

Synthesis of a novel asymmetrical octasubstituted zinc naphthalocyanine

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The synthesis and characterization of a novel asymmetrical octasubstituted zinc naphthalocyanine ($ZnNc(OR_1)_6(OR_2)_2$, $R_1=C_4H_9$, $R_2=CH_2CH_2OCH_3$) made by mixed condensation are described.

Keywords: asymmetrical octasubstituted zinc naphthalocyanine

The phthalocyanine derivatives have been found to be very promising candidates as second-generation photosensitisers for photodynamic therapy (PDT) of cancers, some (such as $MPcSn$) are in phase II clinical trials.¹ Due to their very stable physical and chemical properties, the shelf life of this type of photosensitiser can be very long, but their very low solubility in organic and inorganic solvents entails the use of surfactants such as Tween 80 for the delivery of these photosensitisers to the patients. Much work has been done to “tailor” the physical properties of phthalocyanines for the purpose of better delivery mechanism and higher efficiency for use in PDT, such as introducing substituent groups on the benzene ring, or adding axial ligands.

We focus on compounds that absorb strongly in the red or near-infrared regions, the region of the spectrum within the “therapeutic window” that gives the maximum penetration of light through tissues and is therefore of most use in the treatment of tumors by PDT. Phthalocyanine absorbs very strongly at about 670 nm, introducing four fused benzene ring in the periphery of the macrocycle will move the band of maximum absorption to the red by *ca* 100 nm, further introduction of alkoxy substituents in the 2,4 positions of those fused benzenes will move the band even further to the red, to about 850 nm.² These 2,4-alkoxy substituted naphthalocyanines absorb strongly in the near-IR region. In addition, the introduction of alkoxy substituents will also improve the solubility both in organic and inorganic solvents.

Unsymmetrical phthalocyanines and naphthalocyanines have very distinctive physical properties, and can be used in other areas such as second-order non-linear optics and microelectronics. The synthetic routes to unsymmetrical phthalocyanine derivatives which have been reported include polymer support methods, stepwise synthetic procedures, the condensation of two different substituted phthalonitrile precursors³ and ring enlargement of subphthalocyanines.⁴ In this paper, the mixed precursor condensation route to the synthesis of unsymmetrical octasubstituted zinc naphthalocyanines is chosen.

The synthetic route to asymmetrical octasubstituted zinc naphthalocyanine is shown in Scheme 1. 1,4-dibutoxy-2,3-dicyanonaphthalene (**1**) was prepared by a modification of the method of Cook and Dunn,⁵ Alkylation of 1,4-dihydroxy-2,3-dicyanonaphthalene in DMF gave the 1,4-dibutoxy-2,3-dicyanonaphthalene (**1**) in good yield (55%). 1,4-dihydroxy-2,3-dicyanonaphthalene treated with $MeOCH_2CH_2OTs$ gave 1,4-bis(2-methoxy-ethoxy)-2,3-dicyanonaphthalene (**2**)⁶ in 60% yield. Condensation of **1** and **2** in 3:1 ratio with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst gives a mixture of



Scheme 1

isomers, which were separated by chromatographic methods to give mainly the unsymmetrical naphthalocyanines (**3**).

Linßen and Hanack⁷ used column chromatography to separate statistical condensation mixtures of isomers. Though the condensation of two different precursors in the ratio of 1:1 formed a statistical mixture of the six isomers, the proportion of the six isomers changed when the two precursors were used in different ratios. In our experiment a 3:1 ratio of precursors in the preparation of naphthalocyanine were used, which leads to maximum amount of compound **3**. Compound **3** has good solubility in most common organic solvents, such as toluene, chloroform, dichloromethane, ethyl acetate and tetrahydrofuran.

Compound **3** absorbs strongly at 846 nm; its UV-vis spectrum in toluene is given in Fig. 1. Unlike most of the unsymmetrical phthalocyanines, where Q-band splitting can be observed due to the non-degenerate electronic states, compound **3** shows no splitting of Q-band, this is probably

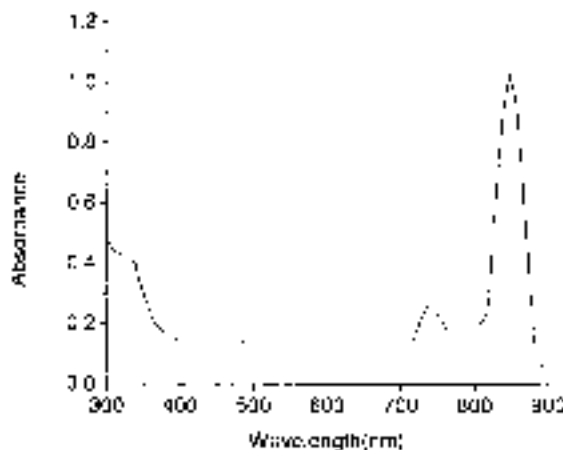


Fig. 1 UV-vis spectra of $ZnNc(OBu)_6(OCH_2CH_2OCH_3)_2$ in toluene.

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† This is a Short Paper, there is therefore no corresponding material in *J. Chem. Research (M)*.

because the "hetero" substituents are not too much different from the major ones, so that the non-degeneracy is not obvious in this compound.

Experimental

Solvents were analytical grade and thoroughly dried before use. BioBeads S-X8 was purchased from Bio-Rad Labs, Richmond, CA. 1,4-dihydroxy-2,3-dicyanonaphthalene was prepared from 2,3-dichloro-1,4-naphthoquinone by the method of Reynolds and Van Allen.⁸ The melting point is uncorrected. Proton magnetic resonance spectra were recorded on a Varian Mercury-300 spectrometer. Mass spectra (FAB) were recorded on a ZAB 3F-HF spectrometer. Elemental analyses were determined on a Perkin-Elmer 204B elemental analysis apparatus. UV-vis spectra were recorded on a Shimadzu UV-3100 or UV-160A spectrometer at 25.0±0.5°C.

Synthesis of 1,4-dibutoxy-2,3-dicyanonaphthalene(1):⁵ Under N₂, a mixture of 1,4-dihydroxy-2,3-dicyanonaphthalene (3.4g, 16mmol), 1-iodobutane (6.0ml, 48.8mmol), K₂CO₃(12g, 87mmol), and DMF(40ml) was heated to 85°C with stirring for 6 h. After cooling, the solution was poured into 200ml of ice-water slurry, stirred for 1h, filtered, dried, and column chromatographed (Al₂O₃, 1:1 toluene-ethyl acetate). A selected portion of the eluent was concentrated to a small volume, diluted with hexane, chilled on ice, and filtered. The colourless crystal was washed with hexane and dried (2.9g, 55%). m.p. 65–68°C. δ_H (CDCl₃): 8.24 (m, 2H, ArH), 7.77 (m, 2H, ArH), 4.44 (t, 4H, OR-1 CH₂), 1.94 (m, 4H, OR-2 CH₂), 1.59 (m, 4H, OR-3 CH₂), 1.03 (t, 6H, CH₃). MS-FAB: *m/z* 323(M⁺+1). Anal. C₂₀H₂₂N₂O₂ Calcd: C, 74.51; H, 6.88; N, 8.69; Found: C, 74.34; H, 6.92; N, 8.54.

Synthesis of 1,4-bis(2-methoxy-ethoxy)-2,3-dicyanonaphthalene(2):⁶ Under N₂, a mixture of 1,4-dihydroxy-2,3-dicyanonaphthalene (2.1g, 10mmol), 2-methoxy-ethyl *p*-tolylsulfonyloxy ester (5.0g, 22mmol), K₂CO₃ (5g, 36mmol), and DMF (20ml) was heated to 85°C with stirring for 6 h. After cooling, the precipitate was filtered off and washed with a small amount of DMF, and the filtrate was evaporated to dryness. The residue was dissolved in 200ml of 1:1 ethyl acetate:diethyl ether, the solution was then washed sequentially with 1 M NaOH (20ml × 2), H₂O(20ml), 1 M HCl(20ml × 2), H₂O(20ml × 2). After drying over Na₂SO₄ and evaporation of the solvent, the compound was recrystallized from methanol several times as colorless needle crystal was obtained(1.9g, 60%). m.p. 104–105°C[lit., 102–103°C]. δ_H (CDCl₃): 8.38 (m, 2H, ArH), 7.78 (m, 2H, ArH), 4.58 (t, 4H, OCH₂CH₂O), 3.84 (t, 4H, OCH₂CH₂O), 3.42 (t, 6H, CH₃).

MS-FAB: *m/z* 327(M⁺+1). Anal. C₁₈H₁₈N₂O₄ Calcd: C, 66.25; H, 5.56; N, 8.58; Found: C, 66.04; H, 5.48; N, 8.36.

Synthesis of naphthalocyanine(3): Under N₂, a mixture of 1,4-dibutoxy-2,3-dicyano naphthalene (966mg, 3mmol), 1,4-bis(2-methoxy-ethoxy)-2,3-dicyanonaphthalene (326mg, 1mmol), zinc acetate (274mg, 1.5mmol) and 1,8-diazabicyclo[5.4.0] undec-7-ene(0.5ml) in 20ml BuOH was heated to reflux for 48 h. The blue-green solution was evaporated to dryness under vacuum. The residue was flash chromatographed (Al₂O₃, 100–200 mesh, 1:1 hexane-ethyl acetate) twice, then chromatographed (Al₂O₃, 200–300 mesh, 1:1 hexane-toluene with an increasing amount of THF). The second fraction was collected and rechromatographed (toluene, BioBeads S-X8). The green fraction was collected and evaporated to dryness giving a dark green solid (75mg, 6%). λ_{max} (toluene): 846 nm (sh, log_e 5.2). δ_H (CDCl₃): 9.24 (m, 8H, ArH), 7.64 (m, 8H, ArH), 5.56 (t, 4H, OCH₂CH₂O), 5.38 (t, 12H, OR-1 CH₂), 3.96 (t, 4H, OCH₂CH₂O), 3.28 (s, 6H, OCH₃), 2.36 (m, 12H, OR-2CH₂) 1.62 (m, 12H, OR-3CH₂), 1.02 (m, 16H, CH₃). MS-FAB: *m/z*: 1357(M⁺+1). Anal. C₇₈H₈₄N₈O₁₀Zn Calcd: C, 68.94; H, 6.23; N, 8.25; Found: C, 68.54; H, 6.14; N, 7.96.

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