

First phthalocyanine– β -cyclodextrin dyads

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Abstract—Novel water-soluble phthalocyanine– β -cyclodextrin dyads were prepared via a statistical cross condensation of a 4-(β -cyclodextrin)phthalonitrile with known phthalonitriles.

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1. Introduction

Phthalocyanines (Pcs) have been intensively studied due to their applications in many scientific areas,¹ their use as photosensitizers (PS) in photodynamic therapy (PDT)² being a most promising one. PDT uses a combination of visible light, oxygen and a photosensitizer to cause photodamage to tumour tissues; it is strongly dependent on the photophysical and photochemical photosensitizer properties. The latter should exhibit high light absorption features in the 600–800 nm region, good selectivity to the target cells, minimal dark toxicity, high singlet oxygen quantum yields formation, amphiphilicity features and others.^{3,4}

Phthalocyanines show a higher molar absorptivity ($>10^5 \text{ M}^{-1} \text{ cm}^{-1}$) at the adequate PDT therapeutic window in comparison with the already established drugs.⁵ However, most Pcs are insoluble in physiological fluids, requiring usually hard formulations to be used.⁶ Different biologically compatible delivery systems have been described in order to solve that limitation, such as incorporation into liposomes, biopolymers and cyclodextrins (CD).^{7,8} In that way, it is expected that these problems could be overtaken if water-soluble phthalocyanines can become available.

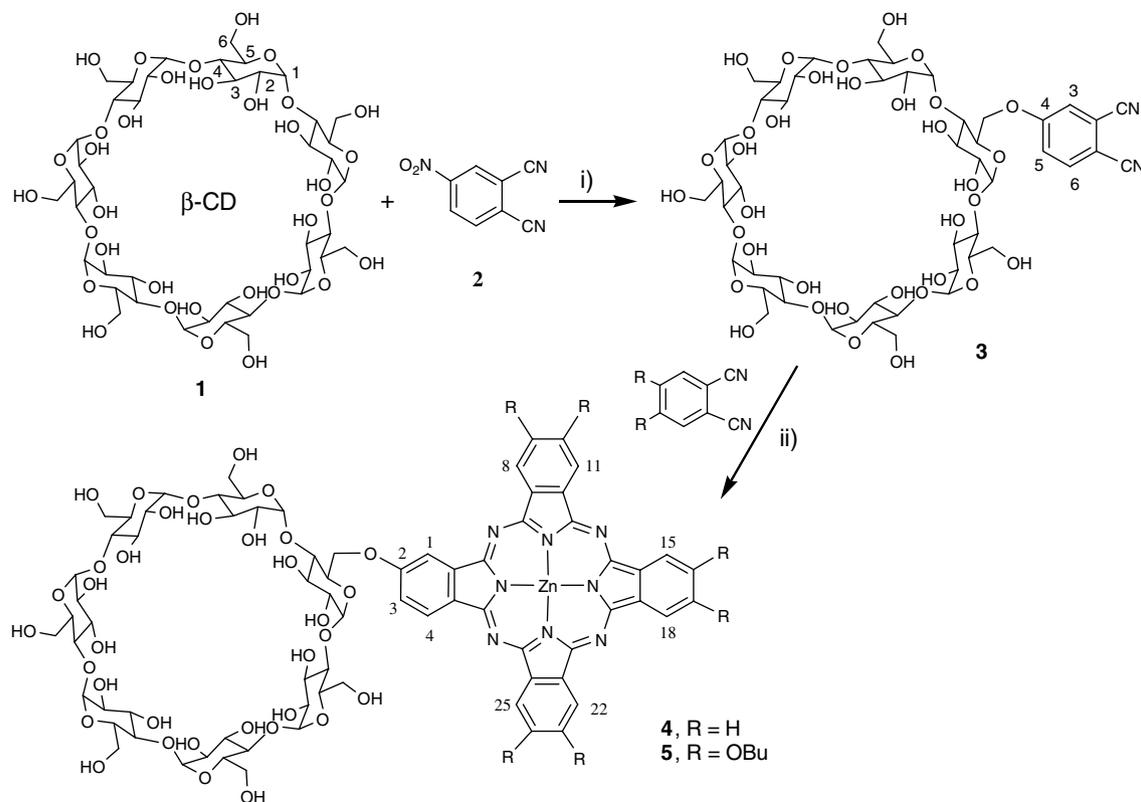
Recently, the syntheses of ionic⁹ and neutral¹⁰ water-soluble phthalocyanine derivatives have been described. In this work, we propose a new methodology to obtain stable water solutions of Pcs using a covalent linkage to the β -cyclodextrin. Furthermore, the CD moiety promotes good amphiphilicity character to the new compounds. It is worth to mention that, as far as cyclodextrins and phthalocyanines are concerned, only inclusion compounds have been described. The exterior hydrophilic properties of the CD combined with its hydrophobic cavity in the centre allow the solubilization of these Pcs in water.^{11,12a}

2. Synthesis

The novel phthalocyanine– β -cyclodextrin (Pc–CD) dyads **4** and **5** were prepared in two steps (Scheme 1). First the 4-(β -cyclodextrin)phthalonitrile **3** was synthesized by coupling β -cyclodextrin **1** with 4-nitrophthalonitrile **2**, at room temperature in DMF, and in the presence of K_2CO_3 .¹³ Then, the Pc–CD dyads **4** and **5** were prepared by statistical cross condensation of the cyclodextrin–phthalonitrile **3** with an excess of phthalonitrile or 4,5-dibutoxyphthalonitrile, respectively, in the presence of zinc chloride. The reactions were carried out in refluxing *N,N*-dimethylaminoethanol (DMAE) affording the desired dyads as well as the symmetric zinc phthalocyanine, formed by self-condensation of the non cyclodextrin–phthalonitrile. The products were purified by silica gel and reverse phase column chromatography using a gradient of THF/ H_2O as the

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Scheme 1. Reagents and conditions: (i) DMF, K_2CO_3 , rt; (ii) DMAE, ZnCl_2 , reflux.

eluent.^{14,15} The structures of dyads **4** and **5** were confirmed by NMR spectroscopy, UV-vis and HRMS-MALDI-TOF.

The ^1H NMR spectra show the resonances of the cyclodextrin protons (δ : 3–6 ppm), as well as the resonances due to the phthalocyanine aromatic protons (δ : 7–9 ppm). For dyad **5**, the resonances of the protons of the six butoxyl groups appear as multiplets in the high field region.

Dyads **4** and **5** give well-defined UV-vis spectra in DMSO, with sharp Q-bands centred at 675–680 nm,

indicating monomeric species in solution. However, the optical features of these compounds in water differ remarkably from those in DMSO (Fig. 1). The B-bands are slightly shifted to shorter wavelength, whereas the Q-bands are also blue-shifted and split in two main absorption bands at 675–680 and 630 nm. The intensity of these bands is much lower than the Q-band in DMSO. It is well known that aggregation in phthalocyanines, due to cofacial arrangement of the macrocycles, gives rise to effects in the UV-vis spectra similar to that described above.^{12b} In our particular case, both monomeric and lower oligomeric (characteristic band at 630 nm) species coexist in the aqueous solution.

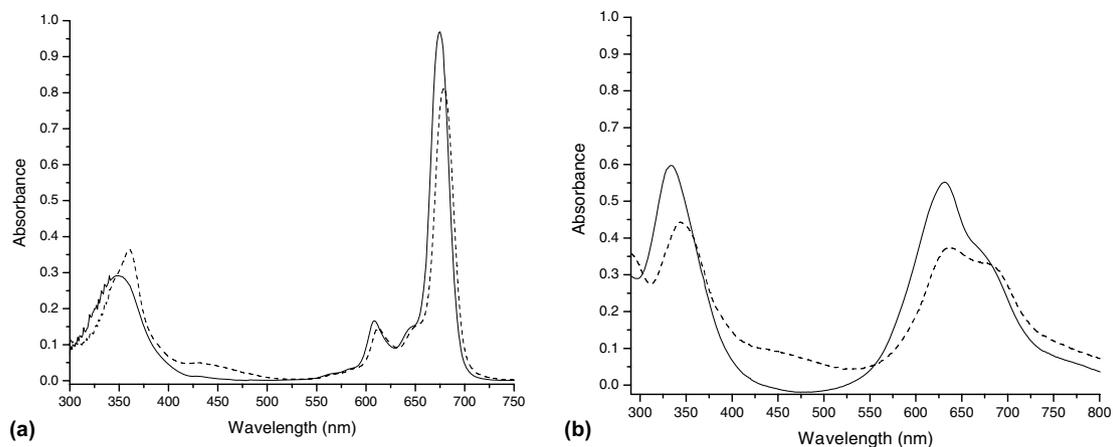


Figure 1. UV-vis spectra of dyads **4** (—) and **5** (---) at the same concentration: (a) in DMSO (4.5 μM) and (b) in water (17 μM).

Beer's law was obeyed for **4** and **5** in DMSO at concentrations lower than 5×10^{-5} mol L⁻¹, and the extinction coefficients are similar to the corresponding symmetric Pcs in the same solvent. The solubility of dyad **4a** in water was determined as being 18 mg/mL. As expected, the water solubility of this dyad is not very different than that of the β -CD (18.5 mg/mL).¹⁶

MS spectra¹⁷ of **4** and **5** provided a definitive proof for their characterization. Peaks for the corresponding molecular ions of **4** and **5** were detected when a matrix assisted laser desorption ionization time-of-flight technique (MALDI-TOF) was used. As expected, complex isotopic distributions were observed for the molecular ions. Both low and high resolution MS spectra were obtained. In the last case the corresponding monoisotopic peak was selected for comparison with the standard. In the case of the starting compound **3**, NaI was added for improving ionization results. In compounds **4** and **5** ionization took place better in the absence of NaI.

3. Summary and outlook

The synthesis of covalently linked phthalocyanine–cyclodextrin dyads has been reached for the first time. MALDI-TOF-MS has proved to be an excellent tool for systematically studying this kind of systems, which otherwise are difficult to characterize. Taking into account the solubility of the dyads in water and the individual optical (Pc) and complexation (CD) properties of both components, this family of compounds may be of interest as water-soluble photosensitizers for PDT, as well as for constructing supramolecular systems for molecular recognition, with potential applications in optical sensing. The organization at a supramolecular level of water-soluble phthalocyanine photoactive assemblies^{18a} and subphthalocyanines^{18b} is also an important goal to be pursued.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.06.068](https://doi.org/10.1016/j.tetlet.2006.06.068).

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- 6-O-[4-(1,2-dicyanobenzene)]- β -cyclodextrin (**3**): β -Cyclodextrin (**1**, 1.96 g, 1.70 mmol) and 4-nitrophthalonitrile (**2**, 0.33 g, 1.87 mmol) were stirred in dry DMF (10.0 mL) at room temperature, under a N₂ atmosphere, in the presence of K₂CO₃ (0.24 g, 1.70 mmol), for 12 h. Compound **3** was precipitated by addition of acetone; it was filtered and recrystallized from H₂O/acetone (1.9 g, 86% yield). ¹H NMR (300.13 MHz, DMSO-*d*₆) δ : 8.02 (d, *J* = 8.8 Hz, 1H, H-6), 7.84 (d, *J* = 2.5 Hz, 1H, H-3), 7.56 (dd, *J* = 8.8, 2.5 Hz, 1H, H-5), 6.05–5.65 (m, 14H, CD–OH-2,3), 5.15–4.84 (m, 7H, CD–H-1), 4.67–4.57 (m, 6H, CD–CH₂OH), 4.10–4.00 (m, 2H, CD–CH₂O–Phth), 3.60–3.40 (m, 40H, CD–H-2,3,4,5 and CD–CH₂OH—overlapped with H₂O); ¹³C NMR (75.47 MHz, DMSO-*d*₆) δ (CD): 55.1 (CH₂O–Phth), 60.1 (CH₂OH), 72.2, 72.5, 72.9, 73.2, 78.3, 79.3, 81.5; δ (phthalonitrile): 102.1, 106.0, 115.9, 116.1, 116.5, 121.5 and 121.8 (CN), 135.7; MS (MALDI-TOF, DHB+NaI), *m/z*: 1283.2 [M+Na]⁺, 1299.2 [M+K]⁺. HRMS (MALDI-TOF, PEG+NaI): *m/z* (C₅₀H₇₂N₂O₃₅Na): calcd: 1283.3787. Found: 1283.3808, *m/z* (C₅₀H₇₂N₂O₃₅K): calcd: 1299.3547. Found: 1299.3561.
- Synthesis of Zn-phthalocyanine–cyclodextrin dyads **4** and **5**. Typical procedure: a solution of compound **3** (0.30 g, 0.24 mmol), 1,2-dicyanobenzene [or 4,5-dibutoxy-1,2-dicyanobenzene (2.4 mmol)] and ZnCl₂ (0.47 g, 1.44 mmol) in DMAE (10.0 mL), under an inert atmosphere, was stirred at 145 °C for 12 h. The product was pre-purified by silica gel column chromatography using THF–H₂O (100:0 to 90:10) as the eluent. Then, the compound was purified by a reverse-phase chromatography using THF–H₂O (90:10) as the eluent. Dyad **4**: Yield: 70 mg (18% yield); ¹H NMR (300.13 MHz, DMSO-*d*₆) δ : 9.40–9.20 (m, 6H, H-8,11,15,18,22,25), 8.93 (d, 1H, *J* = 8.3 Hz, H-4), 8.82 (d, 1H, *J* = 2.3 Hz, H-1), 8.24–8.14 (m, 6H, H-9,10,16,17,23,24), 7.83 (dd, *J* = 8.3, 2.3 Hz, 1H, H-3),

- 6.28–5.77 (m, 14H, CD–OH-2,3), 5.14–4.56 (m, 13H, CD–H-1 and CD–CH₂OH), 4.42–4.35 (m, 2H, CD–CH₂O–Phth), 3.96–3.57 (m, 40H, CD–H-2,3,4,5 and CD–CH₂OH); ¹³C NMR (75.47 MHz, DMSO-*d*₆) δ (CD): 60.0 (CD–CH₂OH), 72.2, 72.5, 73.2, 81.6, 102.0; δ (phthalocyanine): 108.0, 110.0, 111.2, 116.5, 118.1, 121.4, 122.3, 129.3, 132.0, 137.7, 139.6, 152.1, 152.5, 162.0; UV–vis (DMSO): λ_{max} (log ε) = 350 (4.80), 675 (5.31) nm; MS (MALDI-TOF, DHB), *m/z*: 1708.5–1717.5 [M⁺] isotopic pattern. HRMS (MALDI-TOF, PEG): *m/z* (C₇₄H₈₄N₈O₃₅Zn): calcd: 1708.4325. Found: 1708.4381.
15. Dyad **5**: Yield: 90 mg (17%); ¹H NMR (300.13 MHz, DMSO-*d*₆) δ: 9.41 (d, *J* = 8.0 Hz, 1H, H-4), 9.23 (d, *J* = 2.2 Hz, 1H, H-1), 9.07–8.85 (m, 6H, H-8,11,15,18,22,25), 7.97 (dd, *J* = 8.0, 2.2 Hz, 1H, H-3), 6.27–5.59 (m, 14H, CD–OH-2,3), 5.20–5.00 (m, 7H, CD–H-1), 4.59–4.48 (m, 6H, CD–CH₂OH), 4.27–4.18 (m, 2H, CD–CH₂O–Phth), 4.15–3.60 (m, 42H, CD–H-2,3,4,5 and CD–CH₂OH), 2.00–1.20 (4m, 54H, –OBu); UV–vis (DMSO): λ_{max} (log ε) = 360 (4.91), 678 (5.25) nm; MS (MALDI-TOF, DHB), *m/z*: 2140.9–2148.9 [M⁺] isotopic pattern. HRMS (MALDI-TOF, PEG): *m/z* (C₉₈H₁₃₂N₈O₄₁Zn): calcd: 2140.7776. Found: 2140.7825.
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