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Synthesis of Unsymmetrical Alkyloxy/Aryloxy-azaphthalocyanines Based on a Transetherification Reaction

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An approach leading to unsymmetrical azaphthalocyanines (AzaPcs) bearing one aryloxy and seven butoxy substituents on the periphery is described. Several cyclotetramerization methods were tested, including the template effect of a metal salt in a melt/solution and the Linstead method, but only one was found to be suitable for the isolation of unsymmetrical alkyloxy/aryloxy-AzaPcs. Undesired transetherification with alkoxides, which is common with these types of compounds, was considered to be an advantage in this approach, and an unsymmetrical AzaPc was isolated in 10 % yield. An analysis of the transetherification process is also described. Unsymmetrical zinc(II) and magnesium(II) AzaPcs showed excellent spectral properties (λ_{max} = 620 nm; ε = 1.5–2.2 × 10^5 dm^3 mol^{-1} cm^{-1}) as well as promising singlet oxygen (Φ_Δ = 0.44 and 0.26, respectively) and fluorescence quantum yields (Φ_F = 0.50 and 0.65, respectively). The metal-free derivative (λ_{max} = 603 and 640 nm; ε = 0.80 and 1.2 × 10^5 dm^3 mol^{-1} cm^{-1}) dissipated energy in a different way, and the Φ_Δ and Φ_F values were one order of magnitude smaller (0.030 and 0.053, respectively). All the parameters were comparable to the corresponding symmetrical AzaPcs containing eight butoxy substituents, which suggests that an unsymmetrical composition of AzaPc on the periphery has no negative effect on the photophysical or photochemical properties.

Introduction

It is not surprising that phthalocyanines (Pcs), which are structural analogues of porphyrins, have become the target of many research groups, because their promising photophysical and photochemical properties mean that Pcs play an important role in fields such as photodynamic therapy (PDT),[1,2] chemical sensors,[3] catalytic chemistry,[4] photovoltaics,[5–7] and nonlinear optics.[8,9] Their aza analogues, azaphthalocyanines (AzaPcs) from the group of tetrapyrazinoporphyrazines, have comparable properties with several advantages, for example, better solubility and a diverse range of peripheral substituents. Peripheral substitution plays a crucial role in defining the properties of AzaPc and Pc derivatives. It has been shown that alkylsulfanyl-[10] and alkyloxy-substituted[11,12] AzaPcs are characterized by high singlet oxygen (Φ_Δ) and fluorescence quantum yields (Φ_F), which makes them ideal candidates for cancer treatment by PDT, or fluorescence detection. On the other hand, alkylamino substitution leads to values of almost zero for both Φ_F and Φ_Δ because of effective intramolecular charge transfer.[13] Such AzaPcs have recently found application as dark quenchers in DNA hybridization probes.[14] Unsymmetrical compounds, with only one or two modifiable groups on the periphery of the AzaPcs for binding to biomolecules, are highly desirable in the synthesis of conjugates in PDT, fluorescent probes, and dark quenchers, because this prevents unwanted polymerization reactions. Several unsymmetrical alkylsulfanyl-[13,15] as well as alkylamino-substituted[13,14,16] AzaPcs have already been prepared by using the Linstead method,[17,18] employing alkoxides as initiators of cyclotetramerization. However, carbon atoms 5 and 6 of the pyrazine moiety in alkyloxy- or aryloxy-5,6-disubstituted pyrazine-2,3-dicarbonitriles, which are precursors of alkyloxy- and aryloxy-AzaPcs, are highly electron-deficient. That is why application of the Linstead method for cyclotetramerization was reported to always yield transetherification of peripheral substituents by the alkoxide used for initiation.[11,19–21] This problem has only recently been solved for symmetrical AzaPcs bearing peripheral chains connected through oxygen atoms.[11,21,22] However, the synthesis of unsymmetrical alkyloxy- or aryloxy-AzaPcs still represents a challenge. On the other hand, alkyloxy- or aryloxy-substituted Pcs are easily synthesized without any problems with stability of the peripheral substituents.[23,24]

This work mainly concentrates on new synthetic approaches to unsymmetrical aryloxy- and alkyloxy-substituted AzaPcs. Several strategies are discussed for the forma-

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tion of the AzaPc core. Subsequently, the photophysical and photochemical properties of the synthesized unsymmetrical AzaPcs were determined so that their potential in PDT and photodetection applications could be assessed.

Results and Discussion

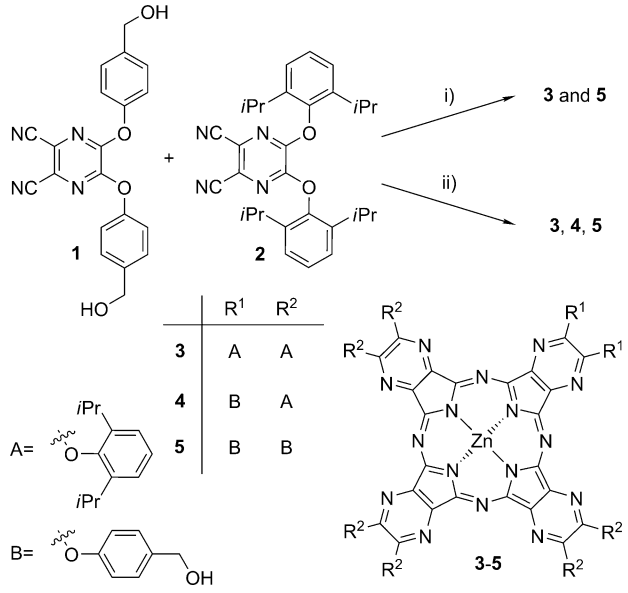
Synthesis

Cyclotetramerization of substituted pyrazine-2,3-dicarbonitriles based on a template effect of a metal salt or a stepwise condensation of precursors after initiation by alkoxide anions (Linstead method) are two general procedures that have been used to generate the AzaPc core. Several approaches allowing selective formation of unsymmetrical Pcs and related compounds have been described.[25,26] However, a statistical condensation starting from two different precursors (A and B) followed by separation of the required congener from a statistical mixture by column chromatography seems to be the simplest technique leading to unsymmetrical AzaPcs of the AAAB type.[27] Furthermore, the use of subazaphthalocyanines (subAzaPcs), which is one of the selective approaches,[28] has not yet been reported, and our own preliminary results indicated that the synthesis of subAzaPcs might be another synthetic challenge.

The structure of the desired unsymmetrical aryloxy-AzaPc of the AAAB type was designed according to the following requirements. Precursor **1**, with two hydroxy groups intended for binding AzaPcs to biomolecules, should form one quarter of the final AzaPc (Scheme 1). The rest of the molecule should be built from precursor **2**, the bulky 2,6-diisopropylphenoxy groups of which preclude undesired aggregation behavior of the final unsymmetrical AzaPc. As mentioned above, the Linstead method of cyclotetramerization leads to transetherification of peripheral alkyloxy- or aryloxy-substituted AzaPcs. For this reason, the template effect was considered first as the cyclotetramerization method so that the peripheral substituents in the precursors **1** and **2** could be retained.

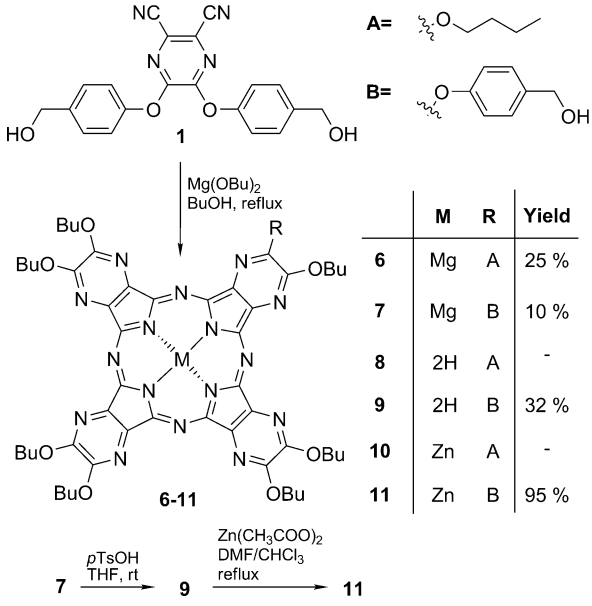
Compounds **1** and **2** (Scheme 1) were mixed in a 1:1 molar ratio with 2 equiv. of $Zn(quinoline)_2Cl_2$ and heated according to the method developed by Mørkved et al.[29] The reaction mixture melted and immediately turned green after applying temperatures higher than 220 °C, indicating the formation of the AzaPc core. However, TLC investigation and MS analysis of the crude reaction mixture showed the presence of only two AzaPcs, **3** and **5**, with no trace of the unsymmetrical congeners. The likely explanation was that the reaction did not take place in solution but in a mixture of solids that melted at high temperatures.

Makhseed et al. published several papers on the synthesis of symmetrical aryloxy-substituted Pcs and AzaPcs in solution.[21,30–32] Similar conditions (quinoline, zinc acetate, 160 °C) were applied for the precursors **1** and **2** in subsequent exploratory reactions (Scheme 1). Mass spectra taken directly from the crude reaction mixture showed mass fragments corresponding to the AzaPc **3** (*m*/*z* = 1992.9), AzaPc **4** (*m*/*z* = 1885.8), and traces of the A_2B_2 congener (*m*/*z* = 1777.7). However, only a negligible amount of **4** was detected on TLC (silica; chloroform/acetone, 20:1; R_f = 0.11) when compared with **3**. No improvement was observed upon changing the ratio of starting materials to 3:1 (excess of **1**) or stepwise addition of **2** to the reaction mixture. Hence, although the synthesis of unsymmetrical aryloxy-substituted AzaPc by using the template effect was clearly successful, the yields were not sufficiently satisfactory to scale-up this reaction.



Scheme 1. Unsymmetrical condensation: template effect of a metal salt. Reagents and conditions: (i) $Zn(quinoline)_2Cl_2$, quinoline (two drops), 240 °C, 10 min; (ii) $Zn(CH_3COO)_2$, quinoline, 160 °C, 24 h.

For this reason, the concept of introducing one functional group to the periphery of the macrocycle was changed. The novel idea was to take advantage of the transetherification reaction, instead of considering it to be a disadvantage. In this new approach, compound **1** reacted with magnesium butoxide in butanol to initiate AzaPc core formation (Scheme 2). At the same time, the butoxide anion, behaving as a strong nucleophile, attacked the electron-deficient carbon atoms at positions 5 and 6 of the pyrazine ring of precursor **1**, as anticipated. The reaction was stopped after 2 h, and the crude mixture was analyzed by mass spectrometry. The mass fragments corresponding to AzaPcs **6** (eight butoxy; *m*/*z* = 1120.5), **7** (seven butoxy, one 4-(hydroxymethyl)phenoxy; *m*/*z* = 1170.4) and the compound bearing six butoxy and two 4-(hydroxymethyl)phenoxy peripheral substituents (*m*/*z* = 1220.5) were detected in the mass spectrum, together with clear signals of the corresponding dimers and trimers (see Figure S1 in the Supporting Information). The mixture was also analyzed by TLC (silica; toluene/pyridine/MeOH, 10:1:1). Selected blue fractions were scraped from the TLC plate and analyzed by mass spectrometry (MS). The two most intense fractions (with approximately the same intensity) corresponded to **6** and **7** (R_f = 0.73 and 0.62, respectively) and were used for subsequent kinetic studies.



	M	R	Yield
6	Mg	A	25 %
7	Mg	B	10 %
8	2H	A	-
9	2H	B	32 %
10	Zn	A	-
11	Zn	B	95 %

Scheme 2. Unsymmetrical condensation, a transetherification approach (**8** and **10** were prepared previously).

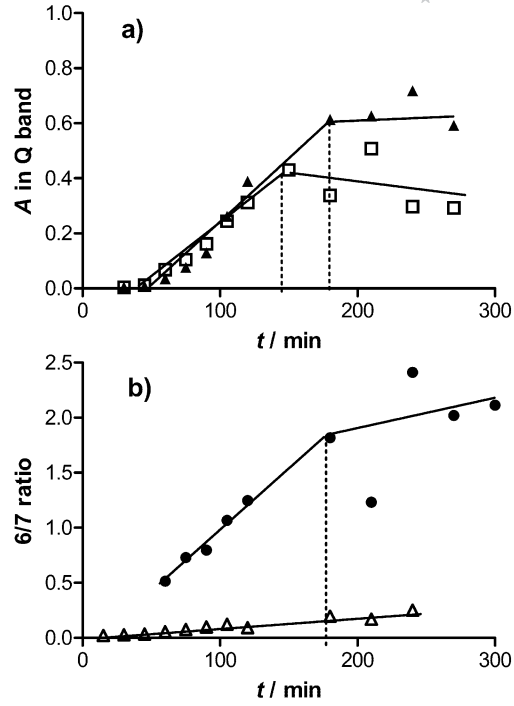


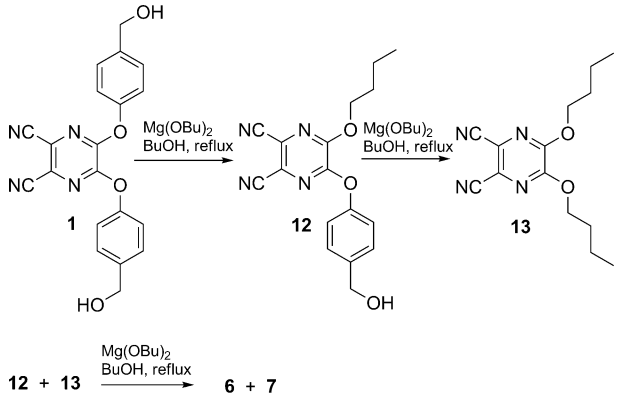
Figure 1. Kinetic study of the transetherification: (a) increase of **6** (filled triangles) and **7** (empty squares) in time. (b) Change of the **6**/**7** ratio with reaction time; (dots) cyclotetramerization of **1** with magnesium butoxide in butanol, (empty triangles) reflux of **7** with magnesium butoxide in butanol. The amounts of **6** and **7** in the reaction mixture used to calculate the **6**/**7** ratio were derived from absorbance at the Q-band and the extinction coefficient in THF.

To shed some light on the transetherification process, the progress of the cyclotetramerization of **1** in excess magnesium butoxide was monitored during the reaction. The quantitative isolation of **6** and **7** from the two-dimensional TLC plate was monitored by UV/Vis spectroscopy (for details see the Experimental Section and the Supporting Information, Figures S2 and S3). The other congeners were not monitored, because their amounts seemed to be low according to MS and TLC analysis. Each experiment was performed in triplicate, and the kinetic behavior was similar for all cases. The results of one representative experiment are depicted in Figure 1.

A slow initial phase of the cyclotetramerization within the first hour was indicated by a light blue-green color of the solution and low absorbance of both products in the Q-band (Figure 1a). Subsequently, the amounts of both AzaPcs were significantly elevated, indicating a rapid cyclotetramerization reaction. The amount of **7** in the solution stopped increasing after approximately 2 h, whereas the amount of **6** continued to increase for a further hour under reflux. The amount of **7** slightly decreased between 2 and 5 h reaction time. Interestingly, initially the amount of **7** slightly exceeded the amount of **6** (Figure 1b). However, the ratio of **6**/**7** increased with further heating and reached a plateau after 3 h, with only a moderate increase thereafter. For comparison, when the same reaction was performed with two precursors (**1** and **13**) instead of only compound **1**, very similar results were obtained with slightly higher ratios of **6**/**7**. To examine the transetherification of the AzaPc core in more detail, isolated **7** was heated to reflux with magnesium butoxide in butanol under the same conditions used for the previous cyclotetramerization studies, and the kinetic results were compared (Figure 1b). In this case, the ratio of **6**/**7** changed very slowly and achieved a value of only 0.25 after 4 h of reaction.

These results point to the following plausible sequence of reactions (Scheme 3). The transetherification runs very rapidly on the pyrazine-2,3-dicarbonitrile **1**, giving rise to compound **12** and, subsequently, to **13**. The latter two compounds undergo statistical condensation to form **6** and **7**. As the transetherification proceeds further, the amount of **13** in the solution increases, and the ratio **6**/**7** also increases due to the changed ratio of the starting materials. The transetherification process of any remaining **12** to give **13** is most likely fully complete after 2 h; thus, compound **7** reaches a plateau (Figure 1a) due to the lack of one precursor. The rest of **13** in solution is transformed into AzaPc **6** within the next hour, and the cyclotetramerization of all pyrazine-2,3-dicarbonitriles is finished after approximately 3 h from the start of the reaction. This is in good agreement with the previously published direct cyclotetramerization of **13** to **6** in which the maximum yield was obtained after the same reaction time of 3 h.[10] The transetherification of the final AzaPc core likely takes place simultaneously, as deduced from the decreasing amount of **7** in the reaction mixture after 2 h. However, this rate is several times lower than the transetherification of the precursors, as shown for the reaction of **7** with magnesium butoxide. As a consequence, this process contributes only slightly to changes in the ratio of **6**/**7**.

Despite the fact that compounds **6** and **7** were substituted by non-branched aliphatic substituents, no aggrega-



Scheme 3. Suggested reactions occurring during transetherification.

tion was observed in the UV/Vis spectra at concentrations used for photophysical and photochemical measurements (see below). Thus, although the steric bulk of the 2,6-diisopropylphenoxy groups considered in the AzaPc template approach may be advantageous, the butoxy groups also seem to be a suitable peripheral substituent that also ensures beneficial properties of the final AzaPcs.

Results of the analysis described above indicated an optimal reaction time of 2 h for the scale-up synthesis of **7** from **1** with a yield of 10%. This yield is typical of AAAB-type congeners from a statistical condensation and is comparable with other reported reactions.[14,15] To investigate the photophysical and photochemical properties of the zinc(II) complex, which is generally more suitable for PDT, it was prepared from **7**. The central, weakly chelated magnesium(II) ion was removed under acidic conditions (*p*-toluenesulfonic acid) to form metal-free **9** in 32% yield. The lower yield of this reaction may be attributed to a loss during purification (strong silica binding of **9**) rather than to low conversion. Heating of **9** in *N*,*N*-dimethylformamide (DMF) with zinc acetate gave zinc complex **11** almost quantitatively (95% yield).

UV/Vis Absorption

The absorption spectra of the prepared AzaPcs in tetrahydrofuran (THF) showed shapes that were typical for Pcs and related compounds, and were composed of a low-energy Q-band and a high-energy B-band at around 620 and 360 nm, respectively (Figure 2, Table 1). The Q-band of metal-free **9** was split due to the loss of symmetry (D_{2h}). The ether linkage between the peripheral substituents and the AzaPc macrocycle caused a small hypsochromic shift of the Q-band in comparison to unsubstituted zinc-AzaPc (ZnAzaPc; λ_{max} = 636 nm in pyridine[33]). Similar observations were previously published.[11] It was also reported that aryloxy substituents caused less pronounced hypsochromic shifts than alkyloxy groups, because aryl moieties contributed to a conjugation of the macrocyclic system.[11] However, taking into account that **7**, **9**, and **11** contain only one aryloxy and seven alkyloxy substituents, it is not surprising that the Q-band positions differed only by 1 nm (Table 1) from the symmetrical derivatives **6**, **8**, and **10**, respectively. All Q-bands were sharp, indicating no aggregation.

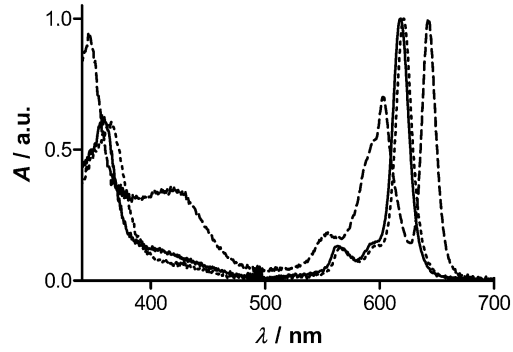


Figure 2. Normalized absorption spectra of **7** (dotted), **9** (dashed), and **11** (full) in THF.

The strength of absorption is a very important parameter in many applications connected with light absorption. Whereas porphyrins have extinction coefficients in the Q-band of only 1000–2000 $dm^3 mol^{-1} cm^{-1}$ and chlorins 20000–30000 $dm^3 mol^{-1} cm^{-1}$, Pcs and AzaPcs achieved values that were generally several times higher.[34,35] This was also valid for compounds studied in this work (see Table 1); ε values were found to be approximately 100000 $dm^3 mol^{-1} cm^{-1}$ for the metal-free derivative and over 150000 $dm^3 mol^{-1} cm^{-1}$ for the metal complexes.

Fluorescence Emission and Singlet Oxygen Production

Quantum yields of singlet oxygen as well as fluorescence were determined in THF by using a comparative method with ZnPc as reference (Φ_Δ = 0.53 in THF,[36] Φ_F = 0.30 in chloronaphthalene[37]) (Table 1). Singlet oxygen production was calculated from the decomposition of the chemical trap 1,3-diphenylisobenzofuran (DPBF). No changes in the ab-

Table 1. Spectroscopic, photophysical, and photochemical properties of studied compounds in THF.

	M	Absorbance: λ_{max} [nm] (ε [10^5 $dm^3 mol^{-1} cm^{-1}$])	Fluorescence: λ_{max} [nm]	Φ_F[a]	Φ_Δ[a]
6	Mg	620 (2.45)	625	0.96	0.26
7	Mg	621 (2.22)	627	0.65	0.26
8	2H	643 (0.98), 603 (0.67)	646	0.056	0.029
9	2H	643 (1.12), 603 (0.80)	647	0.053	0.030
10	Zn	618 (2.42)	623	0.51	0.47
11	Zn	619 (1.53)	625	0.50	0.44

[a] Mean of three independent measurements. Estimated error ±20% and ±10% for Φ_F and Φ_Δ, respectively. No changes in absorption spectra were observed during the measurements.

sorption spectra appeared during measurements, indicating that neither photodegradation nor aggregation of AzaPcs occurred. The Φ_Δ values decreased in the order **11** > **7** > **9**, corresponding to 0.44, 0.26 and 0.030, respectively. Due to their similar peripheral substitution patterns, they did not differ much from the symmetrical compounds, which have Φ_Δ values of 0.47, 0.26 and 0.029 for **10** > **6** > **8**, respectively. It is clear that neither the introduction of a free hydroxy group nor the unsymmetrical composition of the macrocycle negatively influenced the singlet oxygen quantum yields. It is known that zinc(II) chelated in the center of the macrocycle increases the probability of transition of the Pc excited S_1 state to the long-lived triplet T_1 state, as well as extend the T_1 state lifetime.[38] As a consequence, the singlet oxygen quantum yields of ZnPcs are high. This was also valid in this case, and Φ_Δ values of zinc(II) complexes **10** and **11** significantly exceeded the others in the series.

An opposite dependence was found in fluorescence emission. Centrally chelated magnesium(II) increased the fluorescence quantum yields of AzaPcs. The Φ_F of both magnesium complexes **6** and **7** were extremely high (0.96 and 0.65, respectively). On the other hand, both zinc(II) complexes **10** and **11** had lower, but still very strong, Φ_F values of approximately 0.50. Both Φ_F and Φ_Δ values determined for metal-free derivatives were about one order of magnitude lower than for the metal complexes, indicating that they dissipated energy through different pathways. The sum of the quantum yields of **6** was apparently higher than 1, which is not generally possible; however, it was still within the estimated experimental error of 20% and 10% for Φ_F and Φ_Δ, respectively. Fluorescence emission spectra had typical shapes, with only small Stokes shifts (4–6 nm) (Figure 3). Superposing the excitation spectra and the absorption spectra (see Figure S4 in the Supporting Information) lead to the conclusion that the observed fluorescence arose from the studied compounds. The acquired data also suggests that the compounds were exclusively in monomeric forms because the aggregates have different absorption spectra and, besides a few exceptions of J-dimers,[39,40] usually do not fluoresce.

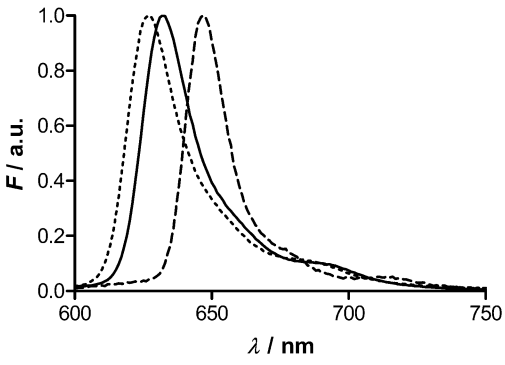


Figure 3. Normalized emission spectra of **7** (dotted), **9** (dashed), and **11** (full) in THF.

Conclusions

A synthetic method that can be used to generate unsymmetrical AzaPcs bearing peripheral substituents connected through oxygen was developed for the first time. Cyclotetramerization methods based on the template effect did not lead to the desired unsymmetrical product either at all or only in very low yield. A detailed study of the Linstead method showed that, under specific conditions, transetherification can be a suitable method that gives unsymmetrical alkyloxy/aryloxy-AzaPcs in reasonable yields. Analysis of the reaction kinetics data showed that the transetherification took place rapidly on pyrazine-2,3-dicarbonitriles, giving new precursors that cyclotetramerized to unsymmetrical AzaPcs. The final AzaPcs undergo the transetherification at much lower rate. The described approach can serve to introduce one modifiable group onto the AzaPc core, which can be used for binding to a target. According to photophysical and photochemical measurements, introduction of the free hydroxy group on the periphery did not influence the good quantum yields of fluorescence, the generation of singlet oxygen, or the absorption spectra. The studied AzaPcs may therefore be suitable substrates for further investigations on photodynamic therapy or fluorescent probes due to the high singlet oxygen and fluorescence quantum yields.

Experimental Section

General: All organic solvents used were of analytical grade. Anhydrous butanol was stored over magnesium and distilled prior to use. All chemicals for synthesis were obtained from established suppliers (Aldrich, Acros, Merck) and used as received. Zinc–phthalocyanine (ZnPc) was purchased from Aldrich. TLC was performed on Merck aluminum sheets with silica gel 60 F254. Merck Kieselgel 60 (0.040–0.063 mm) was used for column chromatography. Melting points were measured with an Electrothermal IA9200 Series digital melting point apparatus (Electrothermal Engineeering Ltd., Southend-on-Sea, Essex, Great Britain). Infrared spectra were measured with a Nicolet 6700 in ATR mode. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury Vx BB 300 spectrometer. Chemical shifts are reported relative to $Si(CH_3)_4$ and were locked to the signal of the solvent. The UV/Vis spectra were recorded with a Shimadzu UV-2401PC spectrophotometer. The fluorescence spectra were obtained with an AMINCO-Bowman Series 2 luminescence spectrometer. MALDI-TOF mass spectra were recorded in the positive reflectron mode with a Voyager-DE STR mass spectrometer (Applied Biosystems, Framingham, MA, USA) in *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile as the matrix. The instrument was calibrated externally with a five-point calibration using Peptide Calibration Mix1 (LaserBio Labs, Sophia-Antipolis, France). High-resolution mass spectra were obtained by using the same instrument, but each spot was further calibrated internally after addition of metal-free azaphthalocyanine with peripheral camphorquinone units[41] to the mass of its monomer (m/z = 954.5030 $[M]^+$) and dimer, which also appeared in the mass spectrum (m/z = 1909.0061 $[2\ M]^+$). Compounds **1**–**3**, **5**, **10**[11] and **6**, **8**, **13**[10] were prepared as reported.

Template Effect; Cyclotetramerization in a Melt: Compounds **1** (83 mg, 0.22 mmol), **2** (107 mg, 0.22 mmol) and $Zn(quinoline)_2Cl_2$

(185 mg, 0.44 mmol, prepared according to literature[29]) were thoroughly mixed, two drops of freshly distilled quinoline were added, and the mixture was heated at 240 °C for 10 min. The solid was washed with water/methanol (1:1) and analyzed by TLC (chloroform/pyridine, 20:1) and by mass spectrometry.

Template Effect; Cyclotetramerization in Solution: Compounds **1** (83 mg, 0.22 mmol), **2** (321 mg, 0.66 mmol) and anhydrous zinc acetate (40 mg, 0.22 mmol) were thoroughly dried in a drying pistol (5 mbar, 78 °C, 5 h), transferred into a round-bottomed flask and put under argon. Freshly distilled quinoline (3 mL) was added, and the mixture was immersed in an oil bath that was preheated to 160 °C and heated for 24 h. Water/methanol (1:1, 10 mL) was added, and the precipitate was collected. The crude mixture was dissolved in pyridine (3 mL) and mixed again with water/methanol (1:1, 20 mL) to remove residual quinoline. The precipitate was collected and dried. The composition of the mixture of products was analyzed by TLC (chloroform/acetone, 20:1) and by mass spectrometry.

Linstead Method of Cyclotetramerization

From Precursor 1: Magnesium turnings (182 mg, 7.49 mmol) and a crystal of iodine were heated to reflux in anhydrous butanol (10 mL) for 3 h. Compound **1** (400 mg, 1.06 mmol) was added, and the mixture was heated to reflux for 2 h. Water/methanol/acetic acid (5:5:1, 20 mL) was poured into the reaction mixture, and the precipitate was collected, washed with water/methanol (1:1) and dried. The desired congener **7** was separated by column chromatography on silica with gradient elution (toluene/pyridine/acetone 15:1:1 and then 8:1:1). The isolated fractions were purified by column chromatography again (toluene/pyridine/acetone 15:1:1) to yield blue solids **6** (74 mg, 25%) and **7** (32 mg, 10%).

(2,3,9,10,16,17,23,24-Octabutoxy-1,4,8,11,15,18,22,25-octaazaphthalocyanininato)magnesium(II) (6): UV/Vis (THF): λ_{max} (ε) = 620 (244700), 596 (br.), 566 (30400), 426 (15400), 365 (138400 $dm^3 mol^{-1} cm^{-1}$) nm. Other analytical data were published elsewhere.[10]

{3,9,10,16,17,23,24-Heptabutoxy-2-[4-(hydroxymethyl)phenoxy]-1,4,8,11,15,18,22,25-octaazaphthalocyaninato}magnesium(II) (7): ^{1}H NMR [300 MHz, $CDCl_3$/[D_5]pyridine (2:1)]: δ = 0.66–0.88 (m, 21 H, $OCH_2CH_2CH_2CH_3$), 1.11–1.42 (m, 14 H, $OCH_2CH_2CH_2CH_3$), 1.51–1.79 (m, 14 H, $OCH_2CH_2CH_2CH_3$), 4.21–4.66 (m, 17 H, $OCH_2CH_2CH_2CH_3$, CH_2OH and CH_2OH), 7.30 (d, J = 8 Hz, 2 H, ArH), 7.41 (d, J = 7 Hz, 2 H, ArH) ppm. ^{13}C NMR [75 MHz, $CDCl_3$/[D_5]pyridine (2:1)]: δ = 13.26, 18.59, 18.62, 18.71, 30.12, 30.16, 30.19, 30.24, 30.63, 63.41, 67.14, 67.22, 67.26, 67.36, 120.53, 127.51, 138.52, 139.75, 140.14, 140.54, 140.61, 140.75, 150.37, 151.52, 151.75, 151.95, 152.05 ppm. IR (ATR): $\tilde{\nu}$ = 2959, 2928, 2873, 1726, 1710, 1692, 1678, 1666, 1659, 1641, 1631, 1620, 1612, 1599, 1502, 1493, 1479, 1462, 1443, 1378, 1305, 1253, 1156, 1116, 1061, 1019, 952, 935, 851, 750 cm^{-1}. MALDI-TOF: m/z = 1170 $[M]^+$, 1193 $[M + Na]^+$, 1209 $[M + K]^+$, 2341 $[2 M]^+$, 2364 $[2 M + Na]^+$, 2380 $[2 M + K]^+$, 3511 $[3 M]^+$, 3534 $[3 M + Na]^+$. HRMS (MALDI-TOF): calcd. for $[M]^+$ 1170.5362; found 1170.5391. UV/Vis (THF): λ_{max} (ε) = 621 (222100), 596 (28800), 566 (28400), 367 (131600 $dm^3 mol^{-1} cm^{-1}$) nm.

From Precursors 1 and 13: Magnesium turnings (182 mg, 7.49 mmol) and a crystal of iodine were heated to reflux in anhydrous butanol (10 mL) for 3 h. Compounds **1** (200 mg, 0.53 mmol) and **13** (147 mg, 0.53 mmol) were added at once, and reflux was continued for 2 h. Purification was achieved as described for **7** to yield blue solids **6** (109 mg, 37%) and **7** (19 mg, 6%). The analytical data were identical to those of the products of cyclotetramerization from precursor **1**.

Kinetic Study: Magnesium turnings (136 mg, 10.2 mmol) and a crystal of iodine were heated to reflux in anhydrous butanol (10 mL) for 3 h. Precursor **1** (300 mg, 0.8 mmol) or **1** (110 mg, 0.4 mmol) and **13** (150 mg, 0.4 mmol) were added. The samples (50 μL) were taken from the reaction at time intervals and diluted with chloroform (1 mL) to ensure complete dissolution. The chloroform solution of the sample (20 μL) was spotted on a TLC plate and two-dimensional TLC (see the Supporting Information) was used to separate **6** and **7**. First, TLC elution was performed with toluene/pyridine/MeOH (10:1:1), then the TLC plate was thoroughly dried, rotated by 90° and the developed with toluene/pyridine/acetone (15:1:1) as mobile phase. Spots corresponding to AzaPcs **6** and **7** were scraped from the TLC plate and quantitatively extracted with THF. The solvent was evaporated to dryness, the sample was then dissolved in THF (2 mL), and the absorption spectrum was recorded. The amounts of **6** and **7** were monitored by observing the intensity of absorption at the Q-band maximum (620 and 621 nm, respectively). In another experiment, magnesium turnings (13.6 mg, 1.0 mmol) and a crystal of iodine were heated to reflux in anhydrous butanol (2 mL) for 3 h, and **7** (94 mg, 0.08 mmol) was added. The reaction was monitored as described above.

2,3,9,10,16,17,23,24-Octabutoxy-1,4,8,11,15,18,22,25-octaazaphthalocyanine (8): UV/Vis (THF): λ_{max} (ε) = 643 (98100), 603 (66600), 593 (54500), 552 (19100), 416 (36500), 346 (96700 $dm^3 mol^{-1} cm^{-1}$) nm. Other analytical data were published elsewhere.[10]

3,9,10,16,17,23,24-Heptabutoxy-2-[4-(hydroxymethyl)phenoxy]-1,4,8,11,15,18,22,25-octaazaphthalocyanine (9): *p*-Toluenesulfonic acid (62 mg, 0.32 mmol) in THF (3 mL) was added to a solution of **7** (38 mg, 0.032 mmol) in THF (10 mL), and the reaction mixture was stirred at room temp. for 2 h. The solution was concentrated under reduced pressure, and water (15 mL) was added. The precipitate was collected and washed thoroughly with water and briefly with methanol. The crude product was purified by column chromatography on silica (chloroform/acetone, 10:1) to yield a green solid (12 mg, 32%). ^{1}H NMR [300 MHz, $CDCl_3$/[D_5]pyridine, (2:1)]: δ = 0.61–1.01 (m, 21 H, $OCH_2CH_2CH_2CH_3$), 1.25–1.58 (m, 14 H, $OCH_2CH_2CH_2CH_3$), 1.61–1.87 (m, 14 H, $OCH_2CH_2CH_2CH_3$), 4.05–4.76 (m, 17 H, $OCH_2CH_2CH_2CH_3$, CH_2OH and CH_2OH) ppm; signals of aromatic hydrogen atoms were not detected. ^{13}C NMR [75 MHz, $CDCl_3$/[D_5]pyridine, (2:1)]: δ = 13.36, 13.42, 13.48, 18.58, 18.65, 18.78, 18.89, 30.04, 30.26, 30.35, 63.64, 67.15, 67.23, 67.35, 67.57, 120.55, 127.46, 151.57 and 151.65 ppm. IR (ATR): $\tilde{\nu}$ = 3297, 2959, 2933, 2873, 1638, 1538, 1505, 1479, 1448, 1379, 1316, 1250, 1191, 1148, 1061, 1018, 949, 925, 808, 741 cm^{-1}. MALDI-TOF: m/z = 1148 $[M]^+$, 1171 $[M + Na]^+$, 1187 $[M + K]^+$, 2297 $[2 M]^+$, 2320 $[2 M + Na]^+$, 2336 $[2 M+ K]^+$. HRMS (MALDI-TOF): calcd. for $[M]^+$ 1148.5668; found 1148.5652. UV/Vis (THF): λ_{max} (ε) = 643 (112500), 604 (79900), 594 (60700), 555 (20600), 418 (39800), 347 (107300 $dm^3 mol^{-1} cm^{-1}$) nm.

(2,3,9,10,16,17,23,24-Octabutoxy-1,4,8,11,15,18,22,25-octaazaphthalocyaninato)zinc(II) (10): UV/Vis (THF): λ_{max} (ε) = 618 (242200), 593 (32400), 563 (31100), 404 (br.), 358 (143500 $dm^3 mol^{-1} cm^{-1}$) nm. Other analytical data were published elsewhere.[10]

{3,9,10,16,17,23,24-Heptabutoxy-2-[4-(hydroxymethyl)phenoxy]-1,4,8,11,15,18,22,25-octaazaphthalocyaninato}zinc(II) (11): Anhydrous zinc acetate (19 mg, 0.104 mmol) in DMF (2 mL) was added to **10** (12 mg, 0.010 mmol) in chloroform (5 mL), and the mixture was heated at 160 °C for 3 h. The chloroform was evaporated, water

(10 mL) was added, and the precipitate was collected and washed thoroughly with water and briefly with methanol. The crude product was purified by column chromatography on silica (chloroform/acetone, 2:1) to yield a green solid (12 mg, 95%). ^{1}H NMR [300 MHz, $CDCl_3$/[D_5]pyridine (2:1)]: δ = 0.70–0.87 (m, 21 H, $OCH_2CH_2CH_2CH_3$), 1.23–1.48 (m, 14 H, $OCH_2CH_2CH_2CH_3$), 1.61–1.85 (m, 14 H, $OCH_2CH_2CH_2CH_3$), 4.38–4.70 (m, 17 H, $OCH_2CH_2CH_2CH_3$, CH_2OH and CH_2OH), 7.39 (d, J = 8 Hz, 2 H, ArH), 7.49 (d, J = 8 Hz, 2 H, ArH) ppm. ^{13}C NMR [75 MHz, $CDCl_3$/[D_5]pyridine (2:1)]: δ = 13.31, 18.68, 18.71, 18.76, 18.78, 30.21, 30.31, 63.55, 67.20, 67.24, 67.26, 120.64, 127.72, 138.63, 139.67, 140.17, 140.36, 140.43, 140.55, 141.98, 150.34, 151.76, 152.00 ppm. IR (ATR): $\tilde{\nu}$ = 2958, 2927, 2872, 1678, 1650, 1640, 1543, 1502, 1441, 1377, 1305, 1254, 1192, 1119, 1062, 1018, 953, 933, 849, 745 cm^{-1}. MALDI-TOF: m/z = 1210 [M]$^+$, 1233 [M + Na]$^+$, 1249 [M + K]$^+$, 2421 [2 M]$^+$, 2444 [2 M + Na]$^+$ and 2460 [2 M + K]$^+$. HRMS (MALDI-TOF): calcd. for [M]$^+$ 1210.4803; found 1210.4841. UV/Vis (THF): λ_{max} (ε) = 618 (153000), 595 (22300), 564 (20200), 360 (92700), 407 (17700 dm^3 mol^{-1} cm^{-1}) nm.

Singlet Oxygen Measurements: Quantum yields of singlet oxygen (Φ_Δ) were determined in THF according to a previously published procedure[42] by using the decomposition of the chemical trap 1,3-diphenylisobenzofuran (DPBF). Zinc–phthalocyanine (ZnPc) was used as a reference (Φ_Δ = 0.53 in THF[36]). In detail, the procedure was as follows: A stock solution of DPBF in THF (5×10^{-5} M, 2.5 mL) was transferred into a 10×10 mm quartz optical cell and bubbled with oxygen for 1 min. A defined amount of stock solution of the tested dye in THF (usually 30 μL) was then added. Absorbance of the final dye solution at the Q-band maximum was always ca. 0.1. The solution was then stirred and irradiated for defined times by using a halogen lamp (Tip, 300 W). Incident light was filtered through a water filter (6 cm) and an orange HOYA G filter to remove infrared light and light < 506 nm, respectively. All experiments were performed three times, and data presented in the paper represent a mean of these three experiments (estimated error ±10%). Singlet oxygen quantum yield (Φ_Δ) was calculated by using Equation (1):

$$\Phi_\Delta^S = \Phi_\Delta^R \frac{k^S I_{aT}^R}{k^R I_{aT}^S} \quad (1)$$

where k is the slope of a plot of the dependence of $\ln(A_0/A_t)$ on irradiation time t, with A_0 and A_t being the absorbances of the DPBF at 414 nm before irradiation and after irradiation time t, respectively. I_{aT} is the total amount of light absorbed by the dye. Superscripts R and S indicate reference and sample, respectively. I_{aT} is calculated as the sum of intensities of the absorbed light I_a at wavelengths from 506 to 800 nm (step 0.5 nm). I_a at a given wavelength is calculated by using Beer's law [Equation (2)]:

$$I_a = I_0\left(1-e^{-2.3A}\right) \quad (2)$$

where transmittance of the filter at a given wavelength is given by I_0, and absorbance of the dye at this wavelength is given by A.

Fluorescence Quantum Yields Measurements: Fluorescence quantum yields (Φ_F) were determined by the comparative method using ZnPc as a reference (Φ_F = 0.30 in chloronaphthalene[37]) in a way similar to that published previously. Thus, THF (2.5 mL) was transferred into a quartz optical cell (10×10 mm), and a defined amount of a stock solution of the studied dye in THF was added to give an absorption at the Q-band maximum of ca. 0.05. Absorption, emission, and excitation spectra were collected. Both reference and sample were excited at 590 nm. Φ_F was calculated by using Equation (3):

$$\Phi_F^S = \Phi_F^R\left(\frac{F^S}{F^R}\right)\left(\frac{1-10^{-A^R}}{1-10^{-A^S}}\right)\left(\frac{n^S}{n^R}\right)^2 \quad (3)$$

where F is the integrated area under the emission spectrum, A is the absorbance at the excitation wavelength (590 nm), and n is the refractive index of the solvent. Superscripts R and S correspond to the reference and sample, respectively. Excitation spectra were collected with emission wavelength fixed at 678 nm. All experiments were performed three times, and data presented in the paper represent a mean of these three experiments (estimated error ±20%).

Supporting Information (see footnote on the first page of this article): Mass spectrum of the crude mixture from the transetherification approach; UV/Vis spectra obtained for the kinetic study; absorption, emission, and excitation spectra of compounds **7**, **9**,and **11**; 2D TLC images.

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