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SOLUBILIZATION OF HYDROPHOBIC ZINC PHTHALOCYANINE DERIVATIVES-SPECTRAL AND PHOTOPHYSICOCHEMICAL CONSEQUENCES

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ABSTRACT

Methods of solubilizing some hitherto insoluble zinc phthalocyanine derivatives (unsubstituted zinc phtalocyanine, ZnPc, zinc tetra-*t*-butylphenoxyphthalocyanine, ZnTBPc, zinc tetranitophthalocyanine, ZnTNPc and zinc naphthalocyanine, ZnNPc) are presented. The spectral and photophysico-chemical changes accompanying the solubilization are also discussed. The identified methods are (i) ring sulphonation and (ii) cyclodextrin encapsulation. The cyclodextrins employed were hydroxypropyl-γ-cyclodextrin and unsubstituted β-cyclodextrin. The formation of the inclusion complexes was confirmed by proton nuclear magnetic resonance spectroscopy and X-ray powder diffraction patterns. Job's plots were employed to confirm the stoichiometry of the inclusion complexes and showed 2:1 and 4:1 (cyclodextrin:phthalocyanine) inclusion behaviour. Sulphonation of the complexes was attended by spectral red-shifting, while cyclodextrin inclusion brought about no noticeable spectral shifts. The solubilized complexes gave higher singlet oxygen quantum yields than their insoluble counterparts, but are less susceptible to photodegradation as depicted in the former's lower photodegradation quantum yield values. Sulphonation of ZnPc resulted in increase in triplet state and singlet oxygen yields. Fluorescence quantum yield values were hardly affected by cyclodextrin encapsulation, while the sulphonated derivatives are less fluorescent.

Key words: Solubilization, Phthalocyanine, Cyclodextrin, Sulphonation, Fluorescence.

INTRODUCTION

The application of metallophthalocyanines as photosensitizers in the photodynamic therapy (PDT) of cancer is well documented in the literature.[1,2] A PDT agent is usually administered via intravenous injection into the patient's blood stream; and since blood itself is a water based system, it becomes imperative that the photosensitizer be water soluble.

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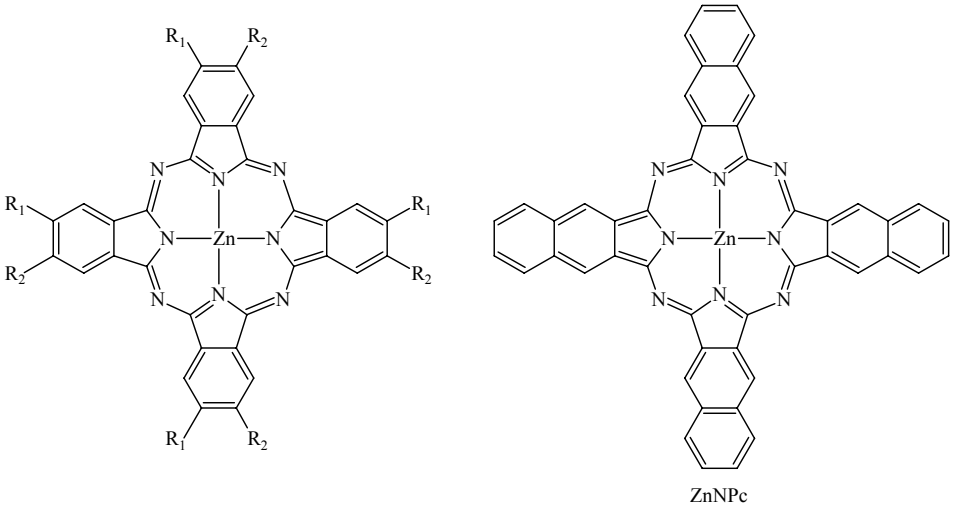
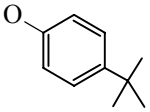
However, most phthalocyanine macrocycles are substantially hydrophobic and hence, the need for their solubilization. Water solubility in metallophthalocyanine derivatives has been achieved via a series of techniques, which include addition of phosphonate and sulphonate ring substituents,[3] ring quaternization,[4] and cyclodextrin encapsulation.[5]

Mixed-sulfonated aluminium phthalocyanine ($AlPcS_{mix}$), commercially known as Photosens®, has been developed as a PDT drug in Russia, and has been used in hospitals with a fair measure of success.[6] There is an aggressive on-going effort to develop other non-transition metal phthalocyanine sulfonates for the same purpose. The study of the photophysical and photochemical behavior of water soluble metallophthalocyanine complexes is of importance for their potential application in PDT.



ZnPc: $R_1 = R_2 = H$

ZnPc $(TBPh)_4$: $R_1 = H$; R_2 =



ZnPc $(SO_3^-)_4$: $R_1 = H$; $R_2 = SO_3^-$

Zn Pc $(NO_2)_4$: $R_1 = H$; $R_2 = NO_2$

Fig. 1: Structures of zinc(II) phthalocyanines derivatives

Cyclodextrins (CDs) are naturally occurring cyclic oligosaccharides composed of six, seven and eight D-glycopyranose residues, called α-CD, β-CD and γ-CD. CDs are soluble to a varying extent in water and have a relatively hydrophobic cavity in the centre. Many different types of organic compounds can be incorporated into the cavities to form inclusion complexes. Inclusion complexes between porphyrin derivatives and CDs have

been reported.[5,7] Due to the large size of the porphyrin molecule, it has been observed that only parts of the molecule are included within the CD cavity. The formation of inclusion complexes of CDs with porphyrins changes the photochemical and photophysical properties of the latter. 1:1 and 2:1 CD : porphyrin inclusion complexes are known.[7,8] This work describes the spectral and photophysicochemical effect that attend the sulphonation and cyclodextrin encapsulation of zinc phthalocyanine derivatives (Fig. 1).

EXPERIMENTAL

Materials

Zinc phthalocyanine (ZnPc) was purchased from Sigma-Aldrich and used as received. Zinc tetranitrophthalocyanine (ZnTNPc),[10,11] zinc tetra-*t*-butylphenoxyphthalocyanine (ZnTBPc),[12] and zinc naphthalocyanine (ZnNPc)[13] were synthesized and characterized in accordance with literature methods. DMSO (SAARCHEM) was dried in alumina before use.

Sulphonation

ZnPc was sulphonated using fuming sulfuric acid (30% SO_3^-) according to reported procedures,[3] to form zinc phthalocyanine sulphonate (ZnPcS)

Cyclodextrin encapsulation

DMSO was employed as solvent for the inclusion process. The inclusion of the complexes into CDs was performed using a 1:6 (MPc:CD) mole ratio. The cyclodextrin was dissolved in DMSO and heated at 80°C for 20 min to afford complete solution. The ZnPc derivative was then added to the CD solution and the reaction mixture heated at 80°C for 24 hrs. The solution was cooled in an ice-bath and kept at 5°C for further 24 hrs. Uncomplexed CD precipitated out during this time and the precipitate was removed by filtration. Ethyl acetate was then added to the solution to precipitate out the inclusion complex, which was then obtained by filtration. β-CD was employed for the inclusion of all complexes except ZnTBPc, which was included in hydroxypropyl-γ-CD due to the larger cavity of this CD, which can accommodate the large tertiary butyl substituents of this compound. The resulting inclusion complexes were used for spectral, photochemical and fluorescence studies. Formation of the complex was confirmed by X-ray powder diffraction and ^{1}H-NMR spectroscopy.

For comparison, ZnPc and ZnNPc were additionally included into β-cyclodextrin by the co-grinding method as follows: β-cyclodextrin (29.2 mg, 2.57 x 10^{-5} mol) was placed in

a small mortar, and the mortar placed in a closed holder containing water to encourage entrapment of water molecules into the cyclodextrins cavity. After 12 hrs, ZnNPc (5 mg, 8.7 x 10^{-6} mol) or ZnPc (3.71 mg, 4.8 x 10^{-6} mol) was added and the mixture thoroughly milled in the mortar and dried in the oven at 100^{o}C for 12 hrs.

The stoichiometry of the inclusion complexes with CD was evaluated by Job's method. Various dilutions of solutions of the ZnPc derivatives and the CDs were mixed to standard volume, the absorption spectra of each solution measured, and Job's plot was constructed from the absorbance differences at the Q band absorption.

Fluorescence, photobleaching and singlet oxygen studies

Fluorescence quantum yields were determined by the comparative method,[14] using chlorophyll a in ether ($\phi_F = 0.32$)[15] as the reference.

Photobleaching (or photodegradation) of the ZnPc complexes and quantum yields for singlet oxygen generation were determined as has been previously explained in detail.[16]

RESULTS AND DISCUSSION

Fig. 2 shows the UV-Vis spectra of the ZnPc derivatives under investigation. The spectra of ZnPc (i), ZnTBPc (ii) and ZnNPc (iii) are typical of monomeric metallophthalocyanine complexes, while that of ZnTNPc (iv) shows cofacial aggregation in DMSO, as depicted by the presence of two non-vibrational peaks in the Q band region.

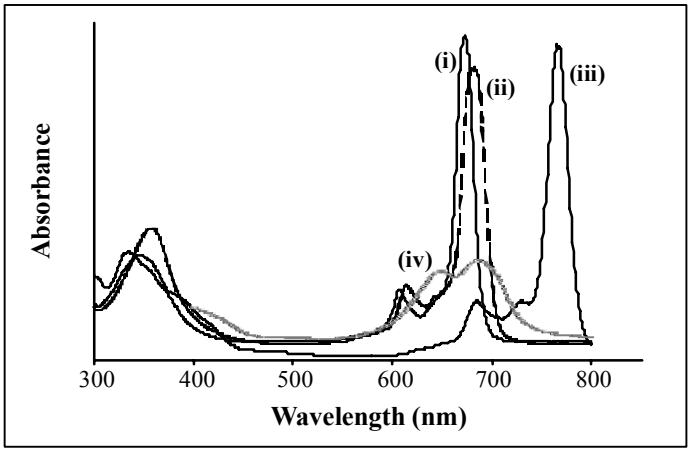


Fig. 2: Electronic absorption spectra of 4 x 10^{-6} mol dm^{-3} ZnPc (i), 6 x 10^{-6} mol dm^{-3} ZnTBPc (ii), 6 x 10^{-6} mol dm^{-3} ZnNPc (iii) and 2 x 10^{-5} mol dm^{-3} ZnTNPc (iv) in DMSO

The lower energy band at 682 nm is due to the monomeric species while the blue-shifted band at 645 nm is due to the aggregated species. The phthalocyanine Q and B arise from π-π* transitions in the macrocycle. The spectrum of ZnPcS in DMSO shows monomeric behaviour at concentrations up to 10^{-5} mol dm^{-3}, where Beer's law was obeyed. Comparing with ZnPc, the ZnPcS is shifted bathochromically by about 3 nm, suggesting that sulphonation probably led to the destabilization of the π-orbitals (HOMO) in the phthalocyanine's electronic structure.

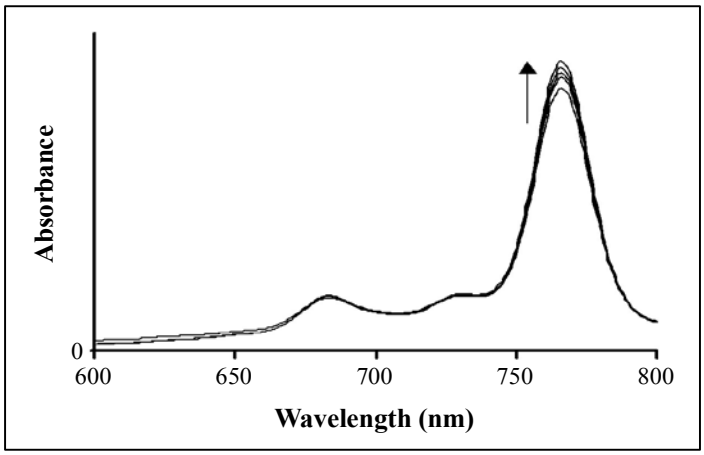


Fig. 3: Absorption spectral changes observed on addition of β-CD to ZnPc solution in DMSO. Ratio ZnPc:CD starting from 1:0 to 1:4 (inner to outer)

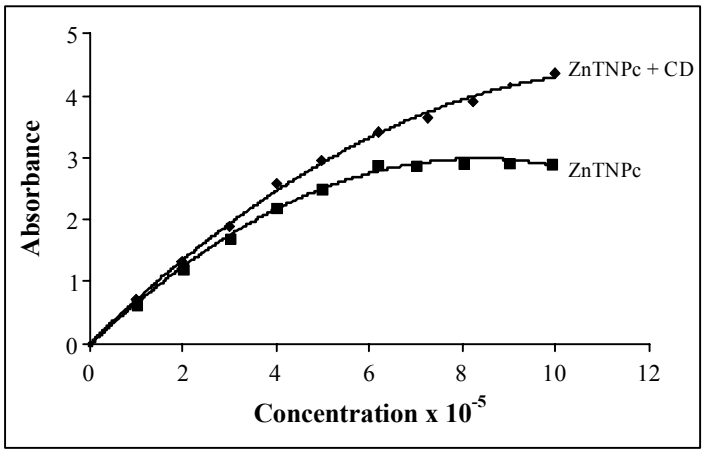


Fig. 4: Deviation from Beer's law for compound ZnTNPc and its inclusion complex with β-cyclodextrin in DMSO

Addition of CD to the monomeric ZnPc derivatives led to a significant increase in the intensity of the absorption peaks, with no observable peak shifts (Fig. 3). Fig. 4 shows that there was improvement in the Beer's law behaviour for the aggregated compound ZnTNPc following formation of the inclusion complex, which is evidenced by the increase in spectral intensity at 682 nm (monomeric band).

The increase in spectral intensities suggests the formation of inclusion complexes between CD and the studied compounds. Such spectral changes have earlier been associated with the formation of inclusion complexes between CDs and porphyrins.[9]

The formation of the solid complex between CD and ZnPc derivatives was confirmed ^{1}H NMR spectroscopy. Typical phthalocyanine ^{1}H NMR peaks (including phenoxy peaks) were found between 7.4 and 9.0 ppm. CD inclusion caused the narrowing of the phthalocyanine (and phenoxy in the case of ZnTBPc) ^{1}H NMR peaks and a significant upfield shift to between 7.1 and 7.8 ppm. Further evidence for inclusion was obtained from the X-ray powder diffraction (XRD, Fig. 5) peaks of the ZnPc inclusion compound, when compared to peaks due to CD or the phthalocyanine compounds alone.

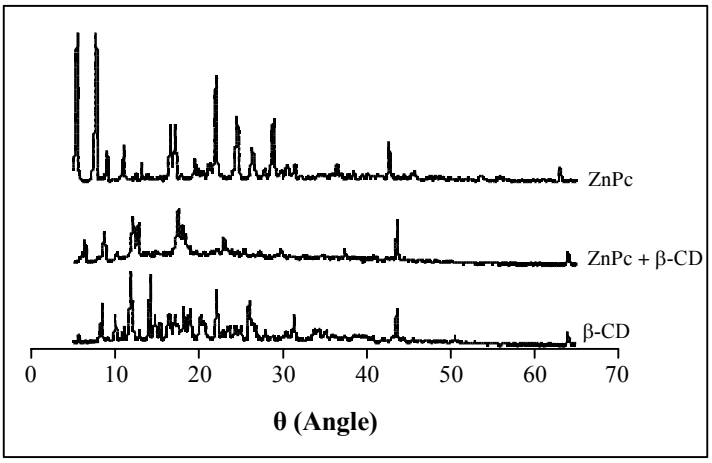


Fig. 5: Powder X-ray diffraction patterns of compound ZnPc, the inclusion complex and β-cyclodextrin

The XRD pattern showed definite differences between the patterns for CD and ZnPc individually with the pattern of the complex and hence, suggesting formation of inclusion complexes. Job's plots for the formation of the inclusion complexes between CDs and ZnPc derivatives were performed. Fig. 6 shows the Job's plot for ZnTBPc; a maximum was observed at an inclusion ratio of about 2:1 (CD:PC).

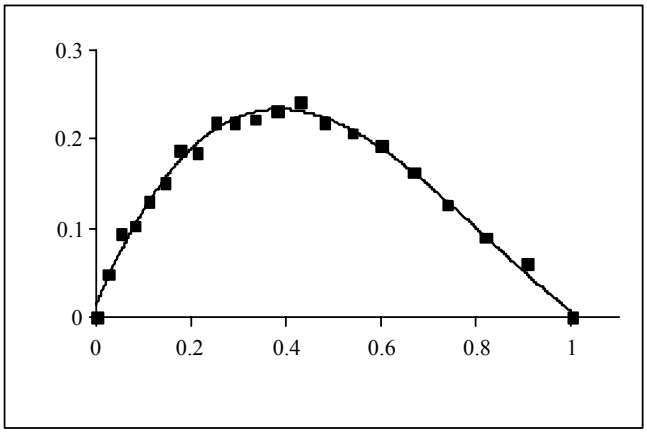


Fig. 6: Job's plot for the inclusion of ZnTBPc into hydroxypropyl-γ-cyclodextrin using DMSO as solvent

This result shows that two CD molecules are involved in the formation of the inclusion complex. ZnPc and ZnNPc also gave 2:1 inclusion complexes. For ZnTNPc, the Job's plot showed some interesting behaviour as maxima were observed at ratios 2:1 and 4:1 (CD:ZnTNPc, Fig. 7). This behaviour is most likely due to the coordination of CD to the aggregated as well as non-aggregated components of the molecule.

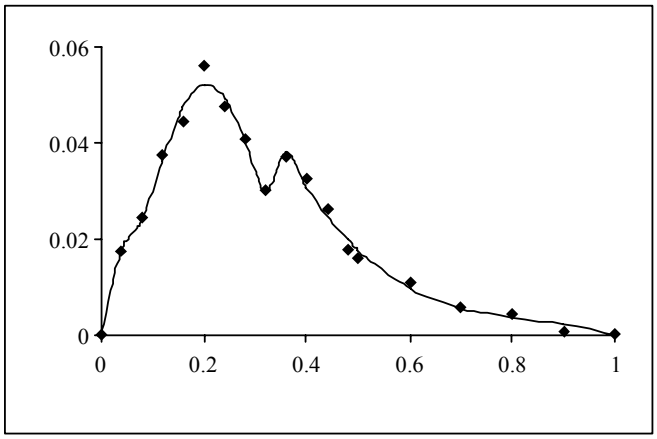


Fig. 7: Job's plot for the inclusion of compound ZnTNPc into β-cylcodextrin using DMSO as solvent

The wavelengths of maximum emission (λ_{max} Fluor) for all complexes are listed in Table 1. Stokes' shifts range between 5 nm and 9 nm, which is typical of MPc complexes. Cyclodextrin inclusion brought about no significant changes in emission wavelengths and

fluorescence quantum yields. However, the inclusion complexes gave higher yields of singlet oxygen (ϕ_Δ), suggesting that the cyclodextrin-included complexes should be better candidates for consideration in PDT applications. Singlet oxygen is the chief cytotoxic species that destroys cancer cells. In the same vein, sulphonation also brought about higher ϕ_Δ values.

Table 1: Effects of suphonation and cyclodextrin inclusion on the spectral, photophysical and photochemical properties of metallophthalocyanine derivatives

Complex	λ_{max} Q band (nm)	λ_{max} Fluor (nm)	Log ε	ϕ_F	ϕ_Δ	$10^5/\phi_p$
Effects of sulphonation						
ZnPc	672	678	5.38	0.20	0.67	2.61
ZnPcS	675	682	5.14	0.14	0.72	13.65
Effects of cyclodextrin inclusion						
ZnPc	672	678	5.38	0.20	0.67	2.61
ZnPc-βCD	672	681		0.18	0.74	0.68
ZnTBPc	681	692	5.15	0.14	0.60	3.33
ZnTBPc-γCD	681	692		0.14	0.75	2.15
ZnTNPc	645, 682	691	4.67, 4.88	0.02	0.11	-
ZnTNPc-βCD	645, 682	691		0.02	0.21	-
ZnNPc	766	773	5.20	0.07	0.19	16.4
ZnNPc-βCD	766	772		0.06	0.27	10.4

Photodegradation is characterized by the reduction in spectral intensity due to the degradation of the phthalocyanine ring. In Table 1, it is clear that cyclodextrin inclusion brought about greater photostability, as judged from their lower values of photodegradation quantum yield (ϕ_p). It is logical to say that the phthalocyanine ring is somehow protected from attack by singlet oxygen. It has been widely accepted that photodegradation of Pc ring is initiated by singlet oxygen, which is generated following irradiation of the Pc molecule.

CONCLUSION

In conclusion, two methods of solubilizing hydrophobic zinc phthalocyanine derivatives were described. Spectral, photophysical and photochemical changes accompanying the solubilization were also discussed. Formation of inclusion complexes

with cyclodextrins were confirmed by NMR and XRD, while their stoichiometries were suggested from Job's plots. Solubilization brought about higher yields of singlet oxygen, while the complexes became more photostable.

REFERENCES

1. I. Rosenthal, Photochem. Photobiol., **53**, 859 (1991).
2. J. D. Spikes, Photochem. Photobiol. B: Biol., **6**, 259 (1990).
3. M. Ambroz**,** A. Beeby, A. J. McRobert, M. S. C. Simpson, R. K. Svensen and D. Phillips, J. Photochem. Photobiol B: Biol., **9**, 87 (1991).
4. A. Ogunsipe, T. Nyokong and M. Durmus, J. Porphyrins Phthalocyanines, **11**, 635 (2007).
5. P. Tau, A.O. Ogunsipe, S. Maree, M. D. Maree and T. Nyokong, J. Porphyr. Phthalocya., **7**, 438 (2003).
6. R. Bonnett, Chemical Aspects of Photodynamic Therapy, Gordon and Breach Science, Canada (2000).
7. S. Hamai and T. Koshiyama, J. Photochem. Photobiol. A: Chem., **127**, 135 (1999).
8. J. S. Manka and D. S. Lawrence, Tetrahedron Lett., **30**, 7341 (1989).
9. X. P. Wang, J. H. Pan and S. M. Shuang, Spectrochim. Acta, **57**, 2755 (2001).
10. N. Kobayashi, H. Lam, W. A. Nevin, C. C. Leznoff and H. Shirai J. Am. Chem. Soc., **116**, 879 (1994).
11. S. Maree and T. Nyokong, J. Electroanal. Chem., **492**, 120 (2000).
12. J. Metz, O. Schneider and M. Hanack, Inorg. Chem., **23**, 1065 (1984).
13. D. Wöhrle, M. Eskes, K. Shigehara and A. Yamada, Synthesis, 194 (1993).
14. S. Maree, D. Phillips and T. Nyokong, J. Porphyr. Phthalocya., **6**, 17 (2002).
15. A. G. Montalban, H. Meunier, R. Ostler, A. Barrett, B. Hoffman and G. Rumbles, J. Phys. Chem., **103**, 4352 (1999).
16. I. Seotsanyana-Mokhosi, N. Kuznetsova and T. Nyokong, J. Photochem. Photobiol. A: Chem., **140**, 215 (2001).

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