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Synthesis and physicochemical behaviour of aluminium trikis and tetrakis (diaquaplatinum) octacarboxyphthalocynine

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ABSTRACT

The combination of chemotherapy and photodynamic therapy was investigated by the synthesis and characterisation of phthalocyanine conjugates with Pt complexes. The complexes synthesized are: hydroxoaluminum trikis(diaquaplatinum) octacarboxyphthalocyanine (OHAlOCPc(Pt)$_3$) and hydroxoaluminum tetrakis(diaquaplatinum) octacarboxyphthalocyanine (OHAlOCPc(Pt)$_4$). The platinated phthalocyanine complexes gave long triplet lifetimes of 577 and 526 μs for OHAlOCPc(Pt)$_3$ and OHAlOCPc(Pt)$_4$, respectively. The triplet quantum yields were found to be 0.45 for OHAlOCPc(Pt)$_3$ and 0.57 OHAlOCPc(Pt)$_4$ while the singlet oxygen quantum yields were found to be 0.38 and 0.48, respectively.

1. Introduction

Recent advances in treatment of tumors have led towards the use of bi-functional agents that allow the combined action of two methods of cancer treatment. Thus there has been interest in synthesizing covalent conjugates of photosensitizers for photodynamic therapy (PDT) of cancer such as phthalocyanines and porphyrins with cytotoxic Pt(II) complexes used in chemotherapy [1–5]. Such conjugates are expected to have high selectivity for tumor cells, allowing for a reduction in doses of platinum drugs, hence reducing their side effects.

Phthalocyanine (Pc) derivatives have gained importance in a number of fields including in their use as photosensitizers [6–10]. The effectiveness of Pc derivatives as PDT agents is due to their high absorption in the phototherapeutic window (600–800 nm) coupled with a long triplet lifetime to generate cytotoxic singlet oxygen ($^1O_2$) [6]. Singlet oxygen is extremely reactive and it destroys biomolecules. High singlet oxygen quantum yields depend on high triplet state quantum yields and lifetimes. Diamagnetic central metals are known to enhance these parameters [6].

Platinum complexes have been used in chemotherapy due to their potency. The most used platinum complex is cis-diamine-dichloro platinum (cisplatin), which is, however associated with many harmful side effects such as: allergy, neurotoxicity and many others [11]. The problem is the poor selectivity associated with cisplatin. The general formula of the first generation platinum complexes used as anti cancer agents is L_2PtX_2, where L is a non-leaving group such as an amine or thiol [11]. X represents good leaving groups such as the halides and carboxylates. The good leaving groups are replaced by water within the cells and leaving the platinum complex to bind irreversibly to biomolecules (DNA and enzymes).

Covalent conjugates of phthalocyanines with platinum complexes have been reported [2–5], but all reported phthalocyanine complexes within the conjugates contained electroactive central metals such as Ru, Co and Fe which are not appropriate for PDT. This study reports on the conjugates of aluminum phthalocyanines with diaquaplatinum. The complex synthesized is hydroxoaluminum trikis(diaquaplatinum) octacarboxyphthalocyanine (abbreviated as OHAlOCPc(Pt)$_3$, Scheme 1) and its behaviour compared to that of hydroxoaluminum tetrakis(diaquaplatinum) octacarboxyphthalocyanine (abbreviated as OHAlOCPc(Pt)$_4$). The latter contains four diaquaplatinum groups, Scheme 1. OHAlOCPc(Pt)$_3$ contains three diaquaplatinum groups leaving two COONa groups which then impart some limited

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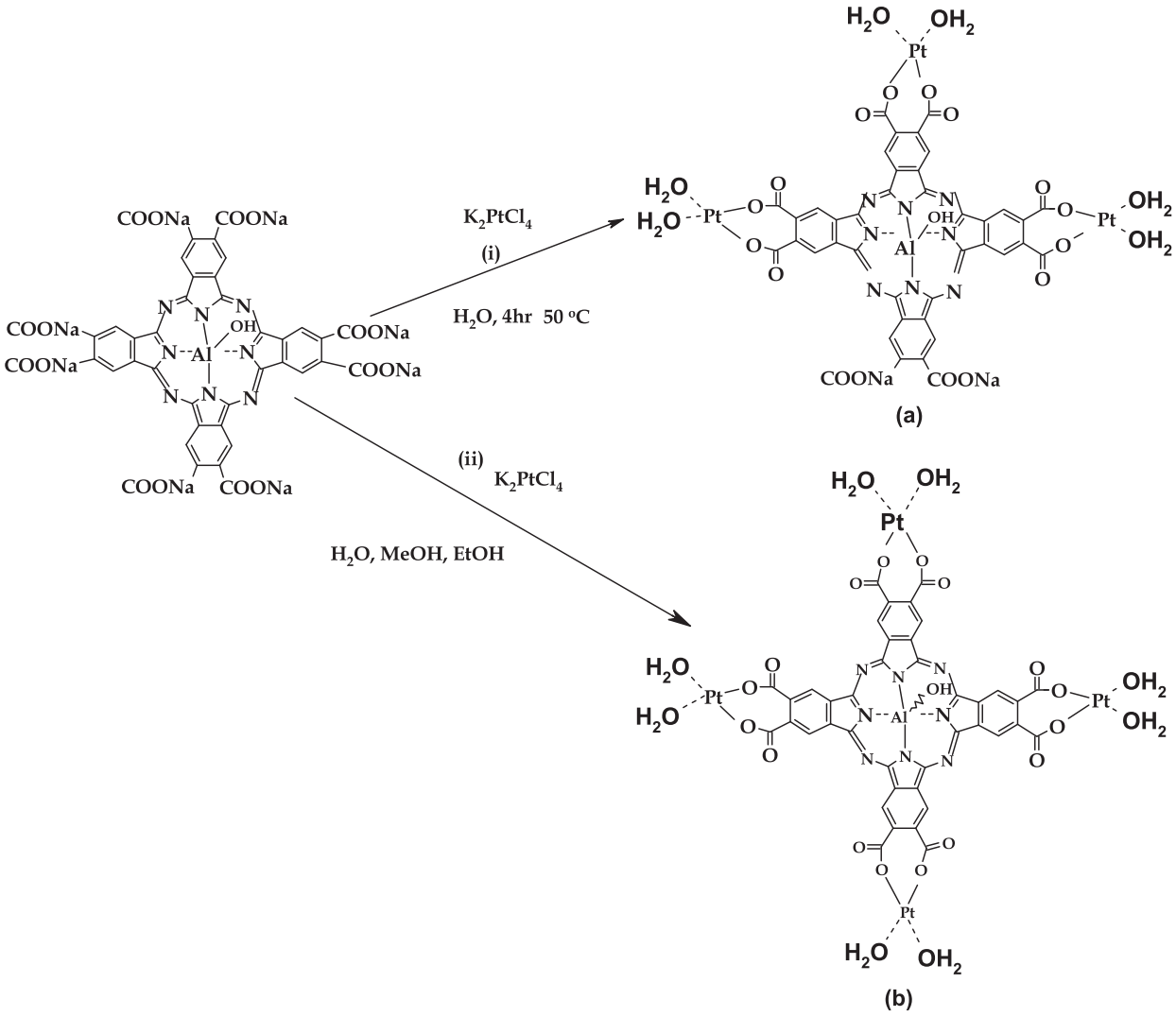

Scheme 1. Synthesis of hydroxoaluminum trikis(diaquaplatinum) octacarboxyphthalocyanine (OHAlOCPc(Pt)$_3$) (a) and hydroxoaluminum tetrakis(diaquaplatinum) octacarboxyphthalocyanine (OHAlOCPc(Pt)$_4$) (b) Ratio of Pc:Pt (i) (1:1.35); (ii) step 1 (1:4.5); step 2 (1:2.8).

solubility of the conjugate in water. The complexes containing four diaquaplatinum groups [2–5] are insoluble in water, water solubility is essential for delivery in PDT.

2. Experimental

2.1. Materials

1,8-Diazobicyclic[5.4.0] undec-7-ene (DBU), oleic acid and platinum acetylacetonoate (Pt(acac)$_2$) were from Fluka. Pyromellic anhydride, diphenyl ether, oleylamine, 1,2- hexadecanediol, 1,3-diphenlyisobenzofuran (DPBF), anthracene-9,10–bis-methylmalonate (ADMA), zinc phthalocyanine (ZnPc) and potassium hexachloroplatinate were from Aldrich. Methanol (MeOH), dimethylsulfoxide (DMSO), aluminium chloride, ethanol (EtOH) and sodium hydroxide were purchased from Saarchem. Hydroxo Al octacarboxy phthalocyanine (OHAlOCPc) and its sodium salt were synthesized according to literature methods [12]. AlPcS$_{Mix}$ (containing a mixture of sulfonated derivatives), used as a standard for the determination of singlet oxygen quantum yields in water, was synthesized according to literature methods [13]. Potassium tetrachloroplatinate was synthesized from potassium hexachloroplatinate according to literature methods [3].

2.2. Equipment

The ultra violet –visible (UV–Vis) spectra were recorded on a Shimadzu UV 2550 UV–Vis/NIR spectrophotometer. IR spectra (KBr pellets) were recorded on a on a Perkin–Elmer Spectrum 100 ATR FT-IR spectrometer. Fluorescence excitation and emission spectra were recorded on a Varian Eclipse spectroflourimeter. Elemental analyses were carried out on a Vario EL III MicroCube CHNS Analyzer. Mass spectral data were collected with a Bruker AutoFLEX III Smartbeam TOF/TOF Mass spectrometer. Transmission electron microscope (TEM) images were recorded using JEOL JEM 1210 at 100 kV accelerating voltage. Energy dispersive spectroscopy (EDS) was done on a INCA PENTA FET coupled to the VAGA TESCAM using 20 kV accelerating voltage.

Fluorescence lifetimes and time resolved spectroscopy (TRES) were measured using a time correlated single photon counting setup (TCSPC) (FluoTime 200, Picoquant GmbH) with a diode laser (LDH-P-670 with PDL 800-B, Picoquant GmbH, 670 nm, 20 MHz repetition rate, 44 ps pulse width). Fluorescence was detected under the magic angle with a peltier cooled photomultiplier tube (PMT) (PMA-C 192-N-M, Picoquant) and integrated electronics (PicoHarp 300E, Picoquant GmbH). A monochromator with a spectral width of about 8 nm was used to select the required emission