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Syntheses and properties of octa-, tetra-, and di-hydroxy-substituted phthalocyanines

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ABSTRACT

The synthesis and photophysical properties of a new series of zinc(II) phthalocyanines (ZnPcs) bearing multiple hydroxy and *tert*-butyl groups are reported. The X-ray structures of two phthalonitriles and one ZnPc are presented. All hydroxy-substituted ZnPcs show low fluorescence quantum yields in DMSO and complete fluorescence quenching in aqueous solutions, but high singlet oxygen quantum yields in DMSO (0.2–0.7). Our results suggest that the tetra- and octa-hydroxy ZnPcs might find application as photosensitizers in the PDT treatment of cancer.

1. Introduction

Phthalocyanines (Pcs) are promising photosensitizers for application in the photodynamic therapy (PDT) of cancers,[1,2] and a few Pc derivatives are currently undergoing clinical evaluations. PDT is a binary treatment modality that involves the activation of a tumor-localized photosensitizer with red light.[3,4] The electronically excited photosensitizer in the triplet state (formed via intersystem crossing from a short-lived excited singlet state) reacts with triplet molecular oxygen to generate in situ singlet oxygen, as well as other cytotoxic reactive oxygen species (ROS), that destroy malignant tissues. PDT has several advantages over other cancer treatments, including its minimal invasiveness and highly tumor-localized nature upon careful light delivery and availability of tumor-specific photosensitizers. One porphyrin derivative, Photofrin®, is FDA-approved for the PDT treatment of melanoma, early and advanced stage cancer of the lung, digestive tract, genitourinary tract, and Barret's esophagus. However this drug absorbs only weakly in the red region of the optical spectrum where light penetrates deepest into human tissues, and therefore has limited application in the treatment of large and/or deep-seated tumors. Since Pcs have characteristic intense absorptions in the red region of the optical spectrum (ca. 700 nm), high photochemical stability, and are effective generators of singlet oxygen, they have been found to be highly promising PDT photosensitizers.[2,5] However, their well-known tendency for aggregation, mainly in aqueous media, and subsequent reduction of their photosensitizing ability has limited their application in PDT.[6] Water-solubilizing and bulky groups, such as carboxylates,[7] pyridyls,[8] sulfonates,[9] phosphonates,[10] carboranyls,[11] and *tert*-butyl[12] groups have been introduced at either the Pc periphery or as axial ligands on metallo-Pcs as a means to minimize Pc aggregation. In particular bulky substituents (such as *tert*-butyl groups) and neutral water-solubilizing groups (such as hydroxy and PEG) at the photosensitizer periphery can potentially increase the amphiphilicity and permeability across cellular membranes of Pcs, while decreasing macrocycle aggregation. Our group[12,13] and others[14] have reported the synthesis and properties of PEG-substituted porphyrins and Pcs, and discovered that multiple PEG groups at the macrocycle periphery can in fact induce aggregation and/or singlet oxygen inactivation. On the other hand multi-hydroxy-substituted macrocycles based on porphyrin,[15,16] chlorin,[17,18] pheophorbide,[19] and Pc[20,21] have been reported and shown to be promising photosensitizers for PDT. One such compound, *meso*-tetra-hydroxyphenylchlorin (mTHPC) known as Foscan, is currently undergoing clinical investigations for application in PDT.[22] Herein we report the synthesis and photophysical properties of a new series of hydroxy-substituted ZnPcs, bearing either two, four or eight hydroxy groups, as well as bulky *tert*-butyl groups.

2. Results and discussion

Three different strategies were employed for the synthesis of octa-, tetra-, and di-hydroxy Pcs, as pure compounds, as shown in Schemes 1–3, respectively. The key precursor to the di- and octa-hydroxy-substituted Pcs, 4,5-di(2,5-di-*tert*-butyl-4-methoxy)phthalonitrile **1**, was prepared in 77% yield from commercially available 4,5-dichlorophthalonitrile and 2,5-di-*tert*-butyl-4-methoxyphenol in the presence of potassium carbonate.[23] Two different methods were investigated for the macrocyclization reaction of phthalonitrile **1**. The first method involved the reaction of

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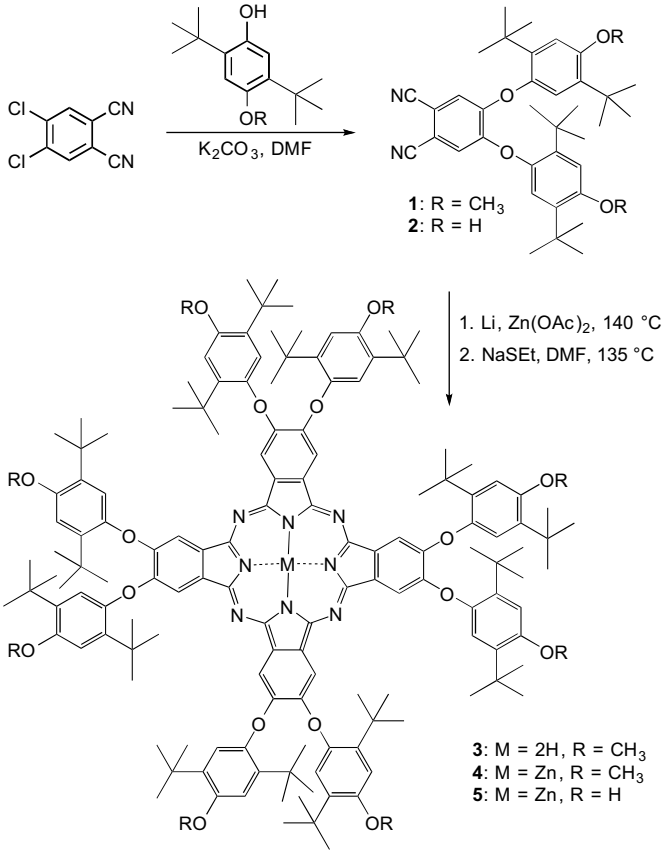
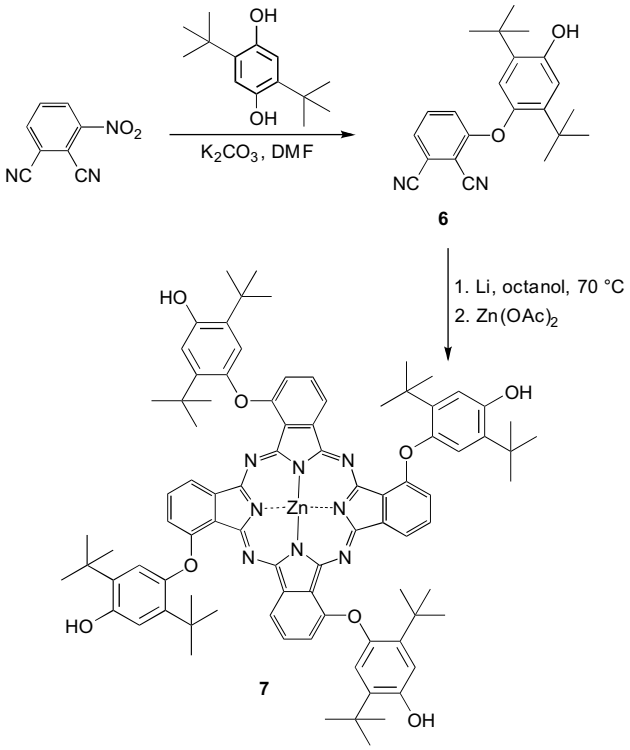
1 and anhydrous zinc acetate in dry NMP as a solvent at 150 °C for 1 day,[23,24] and afforded Zn-Pc **4** in only 9% yield after chromatographic purification. In the second method, precursor **1** was treated with lithium metal in dry pentanol followed by zinc acetate to afford the octamethoxy-substituted Zn-Pc **4** in 31% yield. The metal-free Pc **3** was subsequently isolated in 30% yield upon treatment of Zn-Pc **4** with acetic acid. The molecular structure of Zn-Pc **4** is shown in Figure 1. The structure contains two independent molecules, both lying on inversion centers. Only one of them is shown in the figure. Since the coordination of the Zn atom in each molecule is square pyramidal, with Zn lying slightly (0.28(2) and 0.43(2) Å) out of the plane of the four coordinated basal N atoms, the Zn atoms are disordered into half-populated sites. In one of the two independent Zn complexes, the apical ligand is coordinated solvent methanol. In the other, the apical position appears to be water, but since this site is disordered, sharing a site with solvent dichloromethane, that is uncertain. In both Zn complexes, the 24-atom Pc core is reasonably planar, with mean deviations being 0.06 and 0.03 Å.

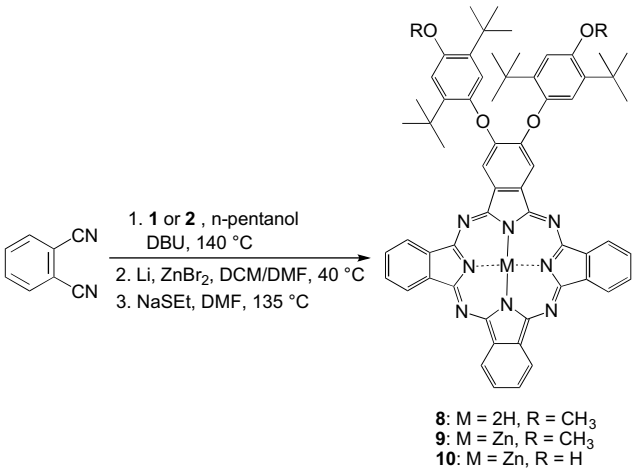
The tetra-hydroxy Zn-Pc **7** was synthesized and isolated as the pure C_{4h} isomer, as indicated in Scheme 2. The precursor 3-(2,5-di-*tert*-butyl-4-hydroxyphenoxy)phthalonitrile **6** was prepared in 38% yield by reacting 3-nitrophthalonitrile with 2,5-di-*tert*-butyl-hydroquinone. A side product isolated from this reaction, in 46% yield, was the corresponding diphthalonitrile species, which might be a valuable precursor in the preparation of Pc dimers. The X-ray structure of phthalonitrile **6** is shown in Figure 2, and that of the diphthalonitrile is shown in Figure 3. In **6**, the CN distances are 1.144(2) and 1.146(2) Å, and the two six-membered rings form a dihedral angle of 71.23(4)°. The conformations of the *tert*-butyl groups are such that the methyl group *anti* to the oxygen substituent is eclipsed with the phenyl plane (C–C–C–C torsion angle



Scheme 1. Synthesis of octa-hydroxy-Pc **5**.



Scheme 2. Synthesis of tetra-hydroxy-Zn-Pc **7**.



Scheme 3. Synthesis of di-hydroxy-Pc **10**.

magnitudes 0.5(2) and 1.1(2)°). In the two independent, centrosymmetric molecules of the diphthalonitrile, the CN distances are in the range 1.143(2)–1.148(2) Å. The dihedral angle formed by the central phenyl ring and each phthalonitrile plane is 64.25(3)° in one molecule and 59.87(3)° in the other. The *tert*-butyl conformations are quite similar to those in **6**, with relevant torsion angle magnitudes 0.9(2) and 9.6(2)°.

Several reagents were investigated for the demethylation of Pc **4**, including boron tribromide,[25,26] boron tribromide dimethylsulfide complex,[27] pyridine hydrochloride,[28] iodotrimethylsilane (TMSI),[29,30] and sodium ethanethiolate.[31,32] In the presence of BBr_3 at −78 °C for 24 h, one, two or three of the *tert*-butyl groups of Pc **4** were also cleaved, as was indicated by MALDI-TOF mass spectrometry, and only 1% of Pc **5** was isolated

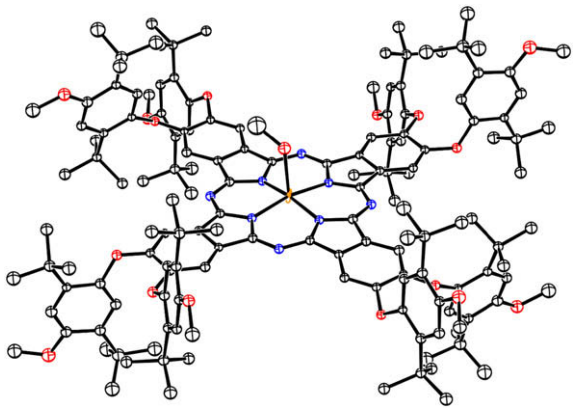


Figure 1. One of the two independent, centrosymmetric molecules of ZnPc **4**. Only one of the disordered Zn positions is shown, and H atoms are omitted.

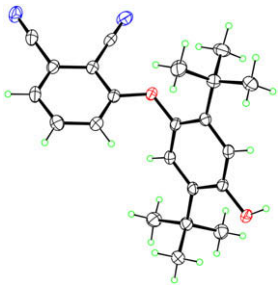


Figure 2. Molecular structure of phthalonitrile **6**.

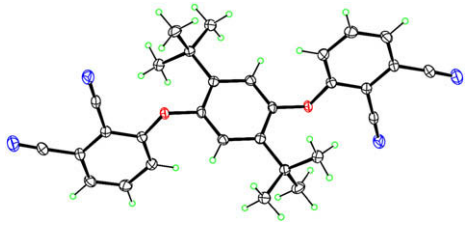


Figure 3. Molecular structure of diphthalonitrile showing only one of the two independent molecules.

after chromatographic purification. When the dimethylsulfide complex $BBr_3 \cdot SMe_2$ was used under similar conditions no Pc **5** was formed even after 2 days, as indicated by MALDI-TOF mass spectrometry. The same result was observed when pyridine hydrochloride or iodotrimethylsilane was used. However, an excess of sodium ethanethiolate in dry DMF under argon at 135 °C for 1 day afforded Pc **5** in 25% yield (5% overall from the commercially available 4,5-dichlorophthalonitrile). The reaction was followed by MALDI-TOF mass spectrometry and partial cleavage of the di(*tert*-butyl)phenoxy groups was also observed to occur under these conditions, leading to the low yield. Pc **5** can also be synthesized directly by cyclotetramerization of the di-hydroxy-substituted phthalonitrile **2** in the presence of lithium metal in dry pentanol, followed by zinc acetate in 9% overall yield (2% from 4,5-dichlorophthalonitrile). Phthalonitrile **2** was obtained in 27% yield from reaction of 2,5-di-*tert*-butyl-hydroquinone with 4,5-dichlorophthalonitrile. Although the overall yield for Pc **5** using the latter synthetic strategy is lower, this methodology involves only two rather than three steps and therefore can be completed within a shorter time period.

The macrocyclization of phthalonitrile **6** under the same conditions as **1** and **2** led to the expected mixture of four possible ZnPc isomers that were difficult to separate.[33,34] Using optimized reaction conditions (vide infra) the major C_{4h} isomer **7** was isolated in 15% yield. The formation of the C_{4h} over the C_{2v}, C_s and D_{2h} structural isomers was favored by a low reaction temperature (70 °C rather than 150 °C normally used in this type of macrocyclization), a longer reaction time (3 days rather than 1 day) and the presence of the bulky *tert*-butyl group at the α position of phthalonitrile **6**, as previously observed.[35,36]

The pure A_3B-type Pc **8** was synthesized from condensation of **1** with a 40-fold excess of phthalonitrile in dry pentanol, using DBU as the catalyst, as shown in Scheme 3. We have previously shown that using such a large excess of phthalonitrile minimizes the formation of the A_2B_2-type Pc products.[11] Under these conditions only the A_3B-type Pc **8** and the unsubstituted A_4-type Pc were obtained, as indicated by MALDI-TOF mass spectrometry of the crude reaction mixture. Since the unsubstituted A_4-type Pc is highly insoluble, it is conveniently removed by filtration, thus greatly simplifying the purification process. The A_3B-type Pc **8** was isolated in 12% yield, after chromatographic purification. The metalation of Pc **8** using zinc(II) dibromide in dry DMF did not afford Pc **9**, due to the poor solubility of the free-base in DMF. However, at reflux in dichloromethane for 2 h and in the presence of zinc(II) dibromide, the ZnPc **9** was obtained in quantitative yield. The deprotection of the methoxy groups of Pc **9** using sodium ethanethiolate under our above optimized conditions produced a mixture of metalated and unmetalated di-hydroxy Pcs. Re-metalation of the soluble di-hydroxy Pcs with zinc(II) dibromide in dry DMF gave the target ZnPc **10** in 10% overall yield. ZnPc **10** was also obtained via condensation of **2** with a 40-fold excess of phthalonitrile in the presence of a catalytic amount of DBU, at 140 °C in dry pentanol. The free-base Pc was identified by MALDI-TOF mass spectrometry (*m*/*z* 954.90), and upon metalation using zinc(II) dibromide in DMF at 40 °C afforded ZnPc **10** in 6% overall yield.

The structures of all Pcs were confirmed by UV–vis, MS, and ^{1}H NMR spectroscopy. While the octa- and tetra-hydroxy Pcs **5** and **7** are highly soluble in polar organic solvents, such as dichloromethane, THF, acetone, methanol, acetonitrile, DMF, and DMSO, the di-hydroxy-Pc **10** is less soluble and has higher tendency for aggregation, even in polar organic solvents such as dichloromethane and methanol (vide infra). In the mass spectrum (ESI) of Pc **5** the molecular ion was observed at *m*/*z* 2338.2421 ($[M+H]^+$) and the double-negative molecular ion at *m*/*z* 1168.6159 ($[M-2H]^{2-}$), according to its assigned structure. Similarly for Pcs **7** and **10** the molecular ions were observed at *m*/*z* 1459.6721 ($[M+H]^+$) and *m*/*z* 1016 ($[M+H]^+$) on their mass spectra (ESI), respectively.

The ^{1}H NMR spectrum of Pc **5** in deuterated acetone shows three sharp downfield signals at 8.8 ppm (singlet), 7.06 ppm (doublet), and 7.03 ppm (doublet), due to, respectively, the Pc backbone and the phenoxy protons at the macrocycle periphery. The OH protons gave a broad signal at 8.1 ppm, while the two types of *tert*-butyl protons appeared upfield at 1.5 and 1.3 ppm, according to the assigned structure. On the other hand, the ^{1}H NMR spectrum for Pc **7** of C_{4h} symmetry is in agreement with previously reported values for C_{4h} Pcs,[37,38] with the phenoxy protons appearing between 7.2 and 7.3 ppm. In addition, as seen in Figure 4, the OH protons of Pc **7** appear at 8.4 ppm, as indicated by the disappearance of this signal upon addition of one drop of D_2O to the NMR solution. The presence of D_2O also caused a more clear slitting (triplet) of the hydrogen at the γ position of the Pc backbone, which suggests that in acetone solution intermolecular hydrogen bonding occurs between the OH groups of different Pc molecules. Such intermolecular hydrogen bonding has been previously observed in the case of a hydroxy-substituted porphyrin.[39] The ^{1}H NMR spectrum of Pc **10** in deuterated DMF shows the aromatic signals

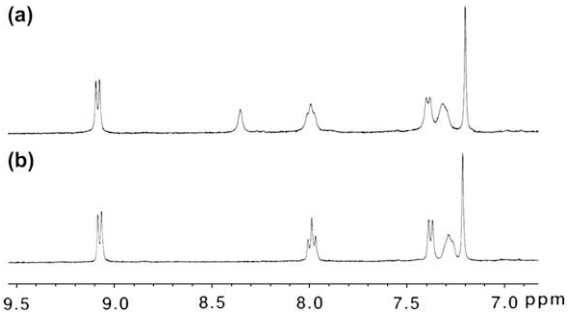


Figure 4. ^{1}H NMR spectra of ZnPc **7** (aromatic region only) in (a) acetone-d_6 and in (b) acetone-d_6 with one drop of D_2O.

downfield at about 7 ppm and aliphatic protons around 3 ppm. The Pc macrocycle protons on the three identical isoindole subunits appear in the downfield region between 8.13 and 9.61 ppm along with two kinds of substituted phenyl ring protons at 7.32 (singlet) and 7.28 (singlet) ppm, respectively.

The absorption spectra of the octa-, tetra-, and di-hydroxy-Pcs **5**, **7**, and **10** in acetone show characteristic strong and sharp Q bands with $\varepsilon > 10^5$ L mol^{-1} cm^{-1}, as shown in Figure 5. As expected, the λ_{max} for the Q bands of Pcs **5**, **7**, and **10** were found to be 679, 698 and 668 nm, respectively. The significant red-shift observed in the case of Pc **7** is due to its substitution at the α (rather than β) position of the macrocycle, as we have previously observed.[40] Table 1 summarizes the spectral properties observed for Pcs **5**, **7**, and **10** in DMSO. All Pcs showed similar Stokes' shifts in DMSO and other polar organic solvents (~3 nm), and 7–12 nm red-shifted Q bands in DMSO compared with other solvents, e.g., acetone. Interestingly, the fluorescence quantum yields of Pcs **5** and **7** were almost two orders of magnitude lower than that found for Pc **10** and other neutral Pcs,[8] maybe as a result of intermolecular hydrogen bonding and assembly of these hydroxy Pcs, as has been previously observed in the case of mTHPC photoproducts.[41] On the other hand, Pcs **5** and **7** showed significantly higher singlet oxygen quantum yields (of the order of 0.7) than the di-hydroxy-Pc **10** (of the order of 0.2) and other previously reported positively charged Pcs.[8] In phosphate buffer at pH 7.4, all Pcs showed significantly less intense Q band absorptions, broadened and red-shifted by 3–12 nm as shown in Figure 5, indicating aggregation. In addition, Pc **10** shows a split absorption with λ_{max} at 628 and 680 nm, suggesting the

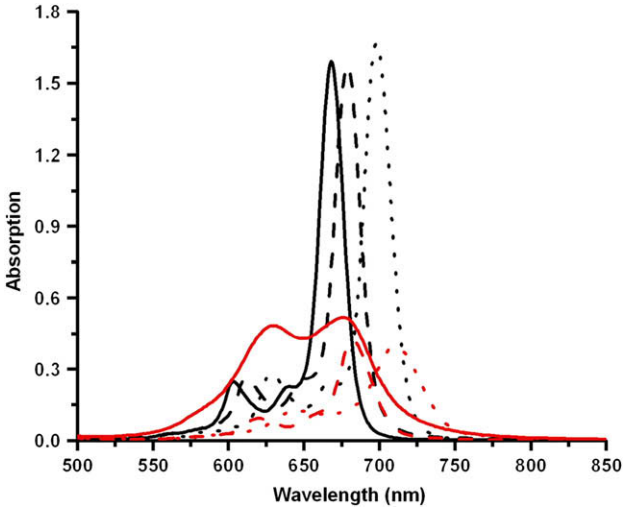


Figure 5. Absorption spectra of ZnPcs **5** (dashed line), **7** (dotted line), and **10** (solid line) at 8 μM solution in acetone (black) and buffer pH=7.4 (red).

Table 1
Spectral properties of ZnPcs **5**, **7**, and **10** in DMSO at room temperature

Pc	Absorption λ_{max} (nm)	Emission[a] λ_{max} (nm)	Φ_f[b]	Stokes' shift (nm)	Φ_Δ[c]
5	686, 618	689	0.004	3	0.692
7	710, 638	713	0.003	3	0.693
10	676, 609	679	0.20	3	0.201

[a] Excitation at 620 nm.
[b] Calculated using ZnPc as the standard.
[c] Determined using ZnPc as reference and DPBF as scavenger.

presence of at least two types of Pc aggregates in aqueous solution. Fluorescence quenching was observed for all Pcs in aqueous solution, as a result of Pc aggregation.

3. Conclusions

The total syntheses of an octa-, a tetra-, and a di-hydroxy-substituted ZnPcs as pure compounds, using different strategies are reported. NMR and spectrophotometric data suggest that these hydroxy-substituted Pcs may undergo intermolecular hydrogen bonding in polar organic solvents, such as DMSO and acetone. The octa- and tetra-hydroxy Pcs have very low fluorescence quantum yields in DMSO (~0.003) and complete fluorescence quenching in aqueous solution; however they were found to have high singlet oxygen quantum yields ~0.7 in DMSO. On the other hand, the di-hydroxy-Pc shows moderate (~0.2) quantum yields in DMSO and similar fluorescence quenching in aqueous solution. Our results suggest that hydroxy-substituted Pcs, in particular tetra and octa-hydroxy Pcs, may have application as photosensitizers in the PDT treatment of cancer, and are worthy of further biological investigation.

4. Experimental

4.1. Syntheses

Silica gel 60 (230×400 mesh, Sorbent Technologies) and alumina gel (50–200 μm, neutral, standard activity I, Sorbent Technologies) were used for column chromatography. Analytical thin-layer chromatography (TLC) was carried out using polyester backed TLC plates 254 (precoated, 200 μm) from Sorbent Technologies. Prep alumina and silica TLC plates (w/UV 254, 1000 μm) were purchased from Sorbent Technologies Inc. All chemicals were purchased from commercial sources and used directly without further purification. NMR spectra were recorded on a DPX-250, ARX-300 or AV-400 Bruker spectrometers (250 MHz, 300 MHz or 400 MHz for ^{1}H, 63 MHz, 75 MHz or 100 MHz for ^{13}C). The chemical shifts are reported in δ ppm using the following deuterated solvents as internal references: CD_2Cl_2 5.32 ppm (^{1}H), 54.00 ppm (^{13}C); $CDCl_3$ 7.24 ppm (^{1}H), 77.23 ppm (^{13}C); CD_3OD 4.87 ppm (^{1}H); CD_3COCD_3 2.04 ppm (^{1}H), 29.92 ppm (^{13}C); DMF-*d* 2.92 ppm (^{1}H), 34.89 ppm (^{13}C); THF-*d* 3.58 ppm (^{1}H). Electronic absorption spectra were measured on a Perkin–Elmer Lambda 35 UV–vis spectrometer. High-resolution ESI mass spectra were obtained on an Agilent Technologies 6210 Time-of-Flight LC/MS. HPLC separation and analyses were carried out on a Dionex system equipped with a P680 pump and a UVD340U detector. Semi-preparative column was Luna C_{18} 100 Å, 5 μm, 10×250 mm from Phenomenex, USA. Analytical HPLC was carried out on a Delta Pak C_{18} 300 Å, 5 μm, 3.9×150 mm (Waters, USA) column; flow rate 1.0 mL/min; injected volume 20 μL; wavelength detection 350 nm; solvent methanol. The singlet oxygen quantum yields, determined with an accuracy of ~10%, were obtained in DMSO at room temperature, using ZnPc (Φ_Δ=0.67) as reference and 1,3-diphenylisobenzofuran

(DPBF) as scavenger, according to a procedure previously described.[8,42] The DPBF absorption decay was followed at 417 nm.

4.1.1. 4,5-Bis(2,5-di-tert-butyl-4-methoxyphenoxy)phthalonitrile (**1**)

4,5-Dichlorophthalonitrile (1 g, 5 mmol) and 2,5-di-*tert*-butyl-4-methoxyphenol (4 g, 16.4 mmol) were dissolved in 30 mL of dry DMF at 95 °C under argon. Potassium carbonate (4.5 g, 32.8 mmol) was added to the reaction solution in 8 portions every 5 min. After 1 day, another portion (2 g, 14.5 mmol) of 2,5-di-*tert*-butyl-4-methoxyphenol was added to the reaction mixture. The reaction was followed by ^{1}H NMR until complete disappearance of monochloro-substituted phthalonitrile. After 24 h, the reaction mixture was cooled to room temperature and poured into 250 mL of ice water. After filtration under vacuum, the crude product was purified by silica gel column chromatography using hexane/dichloromethane 4:1 for elution. The title compound was obtained as a white solid (2.3 g, 77%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.18 (s, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 6.95 (s, 2H, Ar-H), 3.95 (s, 6H, OCH_3), 1.42 (s, 18H, $C(CH_3)_3$), 1.40 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 156.3, 153.3, 145.6, 140.4, 138.6, 120.9, 120.6, 116.0, 111.8, 109.7 (Ar-C, CN), 55.8 (OCH_3), 35.1, 35.0, 30.6, 29.9 ($C(CH_3)_3$). LRMS (MALDI-TOF) m/z 596.87 $[M]^+$, calcd for $[C_{38}H_{48}N_2O_4]^+$ 596.36. HRMS-MALDI m/z 619.3491 $[M+Na]^+$, calcd for $[C_{38}H_{48}N_2O_4Na]^+$ 619.3512.

4.1.2. 4,5-Bis(2,5-di-tert-butyl-4-hydroxyphenoxy)phthalonitrile (**2**)

2,5-Di-*tert*-butyl-hydroquinone (2.3 g, 10.3 mmol) and potassium carbonate (0.7 g, 5.1 mmol) were dissolved in DMF (30 mL). The solution was heated to 50 °C under argon. 4,5-Dichlorophthalonitrile (0.5 g, 2.6 mmol) was dissolved in DMF (10 mL) and added dropwise over a period of 30 min to the reaction mixture. The final mixture was heated at 100 °C for three days. The solution was cooled to room temperature and concentrated under vacuum to a volume of 10 mL. The residue was poured into ice water (100 mL) and acidified upon dropwise addition of 1 N HCl solution, until pH=5. The precipitate was collected by filtration and further purified by column chromatography on silica gel using hexane/dichloromethane 1:1 and methanol/dichloromethane 2:98 for elution. The title compound was obtained as a white solid (0.4 g, 27%). ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.09 (s, 2H, Ar-H), 6.84 (s, 2H, Ar-H), 6.79 (s, 2H, Ar-H), 5.01 (s, 2H, OH), 1.37 (s, 18H, $C(CH_3)_3$), 1.31 (s, 18H, $C(CH_3)_3$). ^{1}H NMR (acetone-*d*, 400 MHz): δ 8.66 (s, 2H, OH), 7.27 (s, 2H, Ar-H), 6.99 (s, 2H, Ar-H), 6.85 (s, 2H, Ar-H), 1.34 (s, 18H, $C(CH_3)_3$), 1.31 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 153.0, 144.8, 139.7, 135.4, 120.8, 120.1, 115.5, 115.4, 109.1 (Ar-C, CN), 34.2, 34.0, 29.9, 28.9 ($C(CH_3)_3$). HRMS-ESI: m/z 567.3219 $[M-H]^-$, 568.3245 $[M]^-$, 1135.6526 $[2M-H]^-$, calcd for $[C_{36}H_{43}N_2O_4]^-$ 567.3228, $[C_{36}H_{44}N_2O_4]^-$ 568.3261, $[C_{72}H_{87}N_4O_8]^-$ 1135.6524. FTIR (solid): 3463.7 (br, OH), 2236.0 (CN) cm^{-1}.

4.1.3. Octamethoxy-Pc (**3**)

Phthalonitrile **1** (0.5 g, 0.84 mmol) was placed in a 25 mL three-necked flask and the flask was evacuated and filled with argon three times. Pentanol (5 mL) was added via syringe and the solution was heated to 120 °C. Lithium (0.048 g, 6.8 mmol) was added and the final reaction mixture was heated to 120 °C for 17 h. The mixture was cooled to room temperature, acetic acid (15 mL) was added, and the mixture stirred for 30 min. The mixture was poured into 200 mL of ice-cold water/methanol 10:1. This mixture was stirred vigorously for 1 h. The precipitate was collected by filtration and re-dissolved in 100 mL of hexane. The impurities were removed by filtration and the solution was dried over anhydrous sodium sulfate overnight. The solvent was evaporated under vacuum and the resulting residue was washed with methanol until the filtrate was colorless. The product was dried under vacuum at 70 °C to afford a green solid (0.15 g, 30%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 8.90 (s, 8H, Ar-H), 7.09 (s, 8H, Ar-H), 7.07 (s, 8H, Ar-H), 3.97 (s, 24H, OCH_3), 1.52 (s, 72H, $C(CH_3)_3$), 1.27 (s, 72H, $C(CH_3)_3$), −0.35 (s, 2H, NH). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 154.7, 152.2, 149.3, 138.7, 137.6, 132.8, 118.3, 113.4, 111.9 (Ar-C), 56.0 (OCH_3), 35.1, 34.8, 30.4, 29.9 ($C(CH_3)_3$). MS (MALDI-TOF) m/z 2388.37 $[M]^+$, calcd for $C_{152}H_{194}N_8O_{16}$ 2388.46.

4.1.4. Octamethoxy-Zn-Pc (**4**)

Method I. Phthalonitrile **1** (0.26 g, 0.4 mmol) and anhydrous zinc acetate (73 mg, 0.4 mmol) were dissolved in dry NMP (5 mL). The solution was heated to 150 °C under argon for 1 day. The solid was collected by filtration and purified by column chromatography on silica gel using hexane/dichloromethane 2:1 for elution, affording Pc **4** in 9% yield. *Method II*. Phthalonitrile **1** (0.38 g, 0.64 mmol) was dissolved in 3 mL of dry pentanol at 135 °C under argon. Lithium (0.1 g, 14 mmol) was carefully added in small pieces to the reaction solution. After 2 min, the reaction solution turned green. After 3 h, anhydrous zinc acetate (400 mg) was added and the solution was refluxed for another 3 h. The solvent was removed under reduced pressure. The dry residue was washed three times with methanol/H_2O (1:1) and extracted with hexane (100 mL). The crude product was purified by column chromatography on silica gel using hexane/dichloromethane (2:1) for elution to afford a green solid (0.12 g, 31%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 8.89 (s, 8H, Ar-H), 7.06 (s, 8H, Ar-H), 7.05 (s, 8H, Ar-H), 3.95 (s, 24H, OCH_3), 1.50 (s, 72H, $C(CH_3)_3$), 1.25 (s, 72H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 154.5, 153.4, 151.6, 149.5, 138.6, 137.4, 134.4, 118.1, 113.4, 111.9 (Ar-C), 56.0 (OCH_3), 35.1, 34.8, 30.3, 29.8 ($C(CH_3)_3$). MS (MALDI-TOF) m/z 2451.80 $[M]^+$, calcd for $C_{152}H_{192}N_8O_{16}Zn$ 2451.38.

4.1.5. Octa-hydroxy-Zn-Pc (**5**)

Method I. Pc **4** (60 mg, 0.024 mmol) and sodium ethanethiolate (900 mg, 9.6 mmol) were dissolved in dry DMF (35 mL). The solution was refluxed at 135 °C for 24 h under argon and the reaction followed by MALDI-TOF mass spectroscopy. The solution was poured into 150 mL of water and the product was extracted with ethyl acetate (50 mL×3) and dried over anhydrous sodium sulfate. The crude product was purified by Sephadex LH-20 eluting with methanol. After purification by HPLC with methanol as the mobile phase, a green solid was obtained (15 mg, 25%). *Method II*. Phthalonitrile **2** (0.08 g, 0.14 mmol) was dissolved in pentanol (3 mL) in a 25 mL three-necked flask. The solution was heated at 135 °C under argon. Lithium (30 mg, 4.3 mmol) was added in small portions and the mixture was heated for another 10 h. The solution was cooled to room temperature, zinc(II) acetate (0.1 g, 0.55 mmol) was added, and the final mixture refluxed at 135 °C for 2 h. The solvent was evaporated under vacuum and the residue was triturated in 100 mL of water. The suspension was kept in the refrigerator for 3 h, then filtered under vacuum, and the green solid washed with water. The crude product was purified by column chromatography on alumina using methanol/dichloromethane 2:98 for elution. The final product was purified by HPLC using methanol as the mobile phase to afford a green solid (8 mg, 9%). ^{1}H NMR (acetone-*d*, 250 MHz): δ 8.82 (s, 8H, Ar-H), 8.09 (br, 8H, OH), 7.06 (s, Ar-H, 8H), 7.03 (s, Ar-H, 8H), 1.46 (s, 9H, $C(CH_3)_3$), 1.31 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (methanol-*d*, 63 MHz): δ 154.5, 153.0, 152.8, 149.5, 139.9, 135.9, 134.6, 119.6, 116.4, 113.2 (Ar-C), 35.4, 35.3, 31.0, 30.1 ($C(CH_3)_3$). MS (MALDI-TOF) m/z 2338.71 $[M]^+$, calcd for $C_{144}H_{176}N_8O_{16}Zn$ 2339.25. HRMS-ESI: m/z 1168.6159 $[M-2H]^{2-}$, calcd for $[C_{144}H_{174}N_8O_{16}Zn]^{2-}$ 1168.6194. t_R=11.227 min (MeOH). HRMS-ESI: m/z 2338.2421 $[M-H]^-$, 1168.6159 $[M-2H]^{2-}$, calcd for $[C_{144}H_{175}N_8O_{16}Zn]^-$ 2338.2455, $[C_{144}H_{174}N_8O_{16}Zn]^{2-}$ 1168.6194. t_R=11.227 min (MeOH). UV–vis (acetone): λ_{max} (log ε) 678.8 (5.3), 612.0 (4.5) nm.

*4.1.6. 3-(2,5-Di-tert-butyl-4-hydroxyphenoxy)phthalonitrile (**6**)*

2,5-Di-*tert*-butyl-hydroquinone (3.2 g, 14 mmol) was dissolved in DMF (100 mL) under nitrogen. Potassium carbonate (2 g, 14 mmol) was added to the solution in five portions. The mixture was heated to 50 °C. 3-Nitrophthalonitrile (2 g, 11 mmol) was dissolved in DMF (40 mL) and added dropwise during a 30 min period to the reaction mixture. The temperature was raised to 100 °C and kept for 20 h. After cooling to room temperature, the mixture was concentrated to 20 mL and poured into water (100 mL). The precipitate was separated by filtration and the solution was evaporated to dryness and further purified by column chromatography on silica gel using methanol/dichloromethane 2:98 for elution. The title compound was obtained as a light yellow solid (1.5 g, 38%). ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.58–7.54 (m, 1H, Ar-H), 7.43–7.41 (m, 1H, Ar-H), 7.04–7.02 (m, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 1.34 (s, 9H, $C(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 162.3, 152.6, 145.1, 140.9, 136.2, 134.9, 126.7, 120.9, 120.3, 117.4, 116.4, 115.9, 113.7, 105.6 (Ar-C, CN), 34.7, 34.5, 30.5, 29.5 ($C(CH_3)_3$). HRMS-ESI: *m*/*z* 347.1766 $[M-H]^-$, 348.1791 $[M]^-$, 695.3580 $[2M-H]^-$, calcd for $[C_{22}H_{23}N_2O_2]^-$ 347.1766, $[C_{22}H_{24}N_2O_2]^-$ 348.1838, $[C_{44}H_{47}N_4O_4]^-$ 695.3597. FTIR (solid): 3440.9 (br, OH), 2243.0 (CN) cm^{-1}.

*4.1.7. Tetra-hydroxy-Zn-Pc (**7**)*

Lithium (0.033 g, 4.6 mmol) was dissolved in octanol (5 mL) and the solution heated to 170 °C. After 1 h, the solution was cooled to 40 °C. Phthalonitrile **6** (50 mg, 0.14 mmol) in dichloromethane (1 mL) was added to the reaction mixture via syringe. After 4 h anhydrous zinc acetate (0.2 g, 1.0 mmol) was added and the reaction mixture was heated at 70 °C for 3 days. Ethanol (10 mL) was added and the solution was concentrated by azeotropic distillation. Hexane (10 mL) was added to the residue and the suspension was centrifuged to afford the crude solid product. The residue was purified by column chromatography on silica gel using methanol/dichloromethane 2:98 for elution. The product was further purified by preparative TLC silica plates eluted with hexane/dichloromethane 1:4 and methanol/dichloromethane 2:98. After purification by HPLC using methanol, the title Pc was obtained as a dark green solid (8 mg, 15%). ^{1}H NMR (acetone-*d*, 400 MHz): δ 9.08 (d, *J*=7.5 Hz, 4H, Ar-H), 8.35 (br, 4H, OH), 7.98 (t, *J*=7.7 Hz, 4H, Ar-H), 7.39 (d, *J*=7.1 Hz, 4H, Ar-H), 7.32 (br, 4H, Ar-H), 7.20 (s, 4H, Ar-H), 1.70 (s, 36H, $C(CH_3)_3$), 1.42 (s, 36H, $C(CH_3)_3$). ^{1}H NMR (acetone-*d* with one drop of D_2O, 400 MHz): δ 9.07 (d, *J*=7.4 Hz, 4H, Ar-H), 7.99 (t, *J*=7.7 Hz, 4H, Ar-H), 7.38 (d, *J*=7.8 Hz, 4H, Ar-H), 7.29 (br, 4H, Ar-H), 7.22 (s, 4H, Ar-H), 1.71 (s, 36H, $C(CH_3)_3$), 1.40 (s, 36H, $C(CH_3)_3$). HRMS-ESI: *m*/*z* 1459.6721 $[M+H]^+$, calcd for $[C_{88}H_{97}N_8O_8Zn]^+$ 1459.6730. UV–vis (acetone): λ_{max} (log ε) 698.2 (5.3), 628.4 (4.5) nm.

*4.1.8. Dimethoxy-Pc (**8**)*

Phthalonitrile **1** (0.3 g, 0.5 mmol) and phthalonitrile (7.6 g, 59.3 mmol) were dissolved in dry pentanol (50 mL) at 140 °C under argon. DBU (0.6 mL) was added dropwise and the reaction mixture was refluxed for 9 h. After cooling to room temperature the solution was poured into methanol (200 mL). The product was collected by filtration and washed repeatedly with methanol and dichloromethane until the filtrate was colorless. The crude product was purified by column chromatography on silica gel using dichloromethane for elution, giving the title Pc as a blue solid (0.06 g, 12%). ^{1}H NMR ($CDCl_3$ with one drop of TFA-*d*, 300 MHz): δ 7.98–7.87 (m, 18H, Ar-H), 4.11 (s, 6H, OCH_3), 1.72 (s, 18H, $C(CH_3)_3$), 1.46 (s, 18H, $C(CH_3)_3$). MS (MALDI-TOF) *m*/*z* 982.81 $[M]^+$, calcd for $C_{62}H_{62}N_8O_4$ 982.49.

*4.1.9. Dimethoxy-Zn-Pc (**9**)*

Pc **8** (0.07 g, 0.7 mmol) and zinc dibromide (0.16 g, 0.7 mmol) were dissolved in dichloromethane (20 mL). The solution was refluxed for 2 h, cooled to room temperature, and filtered to remove excess salt. The residue was purified by column chromatography on silica gel using dichloromethane/THF 20:1 for elution. The title Pc was obtained as a bluish green solid (0.067 g, 96%). ^{1}H NMR (THF-*d*, 250 MHz): δ 9.32–9.27 (m, 4H, Ar-H), 9.22–9.19 (m, 2H, Ar-H), 9.04 (s, 2H, Ar-H), 8.11–8.08 (m, 4H, Ar-H), 8.05–8.02 (m, 2H, Ar-H), 7.31 (s, 2H, Ar-H), 7.17 (s, 2H, Ar-H), 4.01 (m, 6H, Ar-H), 1.61 (s, 18H, $C(CH_3)_3$), 1.38 (s, 18H, $C(CH_3)_3$). MS (MALDI-TOF) *m*/*z* 1044.84 $[M]^+$, calcd for $C_{62}H_{60}N_8O_4Zn$ 1044.40.

*4.1.10. Di-hydroxy-Zn-Pc (**10**)*

Method I. Pc **8** (60 mg, 0.057 mmol) and sodium ethanethiolate (534 mg, 5.7 mmol) were dissolved in dry DMF (20 mL). The same procedure was followed as reported above for the synthesis of Pc **5**. Re-metalation took place with zinc bromide (0.08 g, 0.35 mmol) in DMF (10 mL) to yield a bluish green solid (6 mg, 10%). *Method II*. Phthalonitrile **2** (0.1 g, 0.176 mmol) and phthalonitrile (1.9 g, 15 mmol) were dissolved in dry pentanol (50 mL) and heated to 140 °C under argon. DBU (0.2 mL) was added and the solution stirred at 140 °C for 24 h. The solvent was evaporated to dryness under vacuum. The residue was dissolved in acetone and the byproduct A_4-type Pc was removed by filtration. The crude Pc was purified by alumina column chromatography using methanol/dichloromethane 5:95 for elution to afford the free-base A_3B-type Pc as a blue solid. LRMS (MALDI-TOF) *m*/*z* 954.90 $[M]^+$, calcd for $C_{60}H_{58}N_8O_4$ 954.46. The free-base Pc was dissolved in DMF (20 mL), zinc dibromide (0.16 g, 0.7 mmol) was added, and the mixture was heated to 40 °C for 24 h. The solvent was evaporated under vacuum and the crude product was purified by alumina column chromatography using methanol/dichloromethane 2:98 for elution. Further purification using alumina preparative TLC plates afforded the title Pc as a greenish blue solid (10 mg, 6%). ^{1}H NMR (DMF-*d*, 400 MHz): δ 9.61 (s, 2H, Ar-H), 9.35–9.17 (m, 6H, Ar-H), 8.95 (br, 2H, OH), 8.23–8.13 (m, 6H, Ar-H), 7.32 (s, 2H, Ar-H), 7.28 (s, 2H, Ar-H), 1.60 (s, 18H, $C(CH_3)_3$), 1.46 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (DMF-*d*, 100 MHz): δ 162.9, 154.1, 154.0, 153.9, 153.8, 153.20, 152.3, 147.9, 139.8, 139.1, 139.0, 138.9, 135.3, 134.2, 123.2, 122.9, 122.8, 120.0, 116.2, 111.7 (Ar-C), 29.8 ($C(CH_3)_3$, other carbon signals shielded by DMF-*d*). LRMS (MALDI-TOF) *m*/*z* 1016.25 $[M]^+$, calcd for $C_{60}H_{56}N_8O_4Zn$ 1016.37. UV–vis (acetone): λ_{max} (log ε) 668.2 (5.3), 603.5 (4.5) nm.

4.2. Molecular structures

The crystal structures of Pc **4** and dimer **8** were determined using data collected at low temperature with Mo Kα radiation on a Nonius KappaCCD diffractometer. The structure of phthalonitrile **6** was determined using data collected at low temperature with Cu Kα radiation on a Bruker Apex-II CCD diffractometer. Compound Pc **4** was crystallized as a mixed CH_2Cl_2, CH_3OH, H_2O solvate, and exhibits considerable disorder. Despite the low temperature of data collection, $T=115$ K, the crystals scattered to low resolution (1.04 Å). Anisotropic refinement was possible for only Zn and Cl. The structure contains two independent Zn-phthalocyanine complexes, each lying on an inversion center, with the Zn atom lying slightly out of plane and disordered. For Pc **4**, R=0.138 for 9492 observed data of 14,648 unique data. Phthalonitrile exhibited no disorder, and gave high-resolution data at T=90 K. For **6**, R=0.030 for 3034 observed data of 3289 unique data. The X-ray crystallographic data for Pc **4**, phthalonitrile **6**, and corresponding diphthalonitrile can be found in supplementary publications CCDC-713859, CCDC-713860, and CCDC-713860 respectively, available from the Cambridge Crystallographic Data Centre.

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