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The synthesis and characterization of novel unsymmetrical azaphthalocyanines containing one carboxylic group

Petr Zimcik*, Miroslav Miletin, Zbynek Musil, Kamil Kopecky, Dana Slajsova

Department of Pharmaceutical Chemistry and Drug Control, Faculty of Pharmacy, Charles University in Prague, Heyrovskeho 1203, Hradec Kralove 50005, Czech Republic

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Abstract

Unsymmetrical zinc and magnesium complexes of azaphthalocyanines with one carboxylic group were synthesized using statistical condensation of 5,6-bis(*tert*-butylsulfanyl)pyrazine-2,3-dicarbonitrile (A) and 3-(5,6-dicyano-3-methylpyrazin-2-ylsulfanyl)propionic acid (B) or 6-(3-*tert*-butylsulfanyl-5,6-dicyanopyrazine-2-ylamino)hexanoic acid (C); unsymmetrical AAAB or AAAC azaphthalocyanines were isolated from the mixture. During preparation of Mg complexes of AAAC type, the precursor C had to be esterified before cyclotetramerization and the final azaphthalocyanine was hydrolyzed to yield AAAC of higher purity. The synthesized compounds were characterized using IR, NMR, MS and UV–vis spectroscopy; singlet oxygen quantum yields were measured using DPBF decomposition method. The zinc AAAB complex showed good photodynamic properties indicating that it may be suitable as a third generation photosensitizer.

Keywords: Unsymmetrical substitution; Azaphthalocyanine; Tetrapyrazinoporphyrazine; Monofunctional; Singlet oxygen quantum yield; Carboxylic acid

1. Introduction

In recent years, phthalocyanines and their analogs have become a subject of increasing research interest [1], as commercial dyes, in photovoltaic applications [2] or for non-linear optics [3]. Despite their strong absorption in the far red region, which makes them suitable as potential photosensitizers in photodynamic therapy (PDT) [4–7], this particular application requires higher selectivity to tumor cells. In this context, one approach involves the combination of a photosensitizer with a targeting moiety; compounds of this type are referred to as third generation photosensitizers. The targeting component improves localization of the dye in specific sites and thus increases selectivity, tumor uptake and, consequently, PDT effectiveness; several types of targeting compounds are under investigation and the uses of folic acid [8], polylysine chains [9,10], monoclonal antibodies [11] and steroids [12] have been reported.

Although the syntheses of derivatizable symmetrical phthalocyanines and their aza-analogs from one precursor is relatively straightforward, it leads to compounds containing four (in the case of monosubstituted precursor) or eight (in the case of disubstituted precursor) derivatizable groups (e.g. carboxy- or amino groups). The presence of more than one modifiable group could lead to polymerization; in addition, complex mixtures can arise during conjugation with the targeting compound. Whilst the presence of one functionality seems therefore to be more suitable [13,14], this involves the more complicated syntheses of unsymmetrical compounds that require specific approaches [15,16]—a subphthalocyanine method [17,18], polymeric support method [19–21] or statistical condensation [13,14]. Whilst the latter method is most widely used the ensuing mixture of different Pcs must be chromatographically resolved, which is often problematic owing to the low solubility of Pc in many solvents and the tendency of these planar macrocyclic systems to aggregate. Peripheral

* Corresponding author. Tel.: +420 49 5067257; fax: +420 49 5567167.
E-mail address: petr.zimcik@faf.cuni.cz (P. Zimcik).

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substitution of the Pc macrocycle with bulky substituents prevents this behavior [22,23] allowing chromatographic separation of the desired compounds from admixture [4].

This work concerns the preparation of azaphthalocyanines (AzaPc) containing one carboxylic group. Such molecules can then be combined with targeting moieties to form third generation photosensitizers.

2. Experimental

All organic solvents used for the synthesis were of analytical grade. Anhydrous butanol was stored over magnesium and distilled prior to use. Anhydrous dimethylformamide (DMF) was purchased from Acros. 1,3-Diphenylisobenzofuran (DPBF), 2,2-dimethyl-propane-1-thiol and 3-sulphanylpropionic acid were purchased from Aldrich. 6-Aminohexanoic acid was purchased from Fluka. Zinc phthalocyanine (ZnPc) was obtained from Eastman Organic Chemicals (New York, USA). All chemicals were used as received except for zinc acetate dihydrate (Lachema, Czech Republic), which was dried at 78 °C under reduced pressure (13 mbar) for 5 h. TLC was performed on Merck aluminium sheets with silica gel 60 F_{254}. Merck Kieselgel 60 (0.040–0.063 mm) was used for column chromatography. Melting points were measured on Electrothermal IA9200 Series Digital Melting Point Apparatus (Electrothermal Engineering Ltd., Southend-on-Sea, Essex, Great Britain) and are uncorrected. Infrared spectra were measured in KBr pellets on IR-Spectrometer Nicolet Impact 400. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-Vx BB 300 (299.95 MHz – ^{1}H and 75.43 MHz – ^{13}C). Chemical shifts reported are given relative to internal $Si(CH_3)_4$. UV–vis spectra were recorded on spectrophotometer UV-2401PC, Shimadzu Europa GmbH (Duisburg, Germany). The elemental analysis was carried out on an Automatic Microanalyser EA1110CE (Carlo Erba S.p.A., Milano, Italy). MALDI-TOF mass spectra were recorded in positive reflectron mode on a mass spectrometer Voyager-DE STR (Applied Biosystems, Framingham, MA, USA). For each sample, 0.5 μL of the mixture was spotted onto the target plate, air-dried and covered with 0.5 μL of matrix solution consisting of 10 mg of α-cyano-4-hydroxycinnamic acid in 100 μL of 50% ACN in 0.1% trifluoroacetic acid. The instrument was calibrated externally with a five-point calibration using Peptide Calibration Mix1 (LaserBio Labs, Sophia-Antipolis, France). ESI MS spectra of compound **6** were measured on Quattro Micro™ API (Waters, Milford, MA, USA) in positive electrospray mode. Solution for ESI MS was prepared in methanol and formic acid was added before measurements to support ionization.

Compounds **1** [22], **2** [24], **4** and **5** [25] were prepared according to published procedures in good purity. Compounds **10** and **11** that were isolated from the reaction mixtures showed the same characteristics (R_f values, UV–vis, NMR, IR spectra) as the same compounds prepared before by simple tetramerization of **1** [22], and therefore they are not characterized here.

2.1. 3-(5,6-Dicyano-3-methylpyrazin-2-ylsulfanyl) propionic acid (*3*)

A 1.0 M aqueous solution of NaOH (2.2 mL) was stirred at r.t. and 3-sulphanylpropionic acid (117 mg, 1.1 mmol) was added. The mixture was stirred for 15 min and a solution of **2** (178 mg, 1 mmol) in acetone (10 mL) was added dropwise. The reaction mixture was stirred at r.t. for 1 h with monitoring on TLC using chloroform as a mobile phase. After the reaction was completed, the organic part was evaporated under reduced pressure, and the aqueous solution of **3** was acidified with a few drops of concentrated HCl. The precipitated solid was collected and washed with water. The crude product was purified on silica gel using chloroform/acetic acid 10:1 as the eluent. Yield 98 mg (39%) of light yellow solid; m.p. 143–144 °C; IR, ν (cm^{-1}): 2956, 2862 (alkyl CH), 2234 (C≡N), 1701 (C=O); ^{1}H NMR (acetone-d_6) δ: 2.59 (s, 3H, CH_3), 2.82 (t, 2H, $J = 6.4$ Hz, CH_2), 3.52 (t, 2H, $J = 6.7$ Hz, S–CH_2); ^{13}C NMR (acetone-d_6) δ: 22.1, 26.2, 33.1, 114.6, 114.9, 127.5, 131.0, 157.3, 162.9, 172.7. Anal. calcd for $C_{10}H_8N_4O_2S$: C 48.38; H 3.25; N 22.57; S 12.92%. Found: C 48.05; H 3.28; N 22.42; S 12.59.

2.2. 3,9,10,16,17,23,24-Heptakis(tert-butylsulfanyl)-2-(5-carboxypentylamino)-1,4,8,11,15,18,22,25-octaazaphthalocyaninato magnesium(II) (*6*)

Magnesium (343 mg, 14 mmol) and a small crystal of iodine were refluxed in anhydrous butanol (20 mL) for 4 h. Compounds **1** (459 mg, 1.5 mmol) and **5** (202 mg, 0.5 mmol) were added and the reflux continued for next 2 h. After this time, the dark green solution was cooled down and evaporated. The solid was then suspended in 50% (v/v) acetic acid and stirred at r.t. for 30 min. The green solid was collected and washed thoroughly with water. This mixture of AzaPc was not separated but hydrolyzed immediately. Thus, the green solid was dissolved in THF (50 mL) and a 0.1 M solution (90 mL) of KOH (9 mmol) in water/ethanol (1:10) was added. The reaction was stopped after 24 h of stirring at r.t. and the solvents were evaporated. The solid was suspended in 20% (v/v) acetic acid, stirred for 30 min and collected by filtration with a subsequent washing with water. The product was isolated using column chromatography on silica with chloroform/acetone/methanol 30:1:1 as the eluent. The first intense green fraction corresponds to compound **10**. The next intense green fraction corresponding to product **6** was collected and purified on silica once more with the same eluent. Yield 46 mg (7%); IR, ν (cm^{-1}): 2959, 2922, 2858 (alkyl CH), 1709 (C=O), 1567, 1516, 1456, 1362, 1252, 1233, 1144; ^{1}H NMR (pyridine-d_5) δ: 7.36 (t, 1H, $J = 5.4$ Hz, NH), 4.36 (q, 2H, $J = 6.5$ Hz, NH–CH_2), 2.70–2.57 (m, 2H, CH_2COO), 2.30–2.18 (m, 54H, CH_3), 2.15 (s, 9H, CH_3), 2.09–1.97 (m, 4H, CH_2), 1.97–1.84 (m, 2H, CH_2); ^{13}C NMR (pyridine-d_5) δ: 175.92, 158.74, 158.29, 158.09, 157.99, 157.56, 153.64, 153.25, 152.79, 151.43, 150.74, 150.67, 148.25, 147.06, 145.75, 145.73, 145.59, 145.40, 145.38, 145.27, 140.45, 51.33, 51.29, 51.16, 50.86, 42.58,