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Monomerization and photodynamic activity of Zn(II) tetraalkyltetrapyridinoporphyrazinium derivatives in AOT reverse micelles

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Abstract

Monomerization and photodynamic activity of cationic Zn(II) tetraalkyltetrapyridinoporphyrazinium derivatives bearing *N*-alkyl chains of different length (ZnPc **1** R: $-CH_3$, ZnPc **2** R: $-(CH_2)_{11}CH_3$, ZnPc **3**, R: $-(CH_2)_{15}CH_3$) were evaluated in *n*-heptane/sodium bis(2-ethylhexyl)-sulfosuccinate (AOT)/water micellar system. Absorption and fluorescence spectroscopic studies of these sensitizers were analyzed in *n*-heptane/AOT (0.1 M)/water system by varying the amount of water dispersed in the reverse micelles ($W_0 = [H_2O]/[AOT]$). Under these conditions, the absorbance of the monomeric Q-band (~686 nm) of ZnPcs **1**–**3** increases rapidly until $W_0 \sim 30$ and then the increase becomes steady. These results were also confirmed by fluorescence studies. Analysis of the Q-band at different AOT concentrations, keeping $W_0 = 30$ as constant, was carried out to determine the binding constant (K_b) between these sensitizers and AOT reverse micelles. The values of K of 210, 150 and 34 were found for ZnPcs **1**, **2** and **3**, respectively. Photodynamic activity of these sensitizers was evaluated in AOT system using 9,10-dimethylanthracene (DMA). The photooxidation rate of DMA sensitized by these phthalocyanines follow the order: ZnPc **1** > ZnPc **2** ~ ZnPc **3**. As shown by spectroscopic and photodynamic studies, the AOT reverse micellar system very effectively inhibits the aggregation of phthalocyanines, promoting the formation of photoactive monomeric species.

Keywords: Phthalocyanine; Micelles; AOT; Photodynamic effect; Photosensitizer

1. Introduction

Solubilization of substrates in micellar aggregates plays an important role in biological and industrial processes [1]. In microheterogeneous systems, a solute can be located in a variety of microenvironments namely the organic surrounded solvent, the water pool or at the micellar interface. Among the surfactants capable of forming these aggregates, sodium bis(2-ethylhexyl)sulfosuccinate (AOT) is the one mostly used since solutions of AOT in nonpolar solvents have the remarkable ability to solubilize a large amount of water [1]. Microheterogeneous systems such as reverse micelles are frequently used as an interesting model to mimic the water pockets that are often found in various bioaggregates such as proteins, enzymes and membranes [2,3]. Also, AOT reverse micelles form suitable and variable reaction media depending on water-to-surfactant ratio for the study of different types of organic and enzymatic reactions. Thus, water-soluble and water-insoluble compounds can be dissolved simultaneously in reverse micelles, which simulate a biomimetic microenvironment [4].

Phthalocyanine derivatives exhibit a high absorption coefficient ($\varepsilon > 10^5\ M^{-1}\ cm^{-1}$) in the visible region of the spectrum, mainly in the phototherapeutic window (600–800 nm) and a long lifetime of triplet excited state to produce efficiently $O_2(^1\Delta_g)$ [5]. Based on these properties, one of the most recent and promising applications of phthalocyanine in medicine is in the detection and cure of tumors. Photodynamic therapy (PDT) is an innovative treatment for several types of cancer

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[6,7]. This therapy is based on the administration of a photosensitizer, which is selectively incorporated into tumor cells. The subsequent exposure to visible light in the presence of oxygen specifically inactivates neoplastic cells. The photobiological properties of various phthalocyanine derivatives indicate that they can be very promising photosensitizers for clinical application of PDT [5,8]. In particular, cationic sensitizers have several interesting features, which make these compounds attractive photosensitizers for a variety of biological systems. The combination of hydrophobic and hydrophilic substituents in the sensitizer structure can facilitate membrane penetration and produce a better accumulation in subcellular compartments, enhancing the effective photosensitization [9]. Recently cationic phthalocyanines were also proposed for photodynamic inactivation (PDI) of bacteria in an attempt to overcome the problem of bacterial strains resistant to current antibiotics [10–14].

In previous studies, we have investigated the photodynamic activity of phthalocyanine derivatives in different biomimetic media and in vitro on human carcinoma cells and microorganisms [15–17]. In particular, the photoinactivation capacity of a cationic Zn(II) tetramethyltetrapyridinoporphyrazinium salt was compared with that of a non-charged Zn(II) tetrapyridinoporphyrazine, both in vitro using human red blood (HRB) cells and a typical Gram-negative bacterium, *Escherichia coli*. Both phthalocyanines produce similar photohemolysis of HRB cells, however, only the cationic phthalocyanine produces a high photoinactivation of Gram-negative bacteria [16].

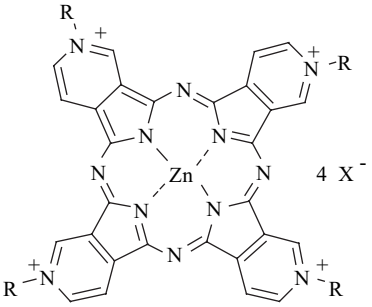
One of the problems that affects the sensitizing ability of the phthalocyanines is its aggregation tendency due to the large π conjugate systems [5]. The aggregates present an efficient nonradiative energy relaxation pathway, diminishing the triplet-state population and the $O_2(^1\Delta_g)$ quantum yield. Therefore, the formation of aggregation precludes the photodynamic activity.

In this paper, the monomerization of cationic Zn(II) tetraalkyltetrapyridinoporphyrazinium derivatives bearing *N*-alkyl chains of different length (ZnPc **1** R: $-CH_3$, ZnPc **2** R: $-(CH_2)_{11}CH_3$, ZnPc **3**, R: $-(CH_2)_{15}CH_3$, Scheme 1) was studied in *n*-heptane/sodium bis(2-ethylhexyl)sulfosuccinate (AOT)/water reverse micelles. Absorption and fluorescence spectroscopic studies of these sensitizers were analyzed in the micellar system by varying the amount of water dispersed in the reverse micelles. The spectra were also studied at different AOT concentrations keeping the amount of water constant. These results were used to determine the binding constant (K_b) between these sensitizers and AOT reverse micelles. The photodynamic activity was evaluated in AOT system using 9,10-dimethylanthracene (DMA). The studies show that AOT reverse micelles can efficiently avoid aggregation of cationic phthalocyanines with potential applications in photodynamic therapy.

2. Materials and methods

2.1. General

UV–vis and fluorescence spectra were recorded on a Shimadzu UV-2401PC spectrometer and on a Spex FluoroMax



ZnPc **1** R: — CH_3 X: I

ZnPc **2** R: — $(CH_2)_{11}CH_3$ X: Br

ZnPc **3** R: — $(CH_2)_{15}CH_3$ X: Br

Scheme 1. Molecular structures of ZnPcs **1**–**3**.

fluorometer, respectively. Mass spectra were recorded with a ZAB-SEQ Micromass equipment. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on an FT-NMR Bruker Avance DPX400 multinuclear spectrometer at 400 MHz. All the chemicals from Aldrich (Milwaukee, WI, USA) were used without further purification. Sodium bis(2-ethylhexyl)sulfosuccinate (AOT) from Sigma (St. Louis, MO, USA) and 5,10,15,20-tetrakis(4-*N*,*N*,*N*-trimethylammoniumphenyl)porphyrin *p*-tosylate (TTAP) from Aldrich were used as received. Solvents (GR grade) from Merck were distilled. Ultrapure water was obtained from Labconco equipment model 90901-01.

2.2. Photosensitizers

According to the synthetic procedure, phthalocyanine macrocycle is obtained as a mixture of the corresponding regioisomers, in which only one is named below. Zinc(II) tetrapyridino[3,4-*b*: 3′,4′-*g*: 3″,4″-*l*: 3‴,4‴-*q*]porphyrazine and zinc(II) tetramethyltetrapyridino[3,4-*b*: 3′,4′-*g*: 3″,4″-*l*: 3‴,4‴-*q*]porphyrazinium tetraiodide (ZnPc **1**) were synthesized as previously described [16]. Zinc(II) tetrapyridino [3,4-*b*: 3′,4′-*g*: 3″,4″-*l*: 3‴,4‴-*q*]porphyrazine was quaternized according to the literature procedure [18]. Zinc(II) tetradodecyltetrapyridino[3,4-*b*: 3′,4′-*g*: 3″,4″-*l*: 3‴,4‴-*q*]porphyrazinium tetraiodide (ZnPc **2**) was obtained by refluxing a mixture of zinc(II) tetrapyridino[3,4-*b*: 3′,4′-*g*: 3″,4″-*l*: 3‴,4‴-*q*]porphyrazine (100 mg, 0.17 mmol) and 10 mL of 1-bromododecane in 10 mL of *N*,*N*-dimethylformamide for 48 h. The solvents were removed under vacuum. The solid was re-suspended in cyclohexane and filtered. It was re-precipitated from methanol/water and the solid washed with hexanes and dichloromethane, to yield 155 mg (58%) of ZnPc **2**. ^{1}H NMR (DMSO-d_6, TMS): δ [ppm] 0.8–0.9 (m, 12H,), 1.1–1.4 (m, 72H), 1.6–1.9 (m, 8H), 3.4–3.6 (m, 8H), 8.0–9.5 (m, 12H). FAB-MS [*m*/*z*] 1257 $(M)^+$ (1256.8424 calculated for $C_{76}H_{112}N_{12}Zn$). Zinc(II) tetrahexadecyltetrapyridino[3,4-*b*: 3′,4′-*g*: 3″,4″-*l*: 3‴,4‴-*q*] porphyrazinium tetraiodide (ZnPc **3**) was synthesized as described above for ZnPc **2** from a mixture of zinc(II) tetrapyridino[3,4-*b*: 3′,4′-*g*: 3″,4″-*l*: 3‴,4‴-*q*]porphyrazine (100 mg,

0.17 mmol) and 10 mL of 1-bromohexadecane in 10 mL of *N*,*N*-dimethylformamide, obtaining 165 mg (54%) of ZnPc **3**. ^{1}H NMR (DMSO-d_6, TMS): δ [ppm] 0.8–0.9 (m, 12H), 1.2–1.4 (m, 104H), 1.6–1.8 (m, 8H), 3.4–3.6 (m, 8H), 8.0–9.5 (m, 12H). FAB-MS [*m*/*z*] 1481 $(M)^+$ (1481.0928 calculated for $C_{92}H_{144}N_{12}Zn$).

2.3. Studies on AOT reverse micelles

A stock solution of AOT (0.1 M) was prepared by weighing and diluting in *n*-heptane [19,20]. The addition of water to obtain the corresponding W_0 was performed using a calibrated microsyringe. The amount of water present in the system was expressed as the molar ratio between water and the AOT present in the reverse micelle ($W_0 = [H_2O]/[AOT]$). To determine the value of K_b, all experimental points were measured three times with different prepared samples. In all the cases, the temperature was kept at 25.0 ± 0.5 °C.

2.4. Steady-state photolysis

Solutions of 9,10-dimethylanthracene (DMA, 35 μM) in 2 mL of *n*-heptane/AOT/water ($W_0 = 30$) and photosensitizer ($\lambda = 670$ nm, absorbance 0.1) were irradiated in quartz cuvettes (1 cm path length cells) with monochromatic light at $\lambda = 670$ nm from a 75 W high-pressure Xe lamp through a high-intensity grating monochromator, Photon Technology Instrument [2]. The light intensity was determined as 1.5 mW/cm^2 (Radiometer Laser Mate-Q, Coherent). The kinetics of DMA photooxidation were studied by following the decrease of the absorbance (A) at $\lambda_{max} = 378$ nm. The observed rate constants (k_{obs}) were obtained by a linear least-squares fit of the semilogarithmic plot of Ln A_0/A vs. time. Photooxidation of DMA was used to determine singlet molecular oxygen, $O_2(^1\Delta_g)$, production by the photosensitizers [2,21]. TTAP was used as the standard ($\Phi_\Delta = 0.73$) [22]. Measurements of the sample and reference under the same conditions afforded Φ_Δ for ZnPcs **1**–**3** by direct comparison of the slopes in the linear region of the plots. All the experiments were performed at 25.0 ± 0.5 °C. The pooled standard deviation of the kinetic data, using different prepared samples, was less than 5%.

3. Results and discussion

3.1. Monomerization in AOT reverse micelles

The absorption spectra of ZnPcs **1**–**3** were analyzed in *n*-heptane/AOT (0.1 M) by varying the amount of water dispersed in the reverse micelles ($W_0 = [H_2O]/[AOT]$). The effect of changing W_0 keeping AOT concentration constant for ZnPc **1** is shown in Fig. 1A. The band at ~686 nm, which can be attributed to the Q-band of the monomeric species, becomes more intense when the W_0 value increases. Similar behavior was found for ZnPcs **2** and **3**. As can be observed, ZnPc **1** is not soluble in AOT system at low W_0. On the other hand, these sensitizers are also extensively aggregated in pure water

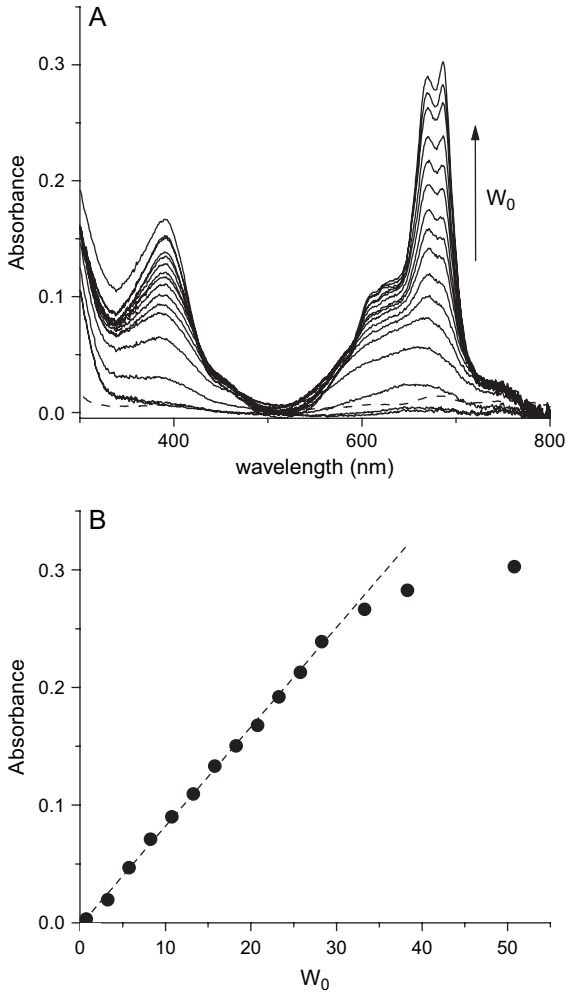


Fig. 1. (A) Absorption spectra of ZnPc **1** in *n*-heptane/AOT (0.1 M) at different W_0 (solid line 0, 0.7, 3.3, 5.7, 8.3, 10.8, 13.3, 15.8, 18.3, 20.8, 23.3, 25.8, 28.3, 33.3, 38.3, and 50.8) and in water (dashed line); (B) variation of absorbance at 686 nm with W_0, [ZnPc **1**] = 2.7 μM.

as shown by the broadening of the bands at 400 and 680 nm, and they are not soluble in *n*-heptane (Fig. 1A). However, deaggregation of phthalocyanine takes place when the amount of dispersed water increases in the micelles. The spectra at high W_0 (>30) show the typical *Soret* (~390 nm) and Q-bands (~686 nm), characteristic of zinc phthalocyanines [16,23]. The two close maxima in the Q-band region reflect that these compounds are a statistical mixture of regioisomers produced by the synthetic method [23,24].

The effect of W_0 upon ZnPc **1** solubility in AOT micelles is illustrated in Fig. 1B. As it can be seen, the absorbance of the monomeric Q-band at 686 nm increases rapidly until $W_0 \sim 30$ and then only small spectroscopic changes are obtained upon $W_0 > 30$. This indicates that the sensitizers are mainly solubilized as monomers in AOT system containing large amount of water.

The steady-state fluorescence emission spectra of ZnPcs **1**–**3** were studied in *n*-heptane/AOT (0.1 M) by varying W_0. As shown above for absorption spectroscopy, the fluorescence intensity increases with the amount of water dispersed in the

reverse micelles. Representative results are observed in Fig. 2A for ZnPc **1**. Aggregated phthalocyanines are nonemissive, [5] therefore, the emission observed upon excitation at 615 nm occurs from the monomeric species. The emission spectra show a typical shape for phthalocyanines with a peak at ~692 nm [16,23]. As can be observed in Fig. 2B, only small changes in the intensity are found upon $W_0 > 30$.

Taking into account the energy of the 0–0 electronic transitions, the energy levels of the singlet excited stated (E_s) were calculated giving values of 1.80, 1.81 and 1.81 eV for ZnPc **1**, **2** and **3**, respectively. These results are in agreement with those previously reported for similar phthalocyanines in different media [23].

The fluorescence excitation spectra of the porphyrins were measured in AOT micelles (Fig. 3A), monitoring the emission at 720 nm. In all cases, the spectra resemble the absorption spectra (Fig. 1A). The trend observed at different W_0 (Fig. 3B) is similar to that observed for the monomeric Q-band absorption (Fig. 1B). These results confirm that the AOT reverse micelles promote demonomerization of the cationic ZnPcs **1**–**3**.

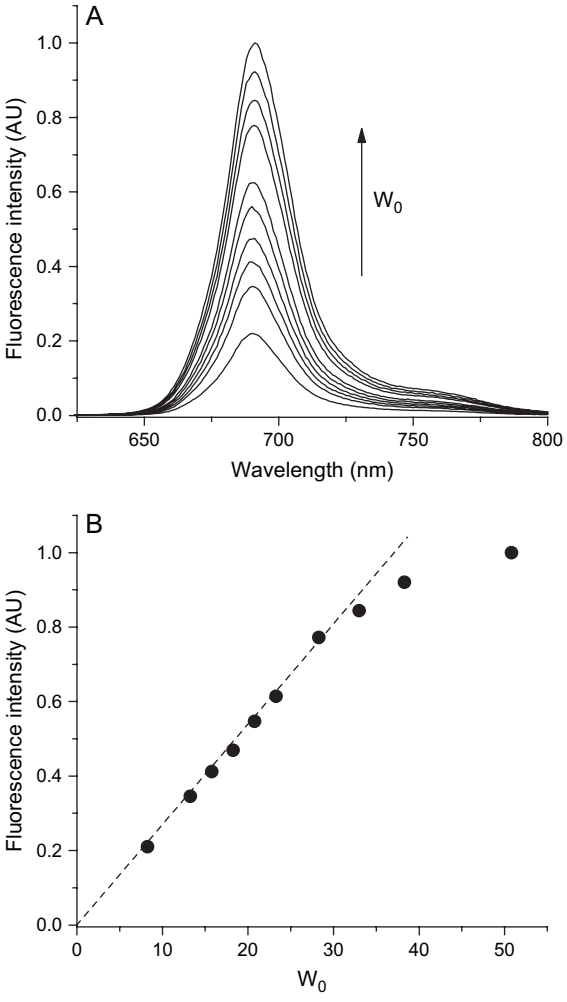


Fig. 2. (A) Fluorescence emission spectra of ZnPc **1** in *n*-heptane/AOT (0.1 M) at different W_0 (8.3, 13.3, 15.8, 18.3, 20.8, 23.3, 28.3, 33.3, 38.3, and 50.8), $\lambda_{exc} = 615$ nm; (B) variation of fluorescence intensity at 692 nm with W_0, [ZnPc **1**] = 2.7 μM.

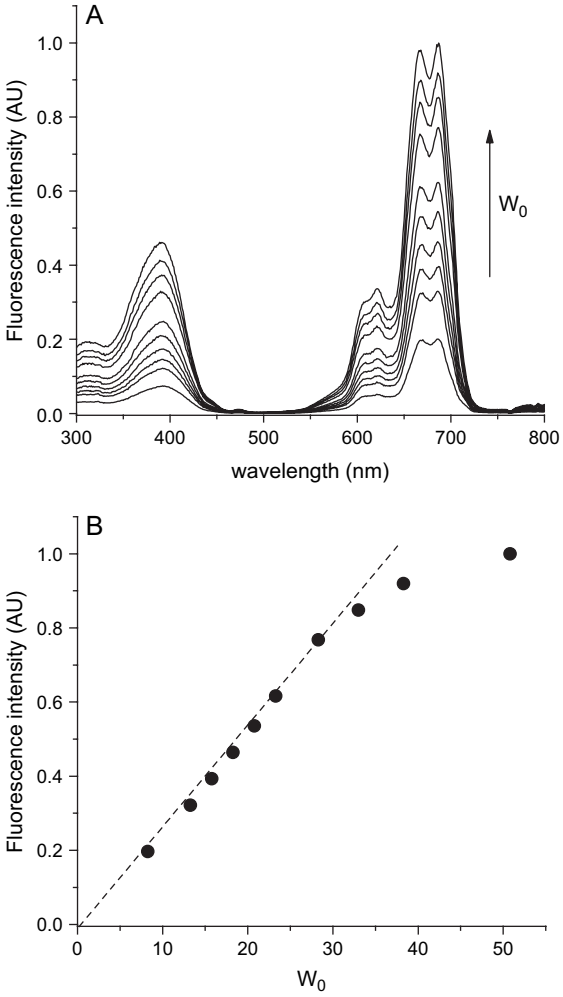


Fig. 3. (A) Fluorescence excitation spectra of ZnPc **1** in *n*-heptane/AOT (0.1 M) at different W_0 (8.3, 13.3, 15.8, 18.3, 20.8, 23.3, 28.3, 33.3, 38.3, and 50.8), $\lambda_{em} = 720$ nm; (B) variation of fluorescence intensity at 686 nm with W_0, [ZnPc **1**] = 2.7 μM.

The deaggregation of cationic phthalocyanines was also analyzed at different AOT concentrations. Thus, when the absorption spectra of ZnPcs **1**–**3** were studied varying AOT concentration at $W_0 = 30$, an increase in the intensity of the *Soret* and Q-bands was observed as the [AOT] increases. Typical results are shown in Fig. 4A for ZnPc **2**. This effect can be attributed to the interaction between the phthalocyanine and the micelle [3,19,20]. The strength of the association between phthalocyanine and AOT was determined through the binding constant, $K_b = [ZnPc_b]/[ZnPc_f][AOT]$ (where the terms $[ZnPc_b]$ and $[ZnPc_f]$ refer to the concentration of bound and free phthalocyanine, respectively, and [AOT] is the total surfactant concentration). Thus, the spectral changes were analyzed using the Ketelaar's Eq. (1) [19]:

$$\frac{1}{A - A_{Hp}} = \frac{1}{(\varepsilon_b - \varepsilon_{Hp})[ZnPc]_0} + \frac{1}{(\varepsilon_b - \varepsilon_{Hp})[ZnPc]_0 K_b [AOT]} \quad (1)$$

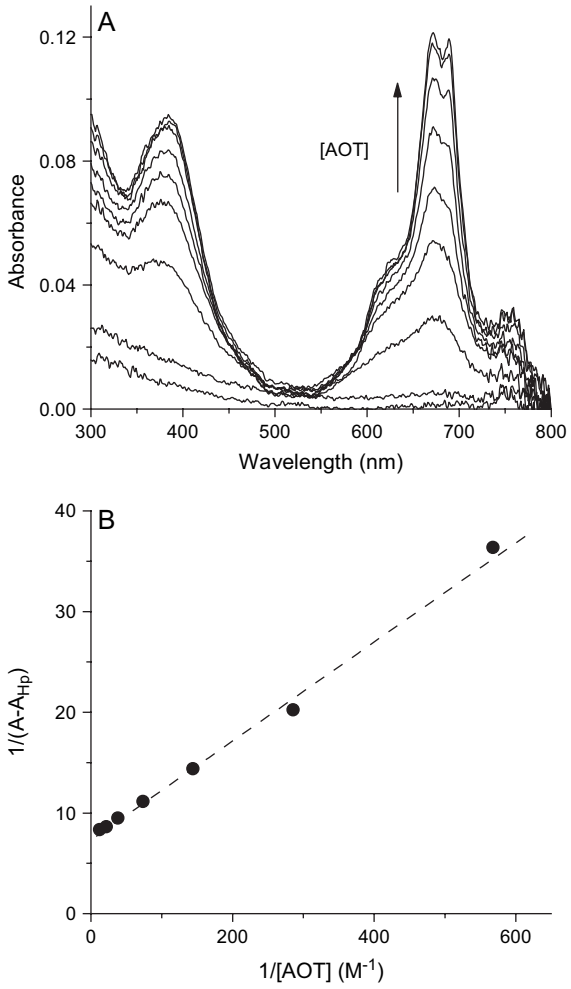


Fig. 4. (A) Absorption spectra of ZnPc **2** in *n*-heptane/AOT/$W_0 = 30$ at different AOT concentrations; (B) variation of $1/(A - A_{Hp})$ vs. AOT concentration for ZnPc **2**. Dotted line: linear regression fit by Eq. (1), $\lambda_{max} = 674$ nm.

where $[ZnPc]_0$ is the total concentration of the phthalocyanine, A is the absorbance at different [AOT], A_{Hp} is the absorbance in *n*-heptane, ε_b and ε_{Hp} are the molar absorptivities for the phthalocyanine bound to the interface and in the organic medium, respectively. Plotting the left-hand side term of Eq. (1) vs. 1/[AOT], the value of K_b can be calculated from the slope and the intercept as it is shown in Fig. 4B for ZnPc **2**. The values of K_b are shown in Table 1. Similar behavior was also obtained from fluorescence emission studies. As can be observed from Table 1, the values of K_b follow the tendency: ZnPc **1** > ZnPc **2** > ZnPc **3**. An increase in the length of *N*-alkyl chains of the sensitizer is accompanied by a decrease in the binding constant of the phthalocyanine with the AOT pseudophase. It can be seen that a higher concentration of AOT also promotes the formation of monomeric phthalocyanines, giving a more intense Q-band absorption and fluorescence emission.

Table 1
Binding constants (K_b), kinetic parameters (k_{obs}) and quantum yield of $O_2(^1\Delta_g)$ production (Φ_Δ) of phthalocyanines in *n*-heptane/AOT (0.1 M)/water ($W_0 = 30$)

Phthalocyanine	K_b (M^{-1})	k_{obs}^{DMA} (s^{-1})	Φ_Δ [a]
ZnPc **1**	210 ± 10	$(8.3 \pm 0.4) \times 10^{-4}$	0.50 ± 0.04
ZnPc **2**	150 ± 6	$(6.3 \pm 0.4) \times 10^{-4}$	0.41 ± 0.03
ZnPc **3**	34 ± 4	$(6.2 \pm 0.4) \times 10^{-4}$	0.42 ± 0.03

[a] Ref. [22], Φ_Δ (TTAP) = 0.73.

3.2. Photodynamic activity of ZnPcs *1–3*

3.2.1. Photooxidation of 9,10-dimethylanthracene (DMA)

The aerobic irradiations with monochromatic light ($\lambda = 670$ nm) of photosensitizers in *n*-heptane/AOT (0.1 M)/water ($W_0 = 30$) were performed in the presence of 9,10-dimethylanthracene (DMA). This substrate quenches $O_2(^1\Delta_g)$ exclusively by chemical reaction [3]. Therefore, it was used in this work to evaluate the ability of the sensitizers to produce $O_2(^1\Delta_g)$. A time-dependent decrease in the DMA concentration was observed by following a decrease in its absorbance (Fig. 5). From first-order kinetic plots the values of the observed rate constant $\left(k_{obs}^{DMA}\right)$ were calculated for DMA (Table 1). The quantum yield of $O_2(^1\Delta_g)$ production (Φ_Δ) was calculated by direct comparison of the k_{obs}^{DMA} values using TTAP as reference, $k_{obs}^{DMA} = (1.1 \pm 0.1) \times 10^{-3}$ s^{-1}, Φ_Δ (TTAP) = 0.73 [22] (Table 1). Under these conditions, the photodynamic efficiency for these phthalocyanines follow the order: ZnPc **1** > ZnPc **2** ~ ZnPc **3**. Therefore, the monomerization of these sensitizers by the AOT micellar system is evidenced by their appropriate production of $O_2(^1\Delta_g)$. These results show that ZnPcs **1–3** can be used as efficient photosensitizers in an organized microheterogeneous media, which mimic biological membranes.

4. Conclusions

The spectroscopic absorption and fluorescence studies indicate that the monomerization of ZnPcs **1–3** in AOT reverse micelles increases with the amount of water dispersed in the micellar system. At low W_0, these ZnPcs show a broadening

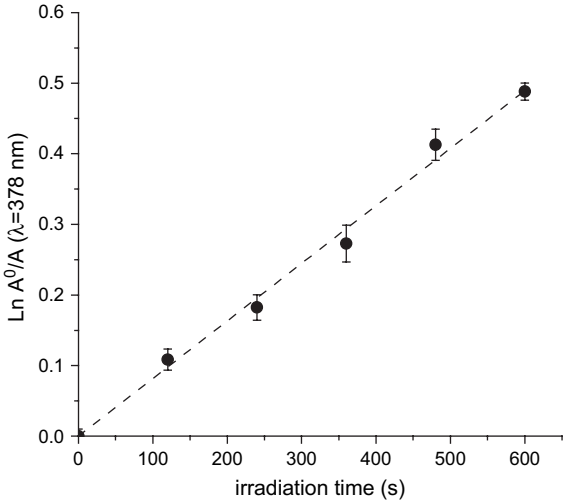


Fig. 5. First-order plots for the photooxidation of DMA (35 μM) photosensitized by ZnPc **1** in *n*-heptane/AOT (0.1 M)/water ($W_0 = 30$); $\lambda_{irr} = 670$ nm. Values represent mean ± standard deviation of three separate experiments.

band at ~650 nm, indicating that they are mainly aggregated, as it is typical for many phthalocyanine derivatives [5,23,25]. However, a sharp absorption band was obtained in AOT micelles at elevated W_0. The interaction between the sensitizers and micellar systems are also evidenced by varying AOT concentration at $W_0 = 30$.

As can be observed in Table 1, a higher efficiency in the $O_2(^1\Delta_g)$ production was found for ZnPc **1** with respect to ZnPcs **2** and **3** in AOT micelles. Similar result was previously found for ZnPc **1** in *N*,*N*-dimethylformamide [16]. These values of $O_2(^1\Delta_g)$ generation are also indicative that AOT micellar media produce monomerization of these cationic phthalocyanines. However, the values of Φ_Δ can significantly change in a different medium, diminishing when the sensitizer is partially aggregated. Also, the biological microenvironment of the sensitizer can induce important modifications in the photophysics of the porphyrin established in solution [26]. In consequence, there are limitations to predict photodynamic efficiencies of sensitizers in biological systems on the basis of photophysical investigations in solution.

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