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Molecular interaction studies of some Co(III)-surfactants with the transport protein

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ABSTRACT

The present work describes the synthesis and the molecular interaction of two single-chain Co(III)-coordinated surfactant complexes with a plasma protein, human serum albumin by using various biophysical and *in silico* techniques. The experimental data reveals that like ordinary classical surfactants, our metallosurfactants also have the tendency to associate themselves and form micelles at critical micelle concentration. The thermodynamic parameters (ΔH°, ΔS°, and ΔG°) derived from the experiment demonstrates that the alkyl chain length and the head group of the Co(III)-surfactant complexes played a vital role in the binding process. Both the physico-chemical and computational docking results indicated that the Co(III)-surfactant complexes are stabilized by hydrogen bonding, hydrophobic and/or van der Waals forces. Thus, the data acquired herein for the interesting class of surfactant complexes will be of significance in metal-based drug discovery and developmental research.

1. Introduction

Classical surfactants are amphiphilic molecules composed of a polar head group and a long hydrophobic tail part which is usually a hydrocarbon residue [1]. Metallomicelles or metallosurfactants are an emerging class of metal-coordinate surfactants in which polar head group of the surfactant molecule contains a metal ion[2]. Like other known conventional surfactants, such as sodium dodecyl sulfate (SDS), dodecyl trimethylammonium bromide (DTAB), the metallosurfactants also have capable of forming micelles at a critical micelle concentration (CMC) [2,3]. Compared to conventional surfactants, most of the metallosurfactants have displayed high impact in pharmaceutical research because of their ability to exhibit the biophysico-chemical characteristics of both a metal ion and surfactant in a single complex system [4,5]. Besides, the transition metal complex containing bipyridine and/or phenanthroline chelators has also attracted interest in the area of biological sciences due to their unique potential anticancer properties [6,7]. At the same time, a number of metal ions, especially, cobalt plays an enormously substantial role in many living organisms [8,9]. Various biologically relevant studies on cobalt coordinated complexes have also been of significance in metallopharmaceutical researches [9–11].

Human serum albumin (HSA) is one of the most abundant globular proteins. Because of its biological importance as a carrier protein and strong biophysical assets, HSA is still an attractive protein target for basic and advanced biomedical research studies till date [12]. It is widely accepted that extensive knowledge of the drug's binding ability to a plasma protein is necessary as it strongly influences the drug pharmacokinetics (i.e. adsorption, metabolism, distribution and elimination). HSA is a multi-domain molecule which provides an excellent ligand binding capacity for several endo- and exogenous compounds. In particular, site I and II are the key regions of drug binding sites located in the hydrophobic cavities in subdomains IIA and IIIA. Also, these sites consist of tyrosine and tryptophan residues which offers an advantage to examine the drug-protein interaction study by intrinsic fluorescence [12]. Thus, the molecular binding studies of organic and/or inorganic metal complexes with HSA have gained substantial interests in pharmacotherapeutic research [13–15]. Recently, many studies have been reported on the interaction of surfactants with protein and the results show that the alkyl chain plays an essential role in the cellular uptake due to its non-covalent interactions with the

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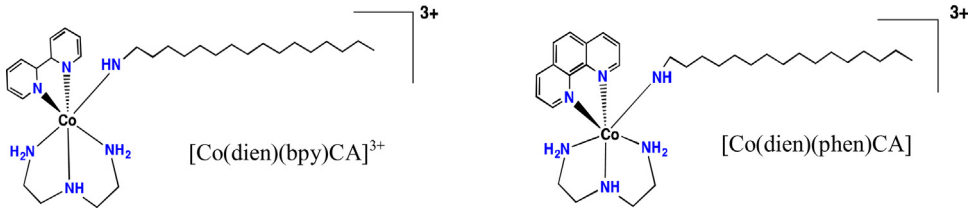

Fig. 1. Structure of Co(III)-surfactants, $[Co(dien)(bpy)CA]^{3+}$ and $[Co(dien)(phen)CA]^{3+}$.

protein [16–20]. Therefore, studies on the interaction of the surfactants containing long alkyl chain are of paramount attention, which prompted us to choose the metal-coordinated surfactant as one of the ligands for our studies.

In recent years, we have been working on the molecular binding studies of several metal-coordinated surfactant complexes with DNA and their anticancer activities in several cancer cell lines [21–23]. The results obtained from these studies revealed that the metallosurfactants exhibited strong binding to DNA than the ordinary metal complexes. Furthermore, this kind of metal-based surfactants showed good antimicrobial activity and induce apoptosis in various cancer cell lines. Thus, continuing our interest on the metallosurfactant, the present work is focussed on understanding the molecular interaction of two newly synthesized single chain cobalt(III)-coordinated surfactant complexes containing 2,2′-bipyridine/1,10-phenanthroline ligands (Fig. 1A) with HSA using various biophysical techniques.

2. Experimental section

2.1. Materials

HSA was purchased from Sigma-Aldrich. Cobalt(II) chloride hexahydrate, 1,10-phenanthroline (phen), 2,2′-bipyridine (bpy), diethylenetriamine (dien) and cetylamine (CA) were obtained from Loba Chem. Stock solutions of HSA and surfactant complexes were prepared in Tris-HCl buffer solution (pH = 7.4) and kept in a refrigerator at 4 °C.

2.2. Preparation of Co(III)-surfactant complexes

The precursor complexes, $[Co(bpy)(dien)Cl]Cl_2{\cdot}4H_2O$ and $[Co(dien)(phen)Br]Br_2{\cdot}2H_2O$ were synthesized as reported previously [24,25].

2.2.1. Preparation of $[Co(dien)(phen)CA](ClO_4)_3{\cdot}3H_2O$

Three grams of $[Co(dien)(phen)Br]Br_2{\cdot}2H_2O$ was dissolved in 20 ml of distilled water, to this solution 3 ml of cetylamine in 5 ml of ethanol was added drop by drop for a period of one hour. During the reaction the reddish solution turned into a dark red with high viscous in nature and the reaction mixture was kept as such at room temperature for 48 h until no observable color change. Thereafter, a saturated solution of sodium perchlorate was added slowly to the dilute perchloric acid. A pasty mass separated out and it was filtered off, washed with a small amount of ethanol followed by acetone. The semisolid thus obtained was then dried over the $CaCl_2$ and stored in a vacuum desiccator. Yield 65%. Anal Calcd: Co, 6.42; C, 41.86; H, 6.59; N, 9.15%. Found: Co, 6.23; C, 40.94; H, 6.12; N, 8.47%. IR(KBr, cm^{-1}): 3462, 2918, 2850,1633,1548, 1434,1116, 857, 716, 636. ^{1}H NMR (DMSO, δ ppm): 0.79-1.50 (Alkyl chain proton), 2.72–2.76 (-CH_2, dien), 5.36, 5.58 (-NH_2, dien), 7.56–9.80 (Ar-H, -NH). ^{13}C NMR (DMSO, δ ppm): 13.88, 22.01, 25.82, 26.88, 28.72, 28.86, 28.93, 31.21, 38.73, 39.97, 40.18, 40.38, 126.94, 127.91, 128.10, 13.90, 140.64, 141.03, 147.02, 151.621, 154.16. λ_{max}, nm (ε, mol^{-1} dm^3 cm^{-1}): 223 (9726), 270(5100), 497(98)

2.2.2. Preparation of $[Co(dien)(bpy)CA](ClO_4)_3{\cdot}3H_2O$

The above experimental procedure was followed for the synthesis of $[Co(bpy)(dien)CA](ClO_4)_3{\cdot}3H_2O$ complex. Yield 60%. Anal Calcd: Co, 6.46; C, 39.34; H, 6.46; N, 9.18%. Found: Co, 6.28; C, 38.98; H, 6.36; N, 9.14%. IR(KBr, cm^{-1}): 3440, 2918, 2850, 1631, 1506, 1469, 1090,776, 720, 639. ^{1}H NMR (DMSO, δ ppm): 0.81–1.33(Alkyl chain proton), 2.71–2.75 (-CH_2, dien), 5.32, 5.52 (-NH_2, dien),7.42-8.69 (Ar-H, −NH). ^{13}C NMR (DMSO, δ ppm): 13.90, 22.05, 25.72, 26.72, 26.92, 28.46, 28.96, 31.24, 38.81, 39.48, 39.69,40.11,120.38, 124.15, 137.26,149.22,155.17. λ_{max}, nm (ε, mol^{-1} dm^3 cm^{-1}): 220(9400), 302(4653), 491(85).

2.3. Instrumentation

Infrared spectra were recorded in the solid state (KBr pellets) on an FTIR spectrophotometer (Perkin Elmer). ^{1}H and ^{13}C NMR spectra of the Co(III)-surfactant complexes were recorded on BURKER 400 MHz NMR spectrometer using DMSO-d_6 solvent. The elemental analysis of samples was determined at Sophisticated Analytical Instruments Facility, IIT Madras, Chennai. Conductivity studies were carried out on aqueous solutions of the Co(III)-surfactants with an Elico conductivity bridge type CM 82 and a dip-type cell with a cell constant of 1.0.

2.4. Critical micelle concentration (CMC)

The CMC values of both the Co(III)-surfactants were measured by conductometry. The conductivity cell was standardized with KCl solution in the suitable concentration range. The cell constant was determined by molar conductivity. Different concentrations of Co(III)-surfactant complexes (10^{-5}–10^{-2} mol L^{-1}) were prepared in the aqueous solution. The molar conductivities of these solutions were measured at three different temperatures 291, 296 and 301 K and the experiments were repeated three times.

2.5. Spectroscopic measurement

The fluorescence spectra were performed on a JASCO PF-6500 spectrofluorimeter with 1 cm quartz cuvette. The emission spectra were recorded in the wavelength range of 290–450 nm by exciting protein at 280 nm using excitation and emission slit width of 3 nm and 5 nm respectively. The synchronous fluorescence spectra were recorded with Δλ = 15 nm as well as Δλ = 60 nm between excitation and emission wavelengths. The required temperature was maintained by a circulating water bath. To eliminate the inner filter, the fluorescence intensity was corrected using the following equation [26],

$$F_{cor} = F_{obs} \times e^{((A_{ex}+A_{em})/2)} \quad (1)$$

where F_{cor} and F_{obs} are the fluorescence intensities corrected and observed, respectively, and A_{ex} and A_{em} are the sum of the absorbance of albumin and Co(III)-surfactants at the excitation and emission wavelengths, respectively.

Absorption spectra were recorded on a UV-1800 Shimazu UV spectrophotometer using cuvette with a 1 cm path length. The