution of pyridine-3-carboxaldehyde (20 mmol, 2.14 g) and sodium cyanide (1.2 mmol, 0.06 g) in pyridine (5 ml) and water (5 ml) was heated under reflux for 1 h. The solvents were removed under reduced pressure, the residue was extracted with acetone (20 ml), and a white, water soluble solid, 0.16 g, m.p. > 280 °C was removed by filtration. A pale yellow oil, 2.0 g (ca. 90%), was obtained from the acetone filtrate, TLC on silica: one major spot, R_f (acetone) = 0.46, and three minor spots; R_f = 0.7 and 0.3–0.1. ^{1}H NMR, with a combination of the pulse techniques COSY, HSQC and HMBC showed the major product to be 2-hydroxy-[di(pyridin-3-yl)]ethane-1-one, the precursor of **1b**. This precursor has been reported, but no physical data were given [21]. ^{1}H/^{13}C NMR ($CDCl_3$): δ, ppm pyridine at carbonyl: *H*2/*C*2, 9.12 (1H, dd, $J_{2,4}$ = 2.3 Hz, $J_{2,5}$ = 0.9 Hz)/150.2; *C*3, 129.2; *H*4/*C*4, 8.20 (1H, ddd, $J_{4,5}$ = 8.0 Hz, $J_{4,2}$ = 2.3 Hz, $J_{4,6}$ = 1.7 Hz)/136.5; *H*5/*C*5, 7.39 (1H, ddd, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 4.9 Hz, $J_{5,2}$ = 0.9 Hz)/123.9; *H*6/*C*6, 8.72 (1H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,4}$ = 1.7 Hz)/154.1. *C*=*O*, 197.4; *H*–*C*(OH), 6.0 (1H, s)/74.7; pyridine at CH(OH): *H*2/*C*2, 8.65 (1H, dd, $J_{2,4}$ = 2.4 Hz, $J_{2,5}$ = 1.1 Hz)/148.9; *C*3, 134.2; *H*4/*C*4, 7.67 (1H, dddd, $J_{4,5}$ = 7.9 Hz, $J_{4,2}$ = 2.2 Hz, $J_{4,6}$ = 1.7 Hz, $J_{4,CH}$ = 0.4 Hz)/135.3; *H*5/*C*5, 7.28 (1H, ddd, $J_{5,4}$ = 7.9 Hz, $J_{5,6}$ = 4.9 Hz, $J_{5,2}$ = 0.9 Hz)/124.2; *H*6/*C*6, 8.50 (1H, dd, $J_{6,5}$ = 4.8 Hz, $J_{6,4}$ = 1.7 Hz)/149.8.

The oily product was dissolved in methanol (5 ml), and a white solid had precipitated after 24 h. The precipitate was isolated by filtration, and two more crops of the same material were obtained from methanol and acetone solutions of the crude product. A total of 0.8 g (33%), m.p. 230–234 °C (decomp.) of nicotinic acid was obtained. ^{1}H NMR ($(CD_3)_2CO$): δ, ppm 4.2 (1H, broad s), 7.54 (1H, ddd, $J_{5,4}$ = 7.9 Hz, $J_{5,6}$ = 4.8 Hz, $J_{5,2}$ = 0.9 Hz), 8.34 (1H, d, app.t, $J_{4,5}$ = 7.9 Hz, $J_{4,2}$ and $J_{4,6}$ = 2.0 Hz), 8.80 (1H, dd, $J_{6,5}$ = 4.8 Hz, $J_{6,4}$ = 1.7 Hz), 9.17 (1H, dd, $J_{2,4}$ = 2.1 Hz, $J_{2,5}$ = 0.7 Hz). The yield of

nicotinic acid is in good agreement with the ratio of signals for pyridoin and nicotinic acid of the crude product. Further attempts to purify and crystallize the pyridoin were unsuccessful.

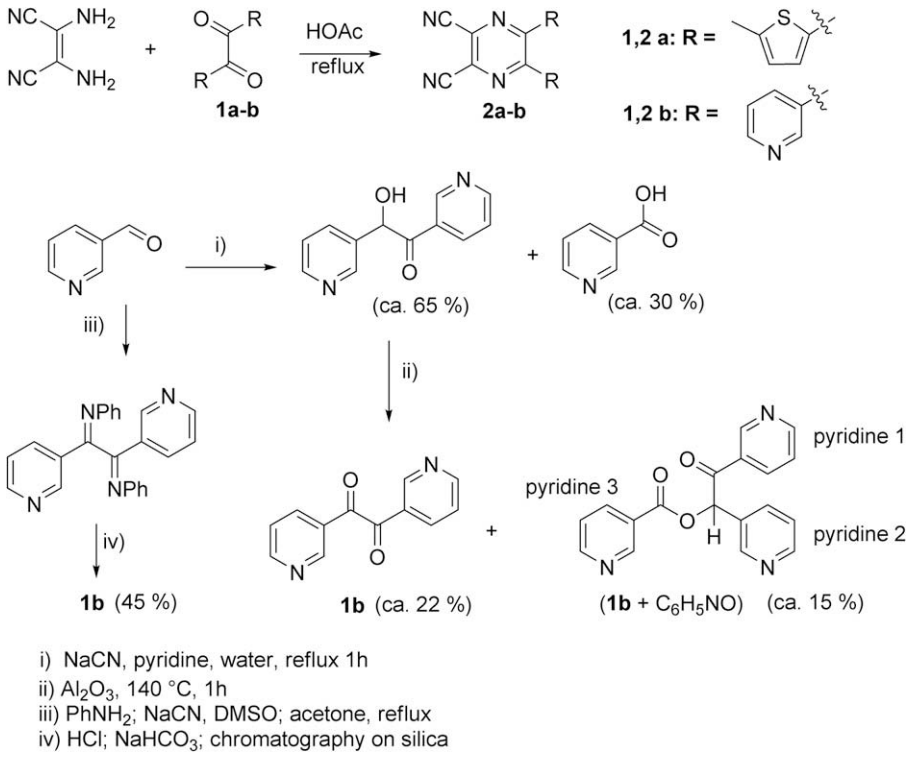
b) Oxidation of crude 2-hydroxy-[di(pyridin-3-yl)]ethane-1-one with alumina. A mixture of 2-hydroxy-[di(pyridin-3-yl)]ethane-1-one (ca. 9 mmol, 1.9 g) and activated alumina (16 g) was heated with stirring in an open flask at 140 °C for 1 h, followed by extraction with acetone and chromatography on silica with acetone. The first fractions, R_f (acetone) = 0.64, gave a yellow solid which was isolated by filtration with hexane. Yield of **1b** 0.44 g (22%), m.p. 75–76 °C. ESIMS *m*/*z* (% rel. int.) 213 (M + 1, 56.4), 244 (M + 1+MeOH, 100). Found 213.06596, calcd. for $C_{12}H_9N_2O_2$ (M + 1) 213.06585. ^{1}H NMR ($CDCl_3$): *δ*, ppm 7.52 (2H, ddd, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 4.9 Hz, $J_{5,2}$ = 0.9 Hz), 8.35 (2H, ddd, $J_{4,5}$ = 8.0 Hz, $J_{4,2}$ = 2.2 Hz, $J_{4,6}$ = 1.7 Hz), 8.90 (2H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,4}$ = 1.7 Hz), 9.22 (2H, dd, $J_{2,4}$ = 2.2 Hz, $J_{2,5}$ = 0.9 Hz). The pulse technique HSQC was used for identification of the ^{13}C signals. ^{13}C NMR ($CDCl_3$): *δ*, ppm 124.0 (pyridine-*C*5), 128.3 (pyridine-*C*3), 137.1 (pyridine-*C*4), 151.5 (pyridine-*C*2), 155.1 (pyridine-*C*6), 191 (*C*=O).

Chromatographic fractions with R_f (acetone) = 0.4 gave a pale yellow, viscous oil, 0.45 g (15%). ESIMS and NMR analyses of this compound are consistent with the formula (**1b** + C_6H_5NO, M = 319); the structure (a mixture of enantiomers) is shown in Scheme 1. ESIMS *m*/*z* (% rel. int.) 320 (M + 1, 100), 352 (M + 1+MeOH, 86). Found 320.10281, calcd for (M + 1) $C_{18}H_{14}N_3O_3$ 320.10297. Found 352.12908, calcd. for (M + 1+MeOH) $C_{19}H_{18}N_3O_4$ 352.12918. NMR analyses were based on COSY, HSQC and HMBC techniques. Corresponding signals; ^{1}H and ^{13}C NMR ($(CD_3)_2CO$) *δ*, ppm, are listed for each of the three pyridine rings, and for the carbons connected to the 3-position of each ring: Pyridine 1: *H*6/*C*6, 8.80 (1H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,4}$ = 1.7 Hz)/154.3; *H*5/*C*5, 7.44 (1H, ddd, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 4.9 Hz, $J_{5,2}$ = 1.1 Hz)/124.0; *H*4/*C*4, 8.27 (1H, ddd, $J_{4,5}$ = 8.0 Hz, $J_{4,2}$ = 2.3 Hz, $J_{4,6}$ = 1.7 Hz)/136.2; *C*3, 129.8; *H*2/*C*2, 9.22 (1H, dd, $J_{2,4}$ = 2.3 Hz, $J_{2,5}$ = 1.1 Hz)/149.8; carbonyl at C3, 191.8. Pyridine-2: *H*6/*C*6, 8.69 (1H, dd, $J_{6,5}$ = 4.8 Hz, $J_{6,4}$ = 1.7 Hz)/151.2; *H*5/*C*5, 7.40 (1H, ddd, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 4.8 Hz, $J_{5,2}$ = 1.0 Hz)/124.3; *H*4/*C*4, 7.91 (1H, m)/136.2; *C*3 128.7; *H*2/*C*2, 8.86 (1H, dd, $J_{2,4}$ = 2.4 Hz, $J_{2,5}$ = 1.0 Hz)/149.8; *CH*–O at C3, 7.09 (1H, s)/75.9. Pyridine-3: *H*6/*C*6, 8.84 (1H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,4}$ = 1.8 Hz)/154.2; *H*5/*C*5, 7.44 (1H, ddd, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 4.9 Hz, $J_{5,2}$ = 1.1 Hz)/123.5; *H*4/*C*4, 8.36 (1H, ddd, $J_{4,5}$ = 8.0 Hz, $J_{4,2}$ = 2.2 Hz, $J_{4,6}$ = 1.8 Hz)/137.5; *C*3, 124.8; *H*2/*C*2, 9.30 (1H, dd, $J_{2,4}$ = 2.2 Hz, $J_{2,5}$ = 1.0 Hz)/151.2; ester–carbonyl at C3, 164.6.

2.2.2. Pyrazine-2,3-dicarbonitriles ***2a–b***

*2.2.2.1. General procedure for the synthesis of pyrazines **2**.* A solution of diaminomaleonitrile (DAMN) (6 mmol, 0.65 g) and either **1a** or **1b** (5 mmol) in glacial acetic acid (15 ml), was heated at 110 °C for 2 h and the solvent was removed under reduced pressure. For **1a** the residue was extracted with DCM and chromatographed on silica with DCM. For **1b** the residue was washed with diethyl ether, and then heated under reflux with water. The brown solid which was isolated by filtration, was heated under reflux with acetone and filtered. The solvent was removed under reduced pressure, diethyl ether was added to the residue, and a tan solid was isolated by filtration.

*2.2.2.2. 5,6-Di(5-methylthiophen-2-yl)pyrazine-2,3-dicarbonitrile (**2a**).* Yield 0.8 g (50%) of orange powder, m.p. 181–182 °C. EIMS: *m*/*z* (% rel. int.) 324 (10.6), 323 (21.2), 322 (M, 100), 321 (23.9), 307 (43.1). Found 322.03373, calcd. for $C_{16}H_{10}N_4S_2$ 322.03469. UV–vis (DCM): λ_{max}, nm (*ε*, M^{-1} cm^{-1}) 410 (25 000), 340 (19 000). ^{1}H NMR ($CDCl_3$): *δ*, ppm 2.57 (6H, d, $J_{Me,4}$ = 1 Hz), 6.75 (2H, dd, $J_{4,3}$ = 3.8 Hz, $J_{4,Me}$ = 1 Hz), 7.56 (2H, d, $J_{3,4}$ = 3.8 Hz). The pulse techniques HSQC and HMBC were used for identification of the ^{13}C signals. ^{13}C NMR ($CDCl_3$): *δ*, ppm 16.02 (*CH*$_3$), 113.40 (*CN*), 127.7 (pyrazine-*C*$_2$, *C*$_3$), 127.2 (thiophene-*C*$_4$), 132.1 (thiophene-*C*$_3$), 136.02 (thiophene-*C*$_2$), 147.6 (pyrazine-*C*$_5$, *C*$_6$), 149.2 (thiophene-*C*$_5$).



Scheme 1. Syntheses of symmetrically substituted pyrazine-2,3-dicarbonitriles **2a–b**.

*2.2.2.3. 5,6-Di(pyridin-3-yl)pyrazine-2,3-dicarbonitrile (**2b**).* Yield 0.85 g (60%) of tan powder, m.p. 254–275 °C (slow decomp., green). A sample was recrystallized from pyridine to give a white powder, m.p. 268–274 °C (green melt). EIMS *m/z* (% rel. int.) 256 (100), 283 (61), 284 (M, 35). Found 284.07896, calcd. for $C_{16}H_8N_6$ 284.08050. UV–vis (DCM): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 320 (12 500). ^{1}H NMR ($CDCl_3$): δ, ppm 7.50 (2H, pyridine-*H*5, ddd, $J_{5,4} = 8.0$ Hz, $J_{5,6} = 4.9$ Hz, $J_{5,2} = 0.9$ Hz), 7.93 (2H, pyridine-*H*4, ddd, $J_{4,5} = 8$ Hz, $J_{4,2} = 2.3$ Hz, $J_{4,6} = 1.7$ Hz), 8.64 (2H, pyridine-*H*2, dd, $J_{2,4} = 2.4$ Hz, $J_{2,5} = 0.9$ Hz), 8.68 (2H, pyridine-*H*6, dd, $J_{6,5} = 4.9$ Hz, $J_{6,4} = 1.7$ Hz). The pulse techniques HSQC and HMBC were used for identification of the ^{13}C signals. ^{13}C NMR ($CDCl_3$): δ, ppm 113.92 (*CN*), 123.6 (pyridine-*C*5), 130.7 (pyrazine-*C*2, *C*3), 131.3 (pyridine-*C*3), 137.4 (pyridine-*C*4), 149.9 (pyridine-*C*2), 151.2 (pyridine-*C*6), 153.0 (pyrazine-*C*5, *C*6).

*2.2.3. Glyoxals **3a–b***

*2.2.3.1. (5-Methylthiophen-2-yl)glyoxal (**3a**).* A solution of 2-methylthiophene (0.05 mol, 4.9 g) in acetic anhydride (0.05 mol, 5.1 g) and 85% phosphoric acid (0.5 ml) was heated at 65 °C for 14 h. The reaction mixture was poured on ice (100 g), extracted with DCM (3 × 30 ml), and counter extracted with water. The oily residue after removal of the solvent was chromatographed on silica with DCM, the fractions with R_f (DCM) = 0.44 were combined and gave 2-acetyl-5-methylthiophene, 5.9 g (84%) as an oil, lit. [22] m.p. 27–28 °C.

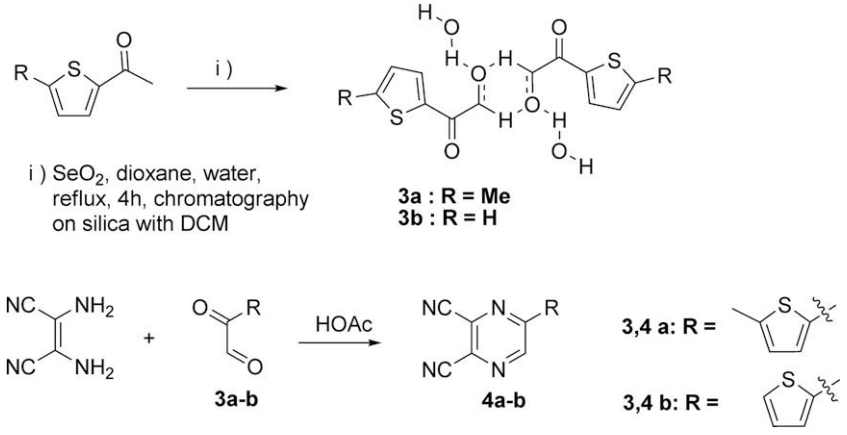
A solution of 2-acetyl-5-methylthiophene (10 mmol, 1.4 g) and selenium dioxide (11 mmol, 1.22 g) in dioxane (5 ml) and water (3 ml) was heated under reflux for 4 h and left at ambient temperature for 14 h. The solid precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The liquid residue was chromatographed on silica with DCM. The solvent was removed, and a pale yellow solid was obtained after trituration with diethyl ether. Yield 0.69 g (45%), m.p. 107–109 °C. EIMS: *m/z* (% rel. int.) 154 (M, 2.8), 127 (4.4), 126 (7.2), 125 (M − CHO, 100). Found 154.00882, calcd. for $C_7H_6O_2S$ 154.00885. ^{1}H NMR ($CDCl_3$): δ, ppm 2.56 (6H, m), 4.92 (2H, d, $J = 10.1$ Hz), 6.12 (2H, d, $J = 10.1$ Hz), 6.85 (2H, dq, $J_{4,3} = 3.9$ Hz, $J_{4,Me} = 0.9$ Hz), 7.88 (2H, d, $J_{3,4} = 3.9$ Hz). ^{13}C NMR ($CDCl_3$): δ, ppm 16.4 (CH_3), 89.72 (aldehyde *C* where the aldehyde oxygen is associated with a water molecule); HSQC shows the H/C connection 6.12 ppm/89.72 ppm, 127.8 (thiophene-*C*4), 136.5 (thiophene-*C*2), 137.3 (thiophene-*C*3), 153.2 (thiophene-*C*5), 185.5 (*C*=O at thiophene-C2, HMBC shows H/C connection 4.92 ppm/185.5 ppm and 4.92 ppm/89.72). No HSQC connection was found for the ^{1}H signal at 4.92 ppm. The structure of hydrated dimer **3a** is shown in Scheme 2.

*2.2.3.2. (Thiophen-2-yl)glyoxal (**3b**).* Compound **3b** was obtained by oxidation of 2-acetylthiophene with selenium dioxide in dioxane as in [23,24]. The crude glyoxal was chromatographed on silica with DCM to give a liquid, which became a semi-solid upon exposure to air for several days. R_f (DCM) = 0.12. Yield approx. 70%. A sample (200 mg) was heated with water (1 ml), left for 2 h and filtered. A white solid (0.1 g) was obtained, m.p. 92–93 °C, lit. [23] m.p. 93 °C. ^{1}H NMR ($CDCl_3$): δ, ppm 4.91 (2H, d, $J = 10$ Hz), 6.19 (2H, d, $J = 10$ Hz), 7.19 (2H, dd, $J_{4,3} = 3.9$ Hz, $J_{4,5} = 4.9$ Hz), 7.77 (2H, dd, $J_{5,4} = 4.9$ Hz, $J_{5,3} = 1.1$ Hz), 8.07 (2H, dd, $J_{3,4} = 3.9$ Hz, $J_{3,5} = 1.1$ Hz). ^{13}C NMR ($CDCl_3$): δ, ppm 89.73 (H–*C*=O, HSQC shows the H/C connection 6.19 ppm/89.73 ppm), 128.72 (thiophene-*C*4), 136.26, 136.34 (thiophene-*C*3 and *C*5), 138.48 (thiophene-*C*2), 185.84 (*C*=O at thiophene-C2). HSQC shows no H/C connection for the ^{1}H signal at $\delta = 4.91$ ppm, but HMBC shows a H/C connection 4.91 ppm/185.84 ppm. The structure of hydrated dimer of **3b** is therefore the same as for **3a** and is shown in Scheme 2.

*2.2.4. Pyrazine-2,3-dicarbonitriles **4a–b***

*2.2.4.1. 5-(5-Methylthiophen-2-yl)pyrazine-2,3-dicarbonitrile (**4a**).* A solution of **3a** (4 mmol, 0.62 g) and DAMN (5 mmol, 0.54 g) in glacial acetic acid (6 ml) was heated at 75–80 °C for 4 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica with DCM. Yield 0.8 g (88%) of an orange powder, m.p. 191–192 °C. EIMS: *m/z* (% rel. int.) 227 (3.2), 226 (M, 8.4), 225 (6.2), 212 (7.5). Found 226.03101, calcd. for $C_{11}H_6N_4S$ 226.03132. UV–vis (DCM): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 375 (31 000). ^{1}H NMR ($CDCl_3$): δ, ppm 2.61 (3H, d, $J_{Me,4} = 1$ Hz), 6.93 (1H, dd, $J_{4,3} = 3.8$ Hz, $J_{4,Me} = 1$ Hz), 7.75 (1H, d, $J_{3,4} = 3.8$ Hz), 9.0 (1H, s, pyrazine-*H*5). The pulse techniques HSQC and HMBC were used for identification of the ^{13}C signals. ^{13}C NMR ($CDCl_3$): δ, ppm 16.1 (CH_3), 112.9 (*CN* at pyrazine-*C*3), 113.4 (*CN* at pyrazine-*C*2), 128.4 (thiophene-*C*4), 128.7 (pyrazine-*C*3), 131.4 (thiophene-*C*3), 133.3 (pyrazine-*C*2), 135.4 (thiophene-*C*2), 142.3 (pyrazine-*C*5), 150.5 (pyrazine-*C*6), 151.0 (thiophene-*C*5).

*2.2.4.2. 5-(Thiophen-2-yl)pyrazine-2,3-dicarbonitrile (**4b**).* A suspension of **3b** (9 mmol, 1.26 g) and DAMN (11 mmol, 1.2 g) in glacial acetic acid (3 ml) was stirred at ambient temperature for 0.5 h. The reaction mixture was diluted with water (25 ml) with sonification. A tan solid was isolated by filtration and then chromatographed on silica with DCM. Yield 0.94 g (50%) of pale yellow crystals, m.p. 205–206 °C decomp. Lit. [25] m.p. 194–197 °C. EIMS: *m/z* (% rel. int.) 213 (13.6), 212 (M, 100), 167 (11.9), 166 (5.7), 165 (14.3). Found 212.01466, calcd. for $C_{10}H_4N_4S$ 212.01567. UV–vis (DCM): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 360 (21 000). ^{1}H NMR ($CDCl_3$): δ,



Scheme 2. Syntheses of unsymmetrically substituted pyrazine-2,3-dicarbonitriles **4a–b**.

ppm 7.28 (1H, dd, $J_{4,5} = 5$ Hz, $J_{4,3} = 4$ Hz), 7.77 (1H, dd, $J_{5,4} = 5$ Hz, $J_{5,3} = 1$ Hz), 7.95 (1H, dd, $J_{3,4} = 4$ Hz, $J_{3,5} = 1$ Hz), 9.12 (1H, s. pyrazine-*H*5). The pulse techniques HSQC and HMBC were used for identification of the ^{13}C signals. ^{13}C NMR ($CDCl_3$): δ, ppm 113.0 (*CN* at pyrazine-*C*3), 113.4 (*CN* at pyrazine-*C*2), 129.7 (pyrazine-*C*3), 129.8 (thiophene-*C*5), 131.0 (thiophene-*C*3), 133.5 (pyrazine-*C*2), 134.7 (thiophene-*C*5), 138.0 (thiophene-*C*2), 142.8 (pyrazine-*C*5), 150.7 (pyrazine-*C*6).

*2.2.5. Compounds **5** and **6***

*2.2.5.1. 2-Hydroxy-1-(5-methylthiophen-2-yl)-2-(pyridin-3-yl)ethanone (**5**).* A solution of 5-methylthiophene-2-carboxaldehyde (15 mmol, 1.9 g), pyridine-3-carboxaldehyde (15 mmol, 1.6 g) and sodium cyanide (3 mmol, 0.15 g) in DMF (2 ml) was heated at 60 °C for 2 h. Ice (ca. 50 g) was added to the dark suspension. The reaction mixture was extracted with DCM, and the organic phase was chromatographed on silica with acetone. A mixture of two aldehydes, 1.2 g (ca 30%) was recovered from the first fractions and the filtrates of the following fractions. The last fractions, R_f (acetone) = 0.74, were dissolved in diethyl ether, and after cooling in ice, a pale yellow solid separated and was isolated. Yield 1.73 g (50%), m.p. 92–95 °C. EIMS: *m*/*z* (% rel. int.) 124 (5-methylthiophene-2-carbonyl radical ion, 100), 106 (pyridine-3-carbonyl radical ion, 35.8). ^{1}H NMR ($CDCl_3$): δ, ppm 2.51 (3H, m, *Me*), 4.6 (1H, broad s, *H*–O), 5.74 (1H, s, HO–C–*H*), 6.76 (1H, thiophene, dq, $J_{4,3} = 3.9$ Hz, $J_{4,Me} = 1.0$ Hz), 7.28 (1H, pyridine, ddd, $J_{5,4} = 8.0$ Hz, $J_{5,6} = 4.9$ Hz, $J_{5,2} = 0.8$ Hz), 7.51 (1H, thiophene, d, $J_{3,4} = 3.8$ Hz), 7.66 (1H, pyridine, ddd, $J_{4,5} = 7.9$ Hz, $J_{4,6} = 1.9$ Hz, $J_{4,2} = 1.9$ Hz), 8.56 (1H, pyridine, dd, $J_{6,5} = 4.9$ Hz, $J_{6,4} = 1.6$ Hz), 8.72, (1H, pyridine, d, $J_{2,4} = 1.7$ Hz). The pulse techniques HSQC and HMBC were used for identification of the ^{13}C signals. ^{13}C NMR ($CDCl_3$): δ, ppm 16.02 (*Me*), 74.24 (H–*C*–OH), 124.06 (pyridine-*C*5), 127.38 (thiophene-*C*4), 135.08 (pyridine-*C*4), 135.13 (thiophene-*C*3), 135.51 (pyridine-*C*3), 136.60 (thiophene-*C*2), 149.13 (pyridine-*C*2), 149.75 (pyridine-*C*6), 152.21 (thiophene-*C*5), 189.96 (*C*=O).

*2.2.5.2. 1-(5-Methylthiophen-2-yl)-2-(pyridin-3-yl)ethanedione (**6**). Method A.* Compound **5** (1.5 mmol, 0.35 g) and activated alumina (3.5 g) were stirred and heated at 120–140 °C in an open flask for 20 min. A colourless liquid distilled to the top of the flask and was identified by TLC on silica (and odour) as 5-methylthiophene-2-carboxaldehyde. The brown solid alumina mixture was stirred with acetone. The acetone extract was chromatographed on silica, and 0.1 g (29%) of **6**, R_f (acetone) = 0.84, was isolated as an orange liquid. ESIMS: *m*/*z* (% rel. int.) 232 (M + 1, 28.7), 264 (M + 1+MeOH, 100). Found 232.04098, calcd. for $C_{12}H_{10}NO_2S$ 232.04268. UV–vis (DCM): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 315 (11 000), 270 (10 500). ^{1}H NMR ($CDCl_3$): δ, ppm 2.62 (3H, dd, $J_{Me,4} = 1.0$ Hz, $J_{Me,3} = 0.4$ Hz), 6.90 (1H, thiophene, dq, $J_{4,3} = 3.9$ Hz, $J_{4,Me} = 1.0$ Hz), 7.47 (1H, pyridine, ddd, $J_{5,4} = 8.0$ Hz, $J_{5,6} = 4.9$ Hz, $J_{5,2} = 0.9$ Hz), 7.72 (1H, thiophene, dd, $J_{3,4} = 3.9$ Hz, $J_{3,Me} = 0.3$ Hz), 8.36 (1H, pyridine, ddd, $J_{4,5} = 8$ Hz, $J_{4,2} = 2.2$ Hz, $J_{4,6} = 1.8$ Hz), 8.86 (1H, pyridine, dd, $J_{6,5} = 4.9$ Hz, $J_{6,4} = 1.8$ Hz), 9.25 (1H, pyridine, dd, $J_{2,4} = 2.2$ Hz, $J_{2,5} = 0.9$ Hz). The pulse techniques COSY, HSQC and HMBC were used for identification of the ^{13}C signals. ^{13}C NMR ($CDCl_3$): δ, ppm 16.32 (*Me*), 123.7 (pyridine-*C*5), 127.9 (thiophene-*C*4), 128.7 (pyridine-*C*3), 137.1 (thiophene-*C*2), 137.4 (pyridine-*C*4), 138.1 (thiophene-*C*3), 151.6 (pyridine-*C*2), 154.5 (pyridine-*C*6), 154.6 (thiophene-*C*5), 183.1 (*CO* at thiophene-*C*2), 190.5 (*CO* at pyridine-*C*3).

Method B. A solution of **5** (4 mmol, 0.9 g), ammonium nitrate (5 mmol, 0.4 g) and cupric acetate (0.01 g) in glacial acetic acid (4 ml) and water (1 ml) was heated under reflux for 1.5 h. The solvents were removed under reduced pressure, and the semi-solid residue was extracted with DCM (3 × 30 ml). The liquid residue after removal of the solvent was chromatographed on silica with acetone. The fractions with $R_f = 0.83$ were combined, and gave 0.3 g (32%) of **6** as a red liquid which was used for synthesis of **7**.

*2.2.6. Pyrazine-2,3-dicarbonitrile **7***

*2.2.6.1. 5-(5-Methylthiophen-2-yl)-6-(pyridin-3-yl)pyrazine-2,3-dicarbonitrile (**7**).* A solution of **6** (1.3 mmol, 0.3 g) and DAMN (3 mmol, 0.3 g) in glacial acetic acid (10 ml) was heated under reflux for 2.5 h. The solvent was removed under reduced pressure, and the solid residue was chromatographed on silica with acetone. The fractions with R_f (acetone) = 0.85 were combined, the solvent was removed under reduced pressure, and the solid residue was triturated (sonication) with diethyl ether and isolated by filtration. Yield 0.24 g (60%) of a yellow powder, m.p. 179–180 °C decomp. EIMS: *m*/*z* (% rel. int.) 305 (6.1), 304 (22.6), 303 (M, 100), 302 (59.3). Found 303.05787, calcd. for $C_{16}H_9N_5S$ 303.05787. UV–vis (DCM): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 390 (24 000), 267 (14 000). ^{1}H NMR ($CDCl_3$): δ, ppm 2.51 (3H, dd, $J_{Me,3} = 1.0$ Hz, $J_{Me,4} = 0.5$ Hz), 6.67 (1H, thiophene, dq, $J_{4,3} = 3.9$ Hz, $J_{4,Me} = 0.5$ Hz), 7.02 (1H, thiophene, dq, $J_{3,4} = 3.9$ Hz, $J_{3,Me} = 0.5$ Hz), 7.49 (1H, pyridine, ddd, $J_{5,4} = 7.9$ Hz, $J_{5,6} = 4.9$ Hz, $J_{5,2} = 0.8$ Hz), 8.00 (1H, pyridine, ddd, $J_{4,5} = 7.9$ Hz, $J_{4,2} = 2.3$ Hz, $J_{4,6} = 1.7$ Hz), 8.82 (1H, pyridine, dd, $J_{6,5} = 4.9$ Hz, $J_{6,4} = 1.6$ Hz), 8.89 (1H, pyridine, dd, $J_{2,4} = 2.3$ Hz, $J_{2,5} = 0.7$ Hz). The pulse techniques HSQC and HMBC were used for identification of the ^{13}C signals. ^{13}C NMR ($CDCl_3$): δ, ppm 15.8 (*Me*), 112.80 (*CN*), 113.10 (*CN*), 123.81 (*C*5, pyridine), 127.52(*C*2 or *C*3, pyrazine), 127.83 (*C*4, thiophene), 130.75 (*C*2 or *C*3, pyrazine), 132.15 (*C*3, pyridine), 133.66 (*C*3, thiophene), 135.59 (*C*2, thiophene), 136.63 (*C*4, pyridine), 149.40 (*C*2, pyridine), 150.23 (*C*6, pyrazine), 150.78 (*C*5, thiophene).

*2.2.7. Compounds **8**–**10***

*2.2.7.1. General procedures for the synthesis of compounds **8**–**10**. Method A.* Compound **2**, **4** or **7** (1 mmol) and dry zinc(II) acetate (1 mmol) were ground in a mortar, transferred to a round bottomed flask, quinoline (0.5 ml) was added, and nitrogen was passed over the reaction mixture for 20 min at ambient temperature. The mixture was heated to 155–185 °C for 10–20 min. Diethyl ether was added, and the dark solid was isolated by filtration. The solid was heated under reflux with a mixture of methanol and water (2:1) for 2 h, then with acetone and water (2:1) for 1 h, and finally heated under reflux with acetone for 1 h. However, compounds **8a** and **10** were treated with methanol, water and acetone at ambient temperature due to extensive decomposition when heated under reflux with these solvents.

Method B. The procedure was the same as for Method A, except that dry zinc(quinoline)$_2$Cl$_2$ complex [26] and quinoline were used instead of zinc(II) acetate and quinoline.

*2.2.7.2. [Octa(5-methylthiophen-2-yl)-(octazaphthalocyaninato)]zinc(II) (**8a**). Method B.* 180 °C, 10 min. Yield 112 mg (33%) of a black-green solid. UV–vis (pyridine): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 679 (195 000), 620 (36 000), 400 (114 000). MALDI-TOF MS *m*/*z* 1353 $[M + H]^+$. The solubility in pyridine was too low for NMR spectroscopy. Compound **2a**, 158 mg (49%), m.p. 175–178 °C, was recovered from the acetone filtrates.

*2.2.7.3. [Octa(pyridin-3-yl)-(octazaphthalocyaninato)]zinc(II) (**8b**). Method B.* 175–180 °C, 20 min. Yield 0.14 g (48%) of a dark green powder. UV–vis (pyridine): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 658 (125 000), 595 (22 000), 375 (77 000). Two equally abundant isomers were observed as seen from ^{1}H NMR and ^{13}C NMR signals using COSY, HSQC and HMBC techniques. Isomer 1: ^{1}H NMR (pyridine-d_5) δ, ppm 7.44 (1H, dd, $J_{5,4} = 8.0$ Hz, $J_{5,6} = 4.8$ Hz), 8.47 (1H, app. dt, $J_{4,5} = 7.9$ Hz, $J_{4,6} = 2$ Hz), 8.83 (1H, dd, $J_{6,5} = 4.8$, $J_{6,4} = 1.6$ Hz), 9.46 (1H, d, $J_{2,4} = 2.3$ Hz). ^{13}C NMR (pyridine-d_5) δ, ppm 124.3 (pyridine-C5, via HSQC), 133.5 (pyridine-C3, via HMBC to pyridine-H5), 138.5

(pyridine-C4), 151.9 (pyridine-C2), 152.3 (pyridine-C6), 152.8 and 152.9 (pyrazine-C5 and pyrazine-C6; by HMBC to pyridine-H2). Isomer 2: ^{1}H NMR (pyridine-d$_5$) δ, ppm 7.38 (1H, dd, $J_{5,4}=7.9$ Hz, $J_{5,6}=4.8$ Hz), 8.10 (1H, app. dt, $J_{4,5}=7.9$ Hz, $J_{4,6}=2$ Hz), 8.83 (1H, dd, $J_{6,5}=4.8$, $J_{6,4}=1.6$ Hz), 9.16 (1H, d, $J_{2,4}=2.3$ Hz). ^{13}C NMR (pyridine-d$_5$) δ, ppm 124.3 (pyridine-C5, via HSQC), 132.7 (pyridine-C3, via HMBC to pyridine-H5), 138.0 (pyridine-C4), 151.5 (pyridine-C2), 152.3 (pyridine-C6), 152.8 and 152.9 (pyrazine-C5 and pyrazine-C6; by HMBC to pyridine-H2). MALDI-TOF MS *m*/*z* 1201 $[M+H]^+$.

*2.2.7.4. [Tetra(5-methylthiophen-2-yl)-(octazaphthalocyaninato)] zinc(II) (**9a**). Method A.* 165 °C, 15 min. Yield 0.16 g (65%) of black powder. UV–vis (pyridine): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 666 (116 000), 610 (29 000), 385 (104 000), 320 (83 000). ^{1}H NMR (pyridine-d$_5$): δ, ppm 2.5 (12H, s), 6.85 (4H, m, thiophene-*H*4), 7.86 (4H, m, thiophene-*H*3), 9.33 (4H, s, pyrazine-*H*5). ^{13}C NMR (pyridine-d$_5$): δ, ppm 28.4 (*C*H$_3$), 127.9 (thiophene-*C*4), 129.0 (thiophene-*C*3), 143.2 (pyrazine-*C*5). The pulse techniques COSY and HMBC were used for the above correlations. MALDI-TOF MS *m*/*z* 969 $[M+H]^+$, 991 $[M+Na]^+$, 1007 $[M+K]^+$.

*2.2.7.5. [Tetra(thiophen-2-yl)-(octazaphthalocyaninato)]zinc(II) (**9b**). Method A.* 175 °C, 10 min. The crude product was chromatographed on silica with pyridine. Yield 0.17 g, (75%) of a black powder. UV–vis (pyridine): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 661 (111 000), 600 (24 000), 375 (79 000) 315 (69 000). ^{1}H NMR (pyridine-d$_5$): δ, ppm 7.25 (4H, m, thiophene-*H*4), 7.80 (4H, broad d, $J_{5,4}=4.9$ Hz), 8.16 (4H, broad d, $J_{3,4}=3.2$ Hz), 9.61 (4H, s, pyrazine-*H*5). ^{13}C NMR (pyridine-d$_5$): δ, ppm 128.4 (thiophene-*C*4), 129.9 (thiophene-*C*3), 132.8 (thiophene-*C*5), 145.4 (pyrazine-*C*5). The pulse techniques COSY and HSQC were used for identifications of the above NMR signals. MALDI-TOF MS *m*/*z* 913 $[M+H]^+$, 935 $[M+Na]^+$, 951 $[M+K]^+$.

*2.2.7.6. [Tetra(5-methylthiophen-2-yl)-tetra(pyridin-3-yl)-(octazaphthalocyaninato)]zinc(II) (**10**). Method B.* 175–180 °C, 15 min. Yield 0.12 g, (38%) of a black powder. UV–vis (pyridine): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$) 673 (117 000), 620 (32 000), 390 (95 000). ^{1}H NMR (pyridine-d$_5$): δ, ppm 2.35 (16H, broad m, C*H*$_3$), 6.76 (4H, m, thiophene-*H*4), 7.49 (4H, m, pyridine-*H*5), 8.17 (4H, m, pyridine-*H*4), 9.23 (4H, m, pyridine-*H*2). ^{13}C NMR (pyridine-d$_5$): δ, ppm 15.5 (*C*H$_3$), 137.3 (pyridine-*C*4), 150.5 (pyridine-*C*2). The pulse techniques COSY and HSQC were used for identifications of the above NMR signals. MALDI-TOF MS *m*/*z* 1277 $[M+H]^+$.

2.3. Singlet oxygen and fluorescence measurements

Singlet oxygen production was monitored as DPBF (1,3-diphenylisobenzofuran) decomposition reactions, as reported by us previously [27,28]. Absorbance of the dyes during singlet oxygen measurements was approximately 0.1 in Q-band maximum. ZnPc in pyridine was used as the reference ($\Phi_\Delta=0.61$) [29]. Fluorescence quantum yields of the dyes were determined in pyridine and calculated as described previously [27]. Absorbance of the dyes during fluorescence measurements was approximately 0.05 in Q-band maximum. Excitation wavelength was 606 nm. ZnPc in pyridine was used as the reference ($\Phi_F=0.20$) [29].

3. Results and discussion

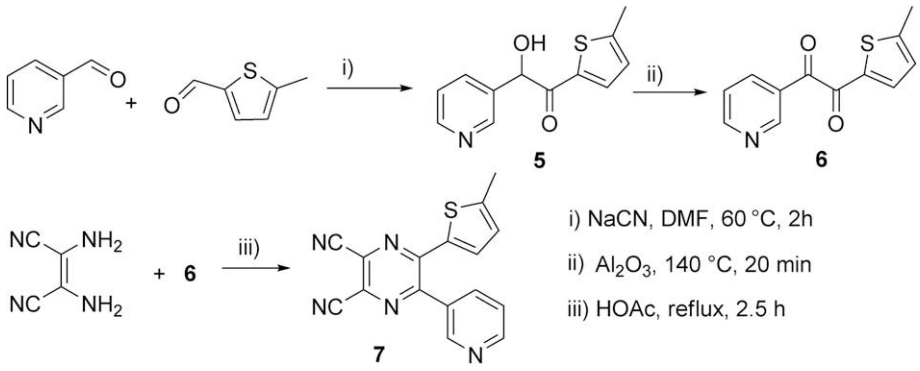
3.1. Syntheses and characterization

Symmetrically substituted pyrazine-2,3-dicarbonitriles, 5,6-di(5-methylthiophen-2-yl)pyrazine-2,3-dicarbonitrile (**2a**), and 5,6-di(pyridin-3-yl)pyrazine-2,3-dicarbonitrile (**2b**), were obtained from condensations of diaminomaleonitrile (DAMN) either with di(5-methylthiophen-2-yl)ethanedione (**1a**), or with di(pyridin-3-yl)ethanedione (**1b**), shown in Scheme 1. Two synthetic methods were explored for the synthesis of **1b**, also shown in Scheme 1.

The unsymmetrical pyrazine-2,3-dicarbonitriles 5-(5-methylthiophen-2-yl)pyrazine-2,3-dicarbonitrile (**4a**) and 5-(thiophen-2-yl)pyrazine-2,3-dicarbonitrile (**4b**) were obtained from reactions of DAMN with either 5-methylthiophene-2-glyoxal (**3a**) or thiophene-2-glyoxal (**3b**) (Scheme 2). Glyoxals **3a** and **3b** were isolated as hydrates after oxidations of the corresponding acetylthiophenes (Scheme 2).

2-Hydroxy-2-(pyridin-3-yl)-(5-methylthiophen-2-yl)ethanone (**5**), was obtained from a mixed benzoin condensation of 5-methylthiophene-2-carboxaldehyde and pyridine-3-carboxaldehyde. Oxidation of **5** with aluminium oxide gave 1-(5-methylthiophen-2-yl)-2-(pyridin-3-yl)ethanedione (**6**). Condensation of DAMN and **6** gave 5-(5-methylthiophen-2-yl)-6-(pyridin-3-yl)pyrazine-2,3-dicarbonitrile (**7**) (Scheme 3).

Pyrazines **2a**–**b**, **4a**–**b** and **7** were chosen in order to compare the influence of peripheral substituents of the corresponding ZnAzaPcs. Thus, the octasubstituted ZnAzaPc derived from monomer **2a** enables a comparison to be drawn between the 5-methylthiophen-2-yl substituent and the previously studied thiophen-2-yl substituent of octa(thiophen-2-yl)ZnAzaPc [10]. A similar comparison can be made between pyridin-3-yl peripheral substituents of the ZnAzaPc obtained from **2b**, and pyridin-2-yl groups of octa(pyridin-2-yl)ZnAzaPc [10]. Tetrasubstituted ZnAzaPcs, obtained from monomers **4**, will indicate how tetrasubstitution compares to octasubstitution in instances where methylthiophene and thiophene are peripheral substituents. Finally, the push–pull impact of the combination of 5-methylthiophen-2-yl and pyridin-3-yl substituents of **7** can be investigated for the corresponding ZnAzaPc. The choice of pyridin-3-yl instead of pyridin-2-yl substituents



Scheme 3. Synthesis of unsymmetrically substituted pyrazine-2,3-dicarbonitrile **7**.

in the present study may seem unmotivated. However, other workers have reported that mixed benzoins could not be obtained from pyridine-2-carboxaldehyde [30].

3.1.1. Ethane-1,2-diones **1a–b**, and **6**

The symmetric ethane-1,2-diones **1a** and **1b** can be prepared by several methods and we have considered the following three: The best known method for synthesis of α-diketones is the cyanide catalyzed condensation of aromatic aldehydes to give benzoins, which can be oxidized to benzils by various oxidants. However, many heterocyclic aldehydes do not undergo benzoin condensation [30] but the reactivity seems difficult to predict [16]. A second method for synthesis of α-diketones is acylation of the heterocycle with oxalyl chloride [17] or with 1,1′-oxalyldiimidazole [20]. A third possibility is formation of an anil from the heterocyclic carboxaldehyde, followed by cyanide catalyzed condensation to the dianil, and finally acid hydrolysis to the α-diketone [19,31].

Benzoin condensation is the obvious choice for synthesis of the unsymmetric ethane-1,2-dione **6**. Our first intention was, therefore, to prepare compounds **1** and **6** by the same type of reactions, *i.e.* benzoin condensations. Di(5-methylthiophen-2-yl)ethanedione (**1a**), was reported many years ago [16] and was obtained (30%) in two steps from a benzoin condensation of 5-methylthiophene-2-carboxaldehyde, followed by oxidation with cupric sulphate and pyridine. A far better yield of compound **1a** (60%) was obtained recently [17] when aluminium chloride was used as catalyst for the acylation of 2-methylthiophene with oxalyl chloride. Although this is the preferred method for synthesis of **1a**, we also prepared **1a** (20–25%) in one step from the cyanide catalyzed condensation of 5-methylthiophene-2-carboxaldehyde [16,18] due to spontaneous air oxidation of the intermediate benzoin.

There are several reported methods for the synthesis of di(pyridin-3-yl)ethanedione (**1b**). No physical data were given for 3,3′-pyridoin [21], but presumably the compound was obtained from a benzoin condensation. Burgess reagent was reported to oxidize 2,2′-pyridoin [32,33] and might be used for oxidation of 3,3′-pyridoin as well. The formation of bis-anils from aromatic carboxaldehydes, and subsequent acid hydrolysis to α-diketones was reported for aromatic compounds in general [31] and specifically for **1b** [19]. However, whereas neutral compounds like benzil precipitate from the acidic solution [31], the pyridine groups of **1b** will be protonated and the reaction mixture must be neutralized with base to obtain **1b**. Compound **1b** was also prepared from a low temperature (−70 °C) reaction between pyridin-3-yl-magnesium bromide and 1,1′-oxalyldiimidazole [20]. However, pyridin-3-yl-magnesium bromide must be prepared by a Grignard exchange reaction of 3-bromopyridine with either an alkyl [34] or an aryl [35] Grignard reagent.

We report two methods for preparation of **1b**. In method A **1b** is obtained from pyridine-3-carboxaldehyde via the dianil [19], but with slight modifications. The intermediate bis-anil was obtained (72%), hydrolysis of the bis-anil gave **1b** (63%), thus, total yield of **1b** was 45%. Method B is a cyanide catalyzed benzoin condensation of pyridine-3-carboxaldehyde, which gave a viscous product. According to NMR analysis this product was a mixture of two major components. These compounds were identified as the pyridoin 2-hydroxy-[di(pyridin-3-yl)]ethane-1-one (ca. 65%), *i.e.* precursor of **1b**, and nicotinic acid (ca. 30%). Nicotinic acid crystallized in portions from acetone and methanol solutions of the crude, and a total of 33% of nicotinic acid was isolated. However, the remaining yellow oil did not crystallize, probably due to the presence of two minor, unidentified compounds, and the expected pyridoin racemate. Various methods [16,30,32] were tested for oxidation of the crude pyridoin, but the resulting product mixtures were not easily purified. The cleanest oxidation was obtained from a reaction of the pyridoin with activated alumina at 140 °C [36]. Compound **1b** (20%), R_f (acetone) = 0.64, was obtained by extraction with acetone and chromatography on silica. Another product, R_f (acetone) = 0.4, was eluted from the silica column as well. This product, 2-(pyridin-3-yl)oxy-1,2-di(pyridin-3-yl)ethanone, is shown in Scheme 1 as (**1b** + C_6H_5NO) and was obtained as a viscous oil. The structure of this "trimer", expectedly a racemic mixture, was confirmed by NMR spectroscopy and ESIMS spectrometry. Therefore, at present, method A seems preferable to the benzoin condensation, but there certainly is room for improved syntheses of **1b**.

The mixed condensation of 5-methylthiophene-2-carboxaldehyde and pyridine-3-carboxaldehyde with sodium cyanide in DMF, gave **5** (50%), 2-hydroxy-1-(5-methylthiophen-2-yl)-2-(pyridin-3-yl)ethanone, as shown in Scheme 3. The structure, *i.e.* with the carbinol group attached to pyridine, was confirmed by NMR analysis. Oxidation of **5** with activated alumina, gave the new compound **6** (ca. 30%) as an orange liquid. Oxidation of **5** with ammonium nitrate, catalyzed by cupric acetate [30] gave approximately the same yield (32%) of **6** as a red liquid. The reason for choosing 5-methylthiophene-2-carboxaldehyde instead of thiophene-2-carboxaldehyde for condensation with pyridine-3-carboxaldehyde is the low reactivity of the methyl derivative towards self-condensation.

3.1.2. Glyoxals **3a** and **3b**

(5-Methylthiophen-2-yl)glyoxal (**3a**) has not been reported earlier and was synthesized in two steps, *i.e.* by acetylation of 2-methylthiophene, followed by oxidation of 2-acetyl-5-methylthiophene with selenium dioxide. NMR analysis of compound **3a** shows a dimer where the aldehyde groups of the two glyoxal molecules form a six-membered ring through hydrogen bonds (Scheme 2). The ^{1}H NMR doublet at 6.12 ppm, J = 10.1 Hz, is the signal of two aldehyde hydrogen atoms, one in each molecule, since both HSQC and HMBC show the H/C connection 6.12 ppm/89.72 ppm. HSQC shows the connection aldehyde H/aldehyde C of one molecule, whereas the long range coupling HMBC shows the connection aldehyde H of one molecule/aldehyde C of the second molecule of **3a**. The ^{1}H NMR doublet at 4.92 ppm, J = 10.1 Hz, is the signal of two water-hydrogen atoms since no HSQC connection was found to any carbon atom. Two HMBC connections were found for the doublet at 4.92 ppm, namely to the aldehyde carbon at 89.72 ppm of the neighbor molecule, and to the carbonyl carbon at 185.5 ppm of the molecule water was attached to. The other hydrogen atoms of the two water molecules would be subject to exchange with water in the solvent and were not identified. Both ^{1}H and ^{13}C NMR spectra of a chloroform solution of **3a** showed a slow change from dimer to monomer after some days. NMR analyses of (thiophen-2-yl)glyoxal **3b** show the same type of hydrated dimer as for **3a**.

3.1.3. Pyrazine-2,3-dicarbonitriles **2**, **4** and **7**

Pyrazine-2,3-dicarbonitriles **2a–b** and **7** were obtained (50–60%) by heating acetic acid solutions of diaminomaleonitrile (DAMN), with ethane-1,2-diones **1a–b** and **6** under reflux. Compound **2b** turned dark green as it melted at 268–274 °C. The green colour indicates cyclotetramerization to the substituted AzaPc, which is noticeable since the analogue 5,6-di(pyridin-2-yl)pyrazine-2,3-dicarbonitrile has a sharp melting point at 174 °C [37] and no trace of green colour was observed at 174–176 °C [38]. Acetic acid solutions of DAMN and glyoxals **3a–b** gave pyrazine-2,3-dicarbonitriles **4a–b** (50–88%) at ambient temperature; the lower reaction temperature is ascribed to less steric hindrance for these glyoxals.

3.1.4. Zinc azaphthalocyanines **8**–**10**

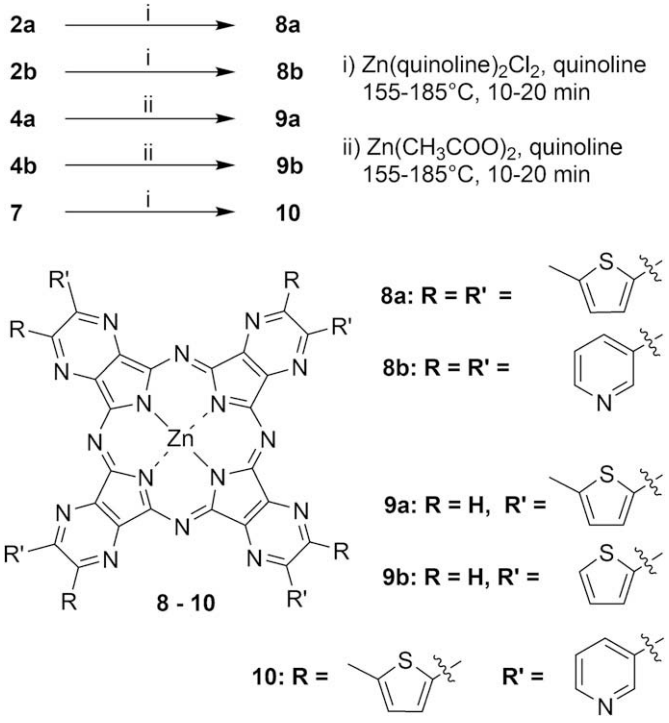
The macrocyclic zinc complexes **8**–**10** were prepared by condensations of monomers **2**, **4** or **7** either with dry zinc(II) acetate and quinoline, or with the salt $Zn(quinoline)_2Cl_2$ [26] and quinoline, at 160–185 °C for 10–20 min (Scheme 4). Except for the tetrasubstituted **9b**, the zinc(II) complexes were obtained in better yields and purity by using $Zn(quinoline)_2Cl_2$ instead of $Zn(OAc)_2$ for the cyclotetramerizations. The substituted ZnAzaPcs **8**–**10** could not be purified by chromatography due to low solubility or strong adsorption on silica or alumina. Compounds **8b**, **9a** and **9b** could be purified by heating under reflux, sequentially with mixtures of methanol and water, acetone and water, and finally with acetone. However, compounds **8a** and **10** were somewhat unstable under reflux, and therefore were treated at ambient temperature and sonication with the above mentioned solvents.

The solubility of **8a** in pyridine was too low for NMR analysis. Two equally strong sets of ^1H and ^{13}C NMR signals were found for octa(pyridin-3-yl) substituted **8b**. One explanation for the appearance of two isomers for **8b** is steric strain between the two pyridine substituents on each pyrazine moiety. Support for this assumption is the observation of one set of ^1H and ^{13}C NMR signals for octasubstituted **10**, where less steric strain is expected between one pyridine and one methylthiophene substituent on each pyrazine moiety.

3.2. UV–vis absorption

The strongest UV–vis absorption band, the Q-band, is observed in pyridine at 636 nm for unsubstituted ZnAzaPc and at 674 nm for its phthalocyanine analogue ZnPc. The 38 nm blue shift for ZnAzaPc is caused by the additional nitrogen atoms in this macrocycle. However, the substituents of ZnAzaPcs **8**–**10** cause red shift of the Q-bands to 660–679 nm as summarized in Table 1.

Thiophen-2-yl contributes somewhat less than 5-methylthiophen-2-yl to the red shift. Thus, eight thiophen-2-yl substituents give a 37 nm red shift to 673 nm [10], whereas eight



Scheme 4. Synthesis and structures of substituted zinc azaphthalocyanines **8**–**10**. Compounds **9** and **10** are unsymmetrical since R differs from R′. Only one possible constitutional isomer is shown for each of compounds **9**–**10**.

Table 1
Spectral, photophysical and photochemical data of the substituted ZnAzaPc in pyridine.

Compound	Peripheral substitution	Absorbance, λ_{max} (nm)	Fluorescence, λ_{max} (nm)	Φ_Δ	Φ_F
ZnAzaPc	H H	636	644	0.487	0.306
8a	5-Methylthiophen-2-yl 5-Methylthiophen-2-yl	679	686	0.196	0.020
8b	Pyridin-3-yl Pyridin-3-yl	658	665	0.505	0.190
9a	5-Methylthiophen-2-yl H	666	673	0.554	0.163
9b	Thiophen-2-yl H	661	669	0.555	0.179
10a	5-Methylthiophen-2-yl Pyridin-3-yl	673	681	0.585	0.125

5-methylthiophen-2-yl groups contribute 43 nm to a Q-band at 679 nm (**8a**). A similar comparison of compounds **9b** and **9a**, with respectively four thiophen-2-yl and four 5-methylthiophen-2-yl substituents, shows Q-band red shifts of 25 nm and 30 nm. The calculated value of the red-shift contribution of one thiophen-2-yl group is 4.8 nm for octasubstitution, and 6.3 nm for for tetrasubstitution. The larger contribution from each substituent in tetrasubstituted macrocycles may be caused by less steric strain between the substituents, and consequently increased possibility for resonance between the macrocycle and substituents. A similar comparison is valid for the contribution from each 5-methylthiophen-2-yl substituent, *i.e.* 5.38 nm (**8a**) and 7.50 nm (**9a**). Compound **8b** absorbs at 658 nm and the red-shift contribution from one pyridin-3-yl substituent is 2.75 nm, calculated from the 22 nm red shifted Q-band of **8b**. This compares well to the Q-band position at 657 nm for the zinc complex with eight pyridin-2-yl substituents [10]. In this case the change in position of substitution from 2- to 3- does not play an important role. Combined substituents of the unsymmetric complex **10** induce a red shifted Q-band which is found at 673 nm. The 37 nm red shift of the Q-band for compound **10** compares well with 33 nm, the calculated sum of contributions from four 5-methylthiophen-2-yl and four pyridin-3-yl substituents in octasubstituted ZnAzaPcs. The small difference between calculated and observed data can be explained by increased steric strain between five- and six-membered peripheral substituents compared to the steric strain between only five-membered substituents.

3.3. Singlet oxygen

Singlet oxygen quantum yields were determined using the specific chemical trap for singlet oxygen, 1,3-diphenylisobenzofuran (DPBF) [27,28]. The singlet oxygen quantum yields (Φ_Δ) were measured in pyridine. A value $\Phi_\Delta = 0.487$ was found for unsubstituted ZnAzaPc. The singlet oxygen production of this macrocycle may be considered as not influenced by the periphery (*i.e.* hydrogens make no contribution to singlet oxygen) and therefore taken as a basic value in the following calculations. A considerably higher singlet oxygen production ($\Phi_\Delta = 0.61$), was observed for unsubstituted ZnPc in pyridine solution [29]. The data obtained for synthesized compounds are summarized in Table 1.

Tetrasubstituted complexes, **9a** with four 5-methylthiophen-2-yl and **9b** with four thiophen-2-yl substituents, do not differ in singlet oxygen production from each other. In other words, the methyl substituent of thiophene has no influence on singlet oxygen production. The value $\Phi_\Delta = 0.635$ was found previously for octa(-thiophen-2-yl)ZnAzaPc [10]. If we subtract $\Phi_\Delta = 0.487$ for ZnAzaPc from this value, the contribution from eight thiophen-2-yl groups is

$\Delta\Phi_\Delta = 0.148$, and for four of them $\Delta\Phi_\Delta = 0.074$. The contribution from four thiophen-2-yl groups of **9b** is $\Delta\Phi_\Delta = 0.555 - 0.487 = 0.068$. Good correlation between these two measured values of $\Delta\Phi_\Delta$ strongly indicates additive contributions from peripheral thiophen-2-yl groups to singlet oxygen production. Unfortunately, due to extensive aggregation (see also below) of compound **8a** in pyridine, the low value $\Phi_\Delta = 0.196$ is not representative for the contribution from eight 5-methylthiophen-2-yl substituents and cannot be used for the calculations. We cannot explain why the methyl groups of **8a** do not have the expected effect of alkyl-substituents, *i.e.* enhanced solubility and less aggregation due to greater distance between the macrocycles. However, the disorder due to unsymmetrical substitution of **9a**, obviously prevents aggregation and improves solubility.

A comparison of $\Phi_\Delta = 0.505$ for octa(pyridin-3-yl)ZnAzaPc (**8b**) and $\Phi_\Delta = 0.531$ for octa(pyridin-2-yl)ZnAzaPc [10], shows that the pyridine-position of attachment to the macrocycle is of some significance. We have observed a similar difference between thiophen-2-yl and thiophen-3-yl peripheral substituents on ZnAzaPc [27].

The measured singlet oxygen production of **10** is $\Phi_\Delta = 0.585$. We consider this value to be the sum of the observed $\Phi_\Delta = 0.554$ for **9a** (having four methylthiophen-2-yl groups) and $\Delta\Phi_\Delta = 0.009$, the contribution from four pyridin-3-yl groups of **8b**. This gives a calculated value $\Phi_\Delta = 0.563$ for **10** in good agreement with observed $\Phi_\Delta = 0.585$ for this compound. These and previous results [10,12,27] indicate that any peripheral substituent on ZnAzaPc will make a specific contribution to the singlet oxygen production of the complex, and such contributions are additive. However, other factors, e.g. aggregation or electron transfer [39], may interfere and must be taken into account.

3.4. Fluorescence

Fluorescence measurements were performed in pyridine. The shapes of the emission spectra were typical for AzaPc derivatives (see example for **9b** on Fig. 1) with only small Stokes shift of the maxima. The excitation spectra were measured for all derivatives and are in perfect accordance with absorption spectra (Fig. 1). This confirmed exclusively monomeric character which is necessary prerequisite for accurate measurements of quantum yields. The absorption spectrum would be altered significantly if dimers or higher aggregates were formed in the solution. However, the fluorescence excitation spectrum is not influenced because the aggregates usually do not fluoresce except for the few examples of J-dimers [39,40]. As mentioned above, compound **8a** showed

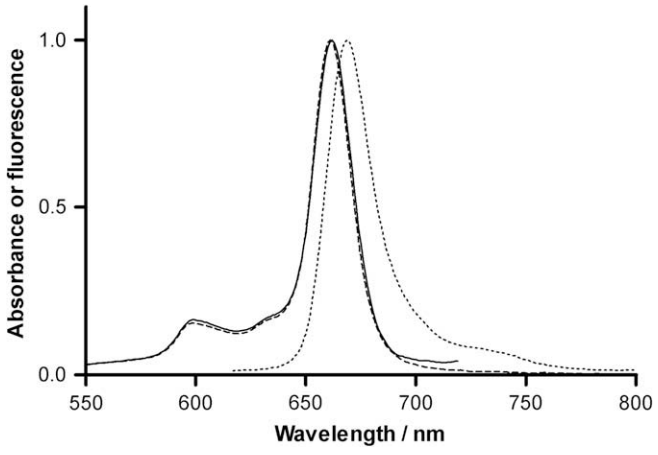


Fig. 1. Normalized UV–vis absorption (dashed), fluorescence excitation (full) and fluorescence emission (dotted) spectra of compound **9b** in pyridine.

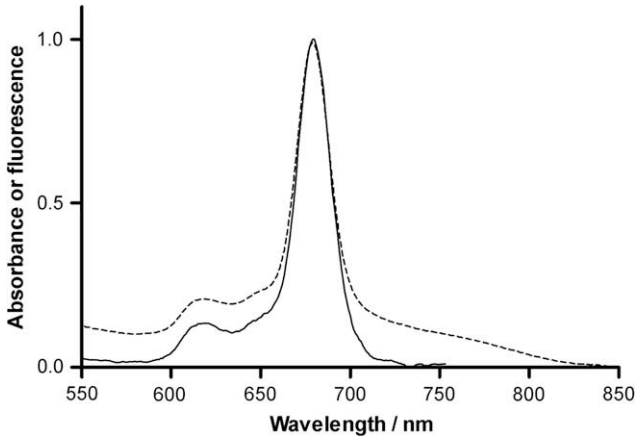


Fig. 2. Normalized UV–vis absorption (dashed) and fluorescence excitation (full) spectra of compound **8a** in pyridine.

important aggregation that decreased its singlet oxygen quantum yield. Therefore as anticipated, its absorption spectrum did not correspond to the excitation spectrum (Fig. 2, note the broad absorption over 700 nm). Also the fluorescence quantum yield Φ_F (Table 1) of **8a** was very low due to extensive aggregation in solution.

The fluorescence quantum yield Φ_F for a pyridine solution of unsubstituted ZnAzaPc is 0.306, whereas $\Phi_F = 0.20$ for the phthalocyanine analogue ZnPc [29]. This indicates a significant influence on fluorescence quantum yields by the additional nitrogen atoms in the macrocyclic core of ZnAzaPc. Together with results from singlet oxygen we may conclude that these nitrogen atoms cause release of the absorbed energy as fluorescence, at the expense of singlet oxygen production.

A general substituent effect which induces higher singlet oxygen production and lower fluorescence quantum yield than unsubstituted ZnAzaPc, is indicated for compounds **8**–**10** (Table 1). However, specific effects on the relation between Φ_F of different substituents was not apparent for these compounds, but further studies of related compounds could give other indications.

4. Conclusion

Important characteristics, such as solubility, UV–vis absorption, singlet oxygen production, fluorescence spectra and quantum yields, are strongly influenced by peripheral substituents on ZnAzaPc. In order to reveal potentially quantitative relations between substituents and these effects, we have investigated ZnAzaPcs with thiophen-2-yl, methylthiophen-2-yl and pyridin-3-yl groups, attached to the macrocycle through carbon–carbon bonds.

The UV–vis absorption spectra of tetrasubstituted complexes **9a** and **9b** show that methylthiophene (of **9a**) makes a larger contribution to the Q-band red shift than thiophene does. A similar comparison between octasubstituted **8a** and octa(thiophen-2-yl)ZnAzaPc confirms this. However, each substituent of tetrasubstituted compounds **9** contributes more to the Q-band red shift than the corresponding substituent of the octasubstituted complexes, most probably caused by some steric hindrance in the octasubstituted complexes. Octa(pyridin-3-yl)ZnAzaPc **8b** has a Q-band absorption at 658 nm, which shows that each pyridine substituent gives a lower contribution to the Q-band red shift than thiophene. Additive and substituent-specific contributions to the Q-band red shift are confirmed for compound **10**.

Generally Φ_Δ values increase with substitution on ZnAzaPc whereas the Φ_F values decrease. The observed singlet oxygen productions of synthesized compounds together with those

investigated previously confirm that contributions to Φ_Δ from the substituents of these compounds are both additive and substituent specific.

As expected, unsymmetrically substituted ZnAzaPcs such as **9** and **10** are more soluble in organic solvents than the symmetrical compounds **8**.

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