Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7358–7361

The synthesis of metal-free octaazaphthalocyanine derivatives containing bulky phenoxy substituents to prevent self-association

Saad Makhseed,[a,*] Fadi Ibrahim,[a] C. Grazia Bezzu[b] and Neil B. McKeown[b]

[a]*Department of Chemistry, University of Kuwait, PO Box 5969, Safat 13060, Kuwait*
[b]*School of Chemistry, Cardiff University, Cardiff CF10 3AT, UK*

Received 23 June 2007; revised 1 August 2007; accepted 6 August 2007
Available online 10 August 2007

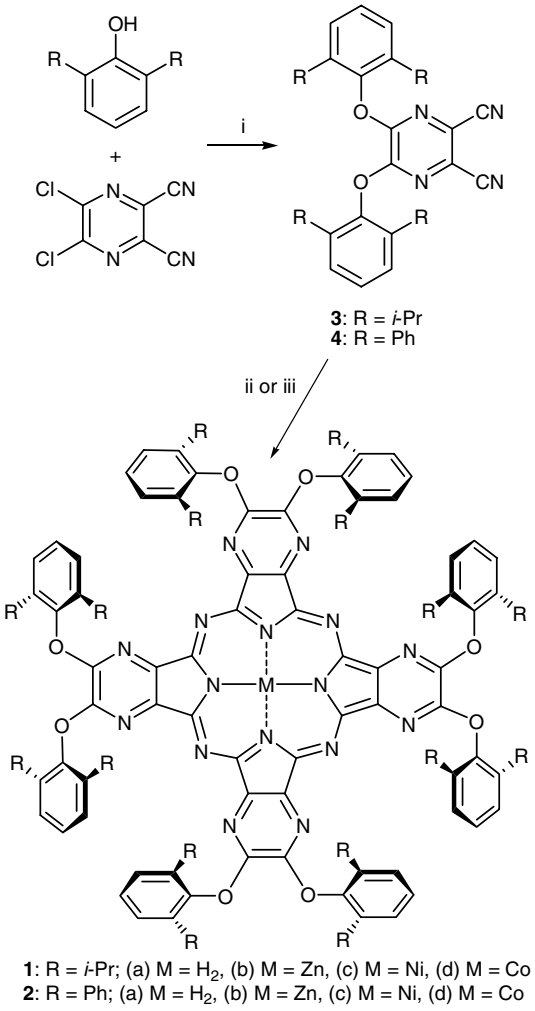
Abstract—Octaazaphthalocyanines with eight phenoxy groups in the peripheral sites are prepared for the first time using the simple synthetic procedure of heating their pyrazine-2,3-dicarbonitrile precursor in quinoline. This process avoids transetherification, which has hindered previous attempts at preparing metal-free octaazaphthalocyanines. Metal-containing derivatives were also prepared by adding the appropriate metal salt to the reaction mixture. Bulky *iso*-propyl or phenyl groups at the 2,6-positions of the phenoxy substituents prevent self-association of the octaazaphthalocyanine cores even in the solid state.

Phthalocyanine (Pc) and its derivatives are of interest due to their outstanding electronic and optical properties. In addition to their extensive role as colourants they find application in nonlinear optics (including optical limitation), as photoconductors, liquid crystalline electronic charge carriers, optical data storage (e.g., as the laser absorption layer within recordable discs), photodynamic cancer therapy, solar energy conversion, catalysis and as the active component of gas sensors.[1,2] The extended planar shape, four-fold symmetry and stability also makes the phthalocyanine macrocycle an excellent building block for use in supramolecular[3] and polymer chemistry.[4]

Analogues of phthalocyanine in which nitrogens replace some of the carbons within the four fused benzo-substituents of the phthalocyanine, possess significantly different physical properties including colour, oxidation potential and stability, which may be beneficial for some of these applications.[5,6] Hence, 1,4,8,11,15,18,22,25-octaazaphthalocyanine (AzaPc), often termed tetrapyrazinoporphyrazine in the literature, and its substituted derivatives have been investigated extensively for applications as photodynamic therapeutics,[7–9] colourants,[10] catalysts,[11] liquid crystals,[12–14] non-linear optical materials[15] and as a red fluorophore.[16,10,17] This latter application is of particular interest as the major phthalocyanine fluorescence band falls in the near-IR region and is largely invisible to the human eye whereas AzaPc has a very strong fluorescence band in the visible spectrum. Large aromatic molecules such as the AzaPcs tend to aggregate strongly in solution and for all of these particular applications performance is dependent on the control over the molecular self-association. For example, the main adsorption band of the AzaPc chromophore in the visible region (e.g., Q-band; $\lambda_{max} \sim 630$ nm whereas for Pc $\lambda_{max} \sim 680$ nm) is broadened and blue-shifted due to the effect of intermolecular exciton interactions. In addition, self-quenching of the photo-generated excited state impairs fluorescence and the ability of the macrocycle to generate the singlet oxygen responsible for photodynamic activity. Recently however, we found that the presence of bulky phenoxy substituents prohibits close self-association of the phthalocyanine macrocycle even within solid thin films and can result in the formation of a remarkable nanoporous cubic crystal.[18] Hence, we undertook the synthesis of the analogous AzaPc derivatives 2,3,9,10,16,17,23,24-octa-(2,6-di-*iso*-propylphenoxy)-1,4,8,11,15,18,22,25-octaazaphthalocyanine **1** and 2,3,9,10,16,17,23,24-octa(2,6-diphenylphenoxy)-1,4,8,11,15,18,22,25-octaazaphthalocyanine **2**, both of which contain a sterically hindered phenoxy substituent at each of the eight peripheral positions of the macrocycle.

* Corresponding author. Tel.: +965 498 5538; fax: +965 481 6482; e-mail: smakhseed@kuc01.kuniv.edu.kw

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.022



Scheme 1. Reagents and conditions: (i) K_2CO_3, DMF, 78 °C, 4 h; (ii) for AzaPcs (**1b–d**) and (**2b–d**): metal salt, quinoline, 160 °C, 24 h; (iii) for AzPcs (**1a**) and (**2a**): quinoline, 160 °C, 24 h.

Pioneering work by Mørkved established that a diverse range of precursors to peripherally substituted AzaPcs can be made readily via the nucleophilic aromatic substitution of 5,6-dichloropyrazine-2,3-dicarbonitrile using amine,[19] thiol[20] or alkyloxy[21] nucleophiles. In most cases cyclotetramerisation of the precursors using lithium or magnesium alkoxide in refluxing alcohol (i.e. the Linstead reaction) was found to proceed smoothly to give the metal-free macrocycle, however, for the alkyloxy-derived precursors (and some thiol-derived precursors)[20] the reaction was accompanied by displacement of the side-chain by the alkyloxide anion initiator.[8] For the synthesis of alkoxy derivatives, this problem is simply avoided by matching the alcohol/alkyloxide with the alkyloxy side-chain desired in the product. However, for the synthesis of the desired octaphenoxy-substituted AzaPcs **1** and **2**, we were faced with the problem that lithium phenolates are not successful for mediating phthalocyanine formation and, furthermore, that phenolate anions are superior leaving groups, relative to an alkyloxide, in aromatic nucleophilic reactions such as the undesired transetherification. Indeed, this latter problem was previously encountered by Mørkved during an attempt to prepare octaphenoxy-AzaPc[21] and accounts for the lack of any literature precedent for phenoxy-substituted AzaPcs in contrast to the many reports of phthalocyanines with this type of substituent.[22–24] However, we hoped that the use of the bulky 2,6-di-*iso*-propyl- or 2,6-diphenyl-phenoxy substituents would hinder the transetherification reaction to allow a successful preparation of the target AzaPcs.

The pyrazine-2,3-dicarbonitrile precursors to AzaPcs **1** and **2**, 5,6-bis(2,6-di-*iso*-propylphenoxy)pyrazine-2,3-dicarbonitrile **3** and 5,6-bis(2,6-diphenylphenoxy)pyrazine-2,3-dicarbonitrile **4**, respectively, were prepared from the reaction between the appropriate phenol and 5,6-dichloro-pyrazine-2,3-dicarbonitrile[20,25] in good yield (Scheme 1).[26] Initial attempts at AzaPc formation using a mixture of lithium pentoxide/pentanol gave reasonable crude yields of macrocycle but ^{1}H NMR analysis indicated substantial substitution of phenoxy groups for pentyloxy side-chains. However, metal ion template reactions in quinoline using zinc acetate, nickel acetate or cobalt(II) chloride gave the appropriate metallated AzaPcs in good isolated yield (50–55%) with complete retention of the phenoxy substituents. Surprisingly, heating precursor **3** in quinoline gave a rapid colour change consistent with macrocycle formation prior to the addition of the metal salt. Analysis of the reaction mixture confirmed that the desired metal free AzaPc (**1a**) had formed with the complete retention of the phenoxy substituents. Based upon this simple procedure, AzaPc (**1a**) was prepared in a very reasonable yield of 40% requiring only recrystallisation for purification. This procedure was also successful for the synthesis of metal free AzaPc (**2a**) from precursor **4**.[27] All AzaPcs gave spectroscopic data consistent with their structures including clusters of peaks, which correspond to the calculated isotope composition of the molecular ion by matrix assisted laser desorption ionisation mass spectroscopy (MALDI-MS).

The formation of the metal free AzaPcs (**1a**) and (**2a**) simply by heating its precursor in quinoline is surprising as this is not a successful procedure for making phthalocyanines from phthalonitriles. The use of a hindered base such as 1,8-diazabicyclo[5,4]-undec-7-ene (DBU) in conjunction with an alcohol can be used with phthalonitriles to prepare metal free phthalocyanines[28] but it is probable that under these conditions, precursors **3** and **4** would undergo transetherification prior to macrocycle formation. It is known that phthalonitriles containing electron-withdrawing substituents undergo cyclotetramerisation under relatively mild conditions[23,24] and it could be that in this case it is the electronic properties of the pyrazine ring that encourages macrocycle formation even without the introduction of an alkyloxide nucleophilic initiator or metal ion template.

As anticipated, AzaPcs (**1a**) and (**2a**), along with their metal ion-containing derivatives (**1b–d**) and (**2b–d**) ($M = Zn^{2+}$, Ni^{2+} and Co^{2+}), show none of the

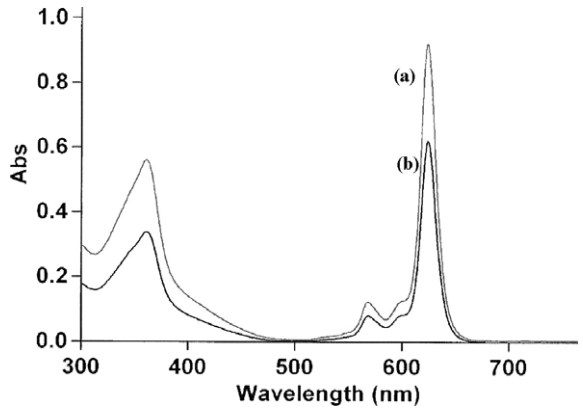


Figure 1. UV–visible adsorption spectrum of AzaPc (**1b**) (a) in THF solution ($c = 1.2 \times 10^{-5}$ M cm^{-3}) and (b) from a solvent cast film.

characteristic spectroscopic indications of self-association in solution (Fig. 1). For example, the appearance of UV–visible spectra (e.g., position and shape of the intense Q-band at $\lambda_{max} = 607$ and 645 nm)[29] and ^{1}H NMR spectra (e.g., chemical shift of internal hydrogens at $\delta = -2.05$ ppm)[30] were independent of concentration. Furthermore, the UV–visible spectra of spin-coated films of AzaPcs (**1a**–**d**) and (**2a**–**d**) were identical to those obtained from dilute solutions indicating that the AzaPc chromophore is not perturbed by intermolecular exciton effects even in the solid state.[31] The high quality of these films and their intense red fluorescence might be of value for device fabrication (e.g., sensors or organic light emitting diodes) and suggests an approach to reducing the adverse effects of aggregation when using AzPc derivatives as photosensitisers in PDT.[9] Furthermore, the surprisingly simple method for the preparation of AzaPcs (**1a**) and (**2a**) involving heating the pyrazinedicarbonitrile precursor in quinoline could be employed for the synthesis of other metal-free AzaPcs for which nucleophilic displacement of substituents is likely to be a problem.[20,21,8]

Acknowledgements

We are grateful for the financial support from the College of Graduate Studies for an MSc candidacy, Research Grant No. SC08/02 and the facilities used from ANALAB, Kuwait University.

References and notes

1. McKeown, N. B. *Phthalocyanine Materials: synthesis, structure and function*; CUP: Cambridge, 1998.
2. Leznoff, C. C.; Lever, A. B. P. *Phthalocyanines: Properties and Applications*; VCH: New York, 1989, 1993, 1996; Vol. 1–4.
3. de la Torre, G.; Claessens, C. G.; Torres, T. *Chem. Commun.* **2007**, 2000.
4. McKeown, N. B. *J. Mater. Chem.* **2000**, *10*, 1979–1995.
5. Kudrevich, S. V.; Van Lier, J. E. *Coord. Chem. Rev.* **1996**, *156*, 163–182.
6. Ghosh, A.; Gassman, P. G.; Almlof, J. *J. Am. Chem. Soc.* **1994**, *116*, 1932–1940.
7. Kudrevich, S. V.; Gal'pern, M. G.; van Lier, J. E. *Synthesis* **1994**, 779–781.
8. Zimcik, P.; Miletin, M.; Kostka, M.; Schwarz, J.; Musil, Z.; Kopecky, K. *J. Photochem. Photobiol., A* **2004**, *163*, 21–28.
9. Kostka, M.; Zimcik, P.; Miletin, M.; Klemera, P.; Kopecky, K.; Musil, Z. *J. Photochem. Photobiol., A* **2006**, *178*, 16–25.
10. Lee, B. H.; Jaung, J. Y.; Jang, S. C.; Yi, S. C. *Dyes Pigments* **2005**, *65*, 159–167.
11. Maizlish, V. E.; Korzhenevskii, A. B.; Klyuev, V. N. *Khim. Geterot. Soed.* **1984**, 1257–1259.
12. Ohta, K.; Watanabe, T.; Hasebe, H.; Morizumi, Y.; Fujimoto, T.; Yamamoto, I.; Lelievre, D.; Simon, J. *Mol. Cryst. Liq. Cryst.* **1991**, *196*, 13–26.
13. Ohta, K.; Watanabe, T.; Fujimoto, T.; Yamamoto, I. *Chem. Commun.* **1989**, 1611–1613.
14. Mohr, B.; Wegner, G.; Ohta, K. *J. Chem. Soc. Chem. Commun.* **1995**, 995–996.
15. Wen, T. C.; Chen, S. P.; Tsai, C. Y. *Synth. Metals* **1998**, *97*, 105–112.
16. Jaung, J. Y.; Matsuoka, M.; Fukunishi, K. *Dyes Pigments* **1999**, *40*, 73–81.
17. Musil, Z.; Zimcik, P.; Miletin, M.; Kopecky, K.; Petrik, P.; Lenco, J. *J. Photochem. Photobiol., A* **2007**, *186*, 316–322.
18. McKeown, N. B.; Makhseed, S.; Msayib, K. J.; Ooi, L.-L.; Helliwell, M.; Warren, J. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7546–7551.
19. Mørkved, E. H.; Kjosen, H.; Ossletten, H.; Erchak, N. *J. Porph. Phthalo.* **1999**, *3*, 417–423.
20. Mørkved, E. H.; Holmaas, L. T.; Kjosen, H.; Hvistendahl, G. *Acta Chem. Scand.* **1996**, *50*, 1153–1156.
21. Mørkved, E. H.; Ossletten, H.; Kjosen, H. *Acta Chem. Scand.* **1999**, *53*, 1117–1121.
22. Wohrle, D.; Eskes, M.; Shigehara, K.; Yamada, A. *Synthesis* **1993**, 194–196.
23. McKeown, N. B. *The Porphyrin Handbook* **2003**, *15*, 61–123.
24. McKeown, N. B. In *Science of Synthesis*; Weinreb, S., Ed.; Thieme: Stuttgart, 2004; Vol. 17, pp 1258–1368.
25. Suzuki, T.; Nagae, Y.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1986**, *23*, 1419–1421.
26. In a typical procedure, finely ground anhydrous potassium carbonate (8.01 g) was added to a stirred solution of 5,6-dichloropyrazine-2,3-dicarbonitrile (2 g, 10 mmol) and 2,6-di-*iso*-propylphenol (4.01 g, 23 mmol) in dry CH_3CN (300 ml). The reaction mixture was heated at 78 °C for 24 h under nitrogen. On cooling, the reaction mixture was poured into 500 ml of distilled water and neutralised with hydrochloric acid (2 M). The resulting precipitate was collected by filtration and recrystallised from *n*-hexane to afford 5,6-bis(2,6-di-*iso*-propylphenoxy)-2,3-dicarbonitrile **3** as a white powder (3 g, 62%); mp 253 °C; found: C, 74.38; H, 7.18; N, 12.03. $C_{30}H_{34}N_4O_2$ requires C, 74.68; H, 7.03; N, 11.62). IR ν (KBr)/cm^{-1} 3069 (ArH); 2237 (CN); δ_H ($CDCl_3$, 400 MHz, 25 °C); 1.25 (d, $J = 6.2$ Hz, 24H); 2.84 (sept, 4H); 7.29 (d, $J = 7.8$ Hz, 4H); 7.38 (t, $J = 7.6$ Hz, 2H); δ_C ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C). 23.78, 28.62, 113.25, 124.82, 125.27, 128.24, 140.40, 146.90, 151.70; *m*/*z* (CI) 482 (M^+).
27. In a typical procedure, a solution of **3** (0.5 g, 1.0 mmol) in dry quinoline (20 ml) was stirred at 160 °C for 24 h under nitrogen. On cooling, the reaction mixture was poured into 200 ml of distilled water. The resulting precipitate was collected and purification was achieved by reprecipitation from $CHCl_3$ into MeOH to give 2,3,9,10,16,17,23,

24-octa(2′,6′-di-*iso*-propylphenoxy)-1,4,8,11,15,18,22,25-octaazaphthalocyanine (**1a**) (0.20 g, 40% yield), mp >300 °C; found: C, 74.61; H, 7.15; N, 11.6, $C_{120}H_{136}N_{16}O_8$ requires C, 74.30; H, 7.28; N, 11.90). IR *v* (KBr)/cm^{-1} 3434 (ArH), 2963 (CH) aliphatic; λ_{max} ($CHCl_3$)/nm: 645, 607, 348; δ_H ($CDCl_3$, 400 MHz, 25 °C); −2.05 (2H, s); 2.37 (d, $J = 6.2$ Hz, 96H); 5.25 (sept, 16H); 8.55 (d, $J = 7.0$ Hz, 16H), 8.63 (t, $J = 7.0$ Hz, 8H); *m*/*z* (MALDI) 1930 (M^+).

28. Wöhrle, D.; Schnurpfeil, G.; Knothe, G. *Dyes Pigments* **1992**, *18*, 91–102.
29. Brewis, M.; Clarkson, G. J.; Humberstone, P.; Makhseed, S.; McKeown, N. B. *Chem. Eur. J.* **1998**, *4*, 1633–1640.
30. Terekhov, D. S.; Nolan, K. J. M.; McArthur, C. R.; Leznoff, C. C. *J. Org. Chem.* **1996**, *61*, 3034–3040.
31. Hassan, B. M.; Li, H.; McKeown, N. B. *J. Mater. Chem.* **2000**, *10*, 39–45.