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Synthesis and physicochemical behaviour of aluminium *bis* and *tris*(diammine platinum) octacarboxyphthalocyanine

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ABSTRACT

Hydroxy aluminium octacarboxy phthalocyanine (Al(OH)OCPc) was conjugated with a diammine platinum complex to give conjugates containing two or three platinum complexes (represented as: Al(OH)OCPc(Pt)$_2$ and Al(OH)OCPc(Pt)$_3$). It was found that the complexes were soluble in water at a pH > 8.2. Both conjugates were found to have two fluorescence lifetimes. The triplet and singlet oxygen quantum yields increased for the conjugates compared to Al(OH)OCPc alone.

1. Introduction

The covalent conjugates of cytotoxic Pt(II) complexes and phthalocyanines (Pcs) are promising candidates for the development of novel dual action anticancer drugs, which combine photosensitizers (e.g. Pcs) for photodynamic therapy (PDT) and chemotherapeutics (Pt complexes). Since it is has been established that Pcs can selectively accumulate in tumor tissue, covalent conjugates of Pcs and Pt(II) complexes can be used to selectively enrich tumor tissues with cytotoxic Pt(II) complexes. The first examples of Pc–Pt conjugates were reported in 2000 by Kobayashi and co-workers [1] where the syntheses of zinc *tetrakis*(*cis*-[(3-oxypyridyl)-N]amminedichloro platinum(II))Pc and zinc *tetrakis*(*cis*-[(3-oxypyridyl)-N]dichloro[sulfinylbis(methane)-S]platinum(II))Pc were described. Since then other covalent conjugates of phthalocyanines with platinum complexes have been reported [2–5]. However, the reported phthalocyanine complexes within the conjugates contained electroactive central metals such as Ru, Co and Fe which are not appropriate for PDT with the exception of the recent AlPc and ZnPc conjugates [6–8]. These conjugates contained platinum coordinated to water molecules. The most used platinum complex for chemotherapeutics is *cis*-diammine-dichloro platinum (cisplatin) [9], hence it is important to study conjugates of Pcs with this diammine Pt complex. This work reports on the conjugation of aluminium octacarboxy phthalocyanine to the diammine platinum complex. The complexes are hydroxoaluminum *tris*(diammine platinum) octacarboxyphthalocyanine (abbreviated as Al(OH)OCPc(Pt)$_3$, Scheme 1) and hydroxoaluminum *bis*(diammine platinum) octacarboxyphthalocyanine (abbreviated as Al(OH)OCPc(Pt)$_2$, Scheme 1). Both Al(OH)OCPc(Pt)$_3$ and Al(OH)OCPc(Pt)$_2$ contain COONa groups which impart limited solubility of the conjugate in water (basic media). The complexes containing four diaquaplatinum groups [2–5] are insoluble in water. Water solubility is essential for delivery in PDT. The choice of Al as a central metal is due to the use of AlPc derivatives in clinical trials in PDT [10]. It is also important to note that porphyrin–platinum complexes bearing diammine substituents were found to be active against cancer cells [11].

2. Experimental

2.1. Materials

cis-Diamminedichloro platinum, anthracene-9,10-*bis*-methylmalonate (ADMA), and silver nitrate were from Aldrich. Methanol (MeOH), dimethylsulfoxide (DMSO), aluminium chloride, ethanol (EtOH) and sodium hydroxide were purchased from Saarchem. Phosphate buffer saline (PBS) was employed for aqueous solutions. Hydroxo Al octacarboxy phthalocyanine ((OH)AlOCPc) and its sodium salt were synthesized according to literature methods [12,13]. AlPcS$_{Mix}$ (containing a mixture of sulfonated derivatives) was synthesized according to literature methods [14].

2.2. Equipment

The ultraviolet–visible (UV–Vis) spectra were recorded on a Shimadzu UV 2550 UV–Vis/NIR spectrophotometer. IR spectra were recorded on a Perkin–Elmer Spectrum 100 ATR FT-IR spectrometer.

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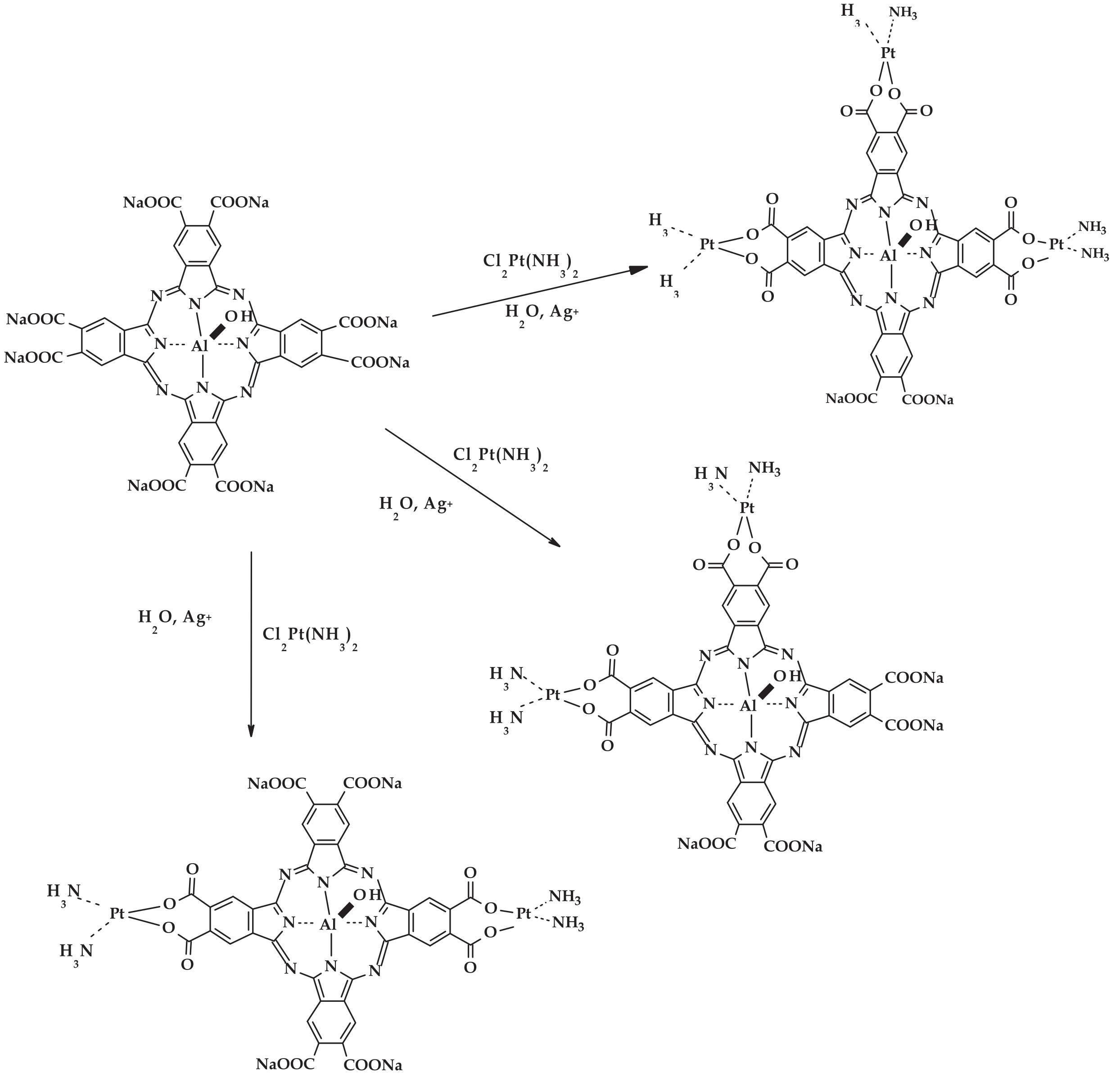

Scheme 1. Synthesis of hydroxoaluminum *tris*(diammine platinum) octacarboxyphthalocyanine (Al(OH)OCPc(Pt)$_3$) and hydroxoaluminum *bis*(diammine platinum) octacarboxyphthalocyanine (Al(OH)OCPc(Pt)$_2$).

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.

Scanning electron microscope/energy dispersive spectroscopy (SEM/EDS) was done on a INCA PENTA FET coupled to the VAGA TESCAM using 20 kV accelerating voltage. In EDS, the relative intensity of an X-ray signal is approximately proportional to the mass concentration of the element concerned. Hence determination of the concentrations of the elements present was done by measuring line intensities for each element in the sample and for the same elements in calibration standards of known composition.

Fluorescence lifetimes 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 wavelength band. The response function of the system, which was measured with a scattering Ludox solution (DuPont), had a full width at half-maximum (FWHM) of 300 ps. All luminescence decay curves were measured at the maximum of the emission peak and lifetimes were obtained by deconvolution of the decay curves using the FluoFit Software program (PicoQuant GmbH, Germany). The support plane approach was used to estimate the errors of the decay times.

A laser flash photolysis system was used to determine the triplet quantum yields and lifetimes. The excitation pulses were produced by a tunable laser system consisting of an Nd:YAG laser (355 nm, 135 mJ/4–6 ns) pumping an optical parametric oscillator (OPO, 30 mJ/3–5 ns) with a wavelength range of 420–2300 nm (NT-342B, Ekspla). The analysing beam source was from a Thermo Oriel xenon arc lamp and a photomultiplier tube was used used as a detector. The signals were recorded with a two channel 300 MHz digital oscilloscope (Tektronix TDS 3032C).