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Photophysical properties of a newly synthesized unsymmetrically substituted zinc phthalocyanine

Ayfer Kalkan Burat *, Hande Pekbelgin Karaoğlu*

Istanbul Technical University, Department of Chemistry, TR34469, İstanbul, Turkey.

Abstract: A novel unsymmetrically substituted zinc phthalocyanine (ZnPc) containing six hexylthio units and a morpholinoethoxy group was synthesized and characterized. Statistical condensation reaction of two different phthalonitriles was used for the preparation of unsymmetrical ZnPc. The novel compound was purified using chromatographic methods with the help of high solubility differences of phthalonitrile derivatives. Characterization of the compound was achieved by using NMR, FT-IR, UV-Vis, and mass spectroscopic methods. The photophysical measurements were made in tetrahydrofuran (THF). Fluorescent quantum yield (Φ_F) and fluorescence lifetime (τ_F) of unsymmetrical ZnPc were determined. Fluorescent quenching experiments were done by adding benzoquinone (BQ) in THF, and Stern-Volmer constant (Ksv) and quenching constant (k_q) values were calculated.

Keywords: Fluorescence, phthalocyanine, quenching, unsymmetric, zinc.

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***Corresponding author.** E-mail: kalkanayf@itu.edu.tr, pekbelgin@itu.edu.tr

INTRODUCTION

Phthalocyanines (Pcs) can be functionalized for a variety of applications, from medicine to technology (1-5). They are also used as second-generation photosensitizers for the photodynamic therapy (PDT) of cancers and for inactivation of bacteria and viruses due to strong absorption in the red-visible region and high efficiency in producing reactive oxygen species (6, 7). The photochemical and physicochemical properties of Pcs can be altered by changing the substituents in the peripheral and non-peripheral positions or by inserting different metal ions in the central cavity (8, 9). Both peripherally and non-peripherally substituted Pcs have already been investigated as photosensitizers for PDT applications because the substituents affect the physicochemical properties of Pcs and the possibility of using them in *vivo* and in *vitro* studies (10, 11). Due to their unique photophysical and photochemical properties, Pc compounds can be applied in medical and industrial product development. For suitable applications, the design of phthalocyanines with desired properties can be accomplished by varying the central metal atoms and the substituents of Pc molecules. The most important problem encountered in the application of unsubstituted Pc is its low solubility in common organic solvents and in water. To improve the solubility of the Pc compound, long alkyne chains or bulky groups can be attached at the peripheral or non-peripheral positions of the macrocycle (8, 9, 12, 13).

Synthesis of Pcs for medical purposes is an important subject of research because it is preferred that the designed molecules do not show aggregation and have a lipophilic-hydrophilic balance. Aggregation of Pcs can be also prevented by peripheral, non-peripheral, or axial substitution of different groups (12, 13). One of these groups is morpholine (1,4-tetrahydro-oxazine), of great industrial importance and a wide range of applications. Morpholine and its derivatives are used as solvents, corrosion inhibitors, rubber additives, antioxidants, as well as in the production of drugs

and herbicides. Morpholine derivatives are also of interest as they show biological activities such as anti-inflammatory, analgesic, antidepressant, and antitumor (14-17).

It has been found that the substitution of morpholine groups into the Pc structure modulates the physicochemical properties and amphiphilic nature of Pcs, thereby facilitating their potential applications in biology and medicine (18). Recently, zinc phthalocyanines conjugated with biotinylated graphene quantum dots (GQDs) have been synthesized by Nyokong et al., and their photophysicochemical properties, and in *vitro* photodynamic activities have been studied. It was reported that cationic ZnPc conjugated with the biotin functionalized GQDs exhibited a relatively better performance (19). In another study published in 2019, tetra-substituted Pcs and their cationic derivatives with morpholine groups at the peripheral and non-peripheral positions were synthesized, and their photodynamic antimicrobial chemotherapy activities were examined, and it was determined that cationic Pcs showed better photodynamic antimicrobial activity (20). In 2017, nonperipherally octasubstituted magnesium Pc (MgPc), and its cationic derivative carrying N-methyl morpholiniumethoxy groups were synthesized, and their photocytotoxicity against bacteria, fungi, and cancer cells were investigated. This work showed that quarternized MgPc has excellent photodynamic activity against planktonic cells of both Gram-negative and Gram-positive bacteria (21). These studies show that morpholine groups positively change the biological activity of Pcs (22). In addition, axially morpholine-disubstituted silicon phthalocyanines exhibited better antifungal photodynamic activity and DNA/BSA binding (23-25).

Symmetrical and unsymmetrical morpholine substituted Pcs, synthesis, and investigation of their electrochemical and physicochemical properties were carried out by our group in previous years (26, 27). In addition, the symmetric octasubstituted Pcs derivative containing hexylthio groups was synthesized beforehand in the literature, and its photophysical and thermal properties were investigated (12). Here, we studied the synthesis and characterization of a novel unsymmetrically substituted zinc phthalocyanine (ZnPc) containing six hexylthio units and a morpholinoethoxy group at peripheral positions. The photophysical properties of this new compound were investigated by fluorescence measurements and compared with its octakis hexylthio substituted derivative in the literature (12). Hexylthio group was chosen for the electron donor property of the sulfur atom and its effect on the electronic properties of Pcs was investigated. In addition, morpholine groups also improve the biological properties of Pcs (18-22). Therefore, in the study the effect of the combination of morpholine group with hexylthio groups, which shifts the Q band absorption to the red, on the photophysical properties of phthalocyanine was also investigated.

EXPERIMENTAL SECTION

Materials and apparatus

An Agilent VNMRS 500 MHz spectrometer was used to determine the ^{1}H-NMR spectrum of the synthesized complex. The FT-IR spectrum of the complex was recorded by using a Perkin-Elmer Spectrum One FT-IR UATR spectrometer. The UV-Vis spectrum of the compound was obtained using a Scinco LabProPlus UV/Vis spectrophotometer. Fluorescence spectra were obtained on Perkin-Elmer LS55 fluorescence spectrophotometer. Bruker Microflex LT MALDI-TOF MS spectrometer was used to record the mass spectrum.

4,5-bis(hexylthio)phthalonitrile (**1**) (28) and 4-(2-morpholinoethoxy)phthalonitrile (**2**) (29) were synthesized as given in the literature. The chemicals and solvents used for the synthesis and purification of compounds **1** and **2** were also obtained from Sigma-Aldrich, Germany.

Preparation

*Synthesis of 2,3,9,10,16,17-Hexakis(hexylthio)-23-(2-morpholinoethoxy)) phthalocyaninatozinc(II) (***3***)*: 100 mg (0.28 mmol) of compound **1**, 23.8 mg (0.09 mmol) compound **2,** 17.0 mg (0.09 mmol) $Zn(CH_3COO)_2$ and a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were refluxed in dry *n*-hexanol under nitrogen (N_2) atmosphere for 24 hours. The mixture of reaction first cooled down to room temperature then precipitated by pouring it into ice-water, and the solid product was washed with methanol (MeOH). Purification of the green compound was carried out by column chromatography on silica gel with dichloromethane (DCM): MeOH (25:1) and then with THF:n-hexane (1:1) as eluent. The compound was finally purified by thin layer chromatography using 25: 1 DCM: n-hexane mixture. Solubility: Soluble in dimethylformamide (DMF), DCM, dimethylsulfoxide (DMSO) and THF. $C_{74}H_{99}N_9O_2S_6Zn$ (1404.41g/mol) Yield: 21 mg, (16 %). FT-IR (υ_{max}/cm^{-1}): 3071 (Ar-C-H), 2953 (Aliph. -C-H), 1240 (C-N), 1100 (C-O-C). UV-Vis λ_{max} (nm) THF: 363, 699. ^{1}H-NMR (500 MHz, $CDCl_3$): δ, ppm 7.63-7.52 (6H, m, Ar-H), 6.97 (2H, s, Ar-H), 6.61 (1H, s, Ar-H), 4.74-4.69 (2H, brs, OCH_2), 3.88-3.87 (4H, t, OCH_2, morpholine), 3.19 (2H, brs, NCH_2), 2.83 (4H, t, NCH_2, morpholine), 2.05-2.02 (12H, t, SCH_2), 1.73-1.69 (12H, m, S-C-CH_2), 1.50-1.42 (36H, m, C-C-CH_2), 1.01-0.92 (18H, t, CH_3). ^{13}C-NMR (500 MHz, $CDCl_3$): δ, ppm 186.30, 151.51, 149.33, 149.11, 148.89, 144.63, 144.35, 135.88, 135.63, 135.43, 135.24, 130.84, 129.45, 128.76, 128.22, 125.47, 123.31, 123.11, 122.91, 119.53, 68.12, 67.09, 58.12, 54.37, 34.22, 31.65, 30.30, 29.39,

22.66, 14.14. Anal. Calc. for $C_{74}H_{99}N_9O_2S_6Zn$ (1404.41 g/mol) %: C, 63.29; H, 7.11; N, 8.98 Found: C, 63.65; H, 7.34; N, 8.61. MS (MALDI-TOF): m/z 1404.5 $[M]^+$.

Photophysical parameters

Fluorescence quantum yield and fluorescence lifetime:

The fluorescence quantum yield (Φ_F) was determined by using a comparative method. The equation used in the comparative method is as follows, and ZnPc in DMF solution was used as standard. (Φ_F = 0.17) (30, 31):

$$\Phi = \Phi_{F(STD)} \frac{F A_{Std} \eta^2}{F_{Std} A \eta_{Std}^2} \qquad \text{(Eq. 1)}$$

In Eq. 1, F and F_{Std} denote areas under the fluorescent emission curves of compound **3** and its standard, respectively. The absorbances of standard solution and compound **3** are expressed as A_{Std} and A, respectively. n_{Std} and n indicate the refractive indices of solvents (n_{DMF} = 1.496, n_{THF} =1.4072).

Fluorescence lifetime (τ_F) indicates the meantime of the substance in the excited state prior to fluorescence and is calculated by the PhotochemCAD program using the Strickler-Berg equation. As an expected result of Eq. 2, the fluorescence quantum yield (Φ_F) and the fluorescence lifetime (τ_F) are directly proportional. In addition, the natural radiative lifetime (τ_o) was calculated using Eq. 2. (30, 31):

$$\Phi_F = \frac{\tau_F}{\tau_0} \qquad \text{(Eq. 2)}$$

Fluorescent quenching by 1,4-benzoquinone

Fluorescent quenching experiments were done by adding the different concentrations of BQ solutions up to 0.040 M to the fixed concentration solution of compound **3**. As a result of fluorescent quenching experiments, an energy transfer took place between compound **3** and BQ. Fluorescence spectra of compound **3** were recorded after each BQ addition. The change in the fluorescence spectra of compound **3** was evaluated to be consistent with the kinetic mechanism of the Stern-Volmer (SV) equation (Eq 3) (32):

$$\frac{I_0}{I} = 1 + K_{SV}[BQ] \qquad \text{(Eq. 3)}$$

I_0 is the fluorescence intensity of the fluorophore before the quencher is added, while I is the fluorescence intensity in the presence of the quencher. The concentration of the quencher is represented by [BQ] and the Stern-Volmer constant by K_{SV} found in the graph from [BQ] to I_0/I. The bimolecular quenching constant (k_q) is calculated from Eq. (4) (33):

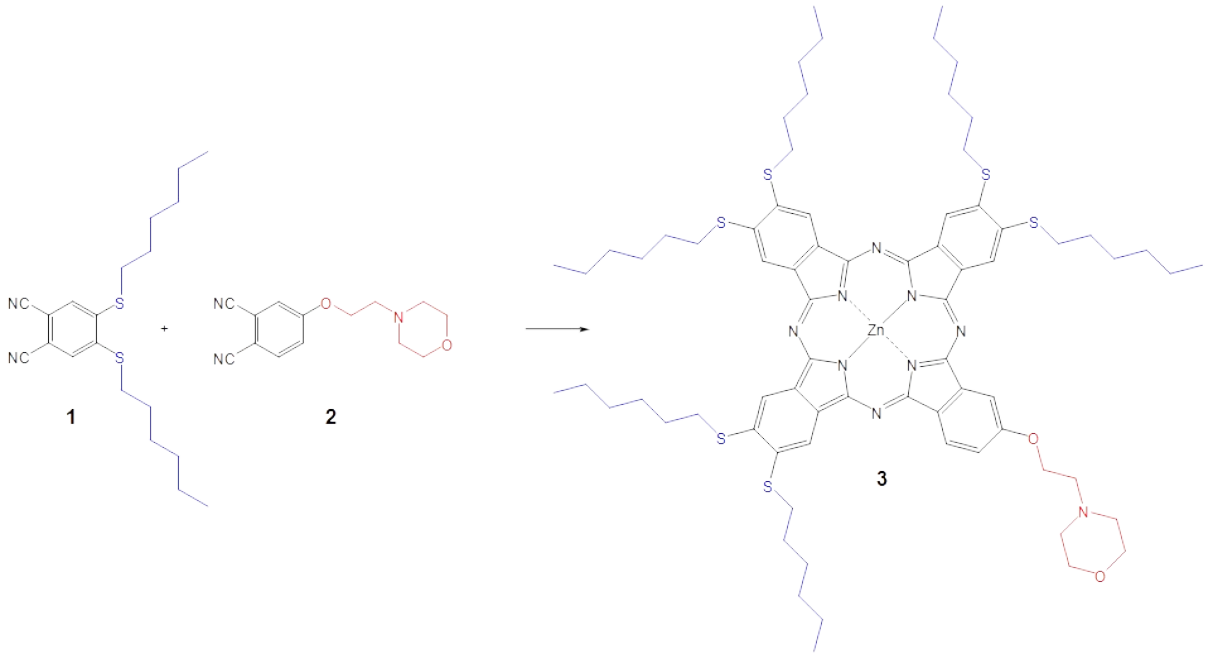
$$K_{SV} = k_q \times \tau_F \qquad \text{(Eq. 4)}$$

RESULT AND DISCUSSION

Synthesis and spectroscopic characterization

Basically, three different methods are used for the synthesis of unsymmetrical Pcs. These are polymeric support method (34, 35), ring-expansion of sub-phthalocyanine (SubPc) (36, 37) and statistical condensation of phthalonitriles (two different phthalonitrile derivative, A and B) (38-40), respectively. In order to use the polymeric support method, the Pc must have a group that can be attached to the polymer. In the ring-expansion method, the SubPc is first synthesized in the A_3 structure, and then the ring expansion is made. Here, the statistical condensation method was used to prepare the A_3B type unsymmetrical Pc. Pc derivatives containing mostly A_4 and A_3B were synthesized as a result of cyclotetramerization of two different phthalonitrile compounds whose reactivities were close to each other. While the solubility of the phthalonitrile derivative (**1**) containing the hexylthio group is too high, the low solubility of compound **2** facilitated the isolation of the unsymmetric Pc. Targeted A_3B Pc was isolated by sequential chromatographic purification methods.

Compound **1** and compound **2** were used as starting materials to obtain compound **3**. Compound **1** was synthesized as a result of the base-catalyzed aromatic displacement reaction of hexanethiol with 4,5-dichlorophthalonitrile. The reaction was accomplished in dry DMF, with the addition of K_2CO_3 at 60 °C for 8 h, and the product was purified by crystallization in MeOH. Compound **2** was obtained, under conditions similar to the synthesis of compound **1**, by the reaction of 4-nitro phthalonitrile with 2-morpholinoethanol. The reaction was completed at 50 °C for 72 hours using dry DMF and K_2CO_3 under nitrogen atmosphere. Column chromatography was used for the purification of the white product (silica gel, 1:1 chloroform ($CHCl_3$):acetone). Cyclotetramerization of the phthalonitrile derivatives **1** and **2** with anhydrous $Zn(CH_3COO)_2$ and DBU in *n*-hexanol at 160 °C over a 24-hour period at an appropriate ratio led to the formation of the desired compound **3** (Scheme 1). A number of chromatographic methods were used to purify the raw product. 25: 1 DCM: MeOH followed by 1: 1 THF: hexane solution mixtures were used as the mobile phase in column chromatography. Finally, pure compound (**3**) was obtained by thin-layer chromatography using a 25: 1 DCM: hexane mixture as eluent. Compound **3** dissolves in THF, DCM, DMSO, and DMF with a reaction yield of 16%.



Scheme 1: Synthetic route to unsymmetric ZnPc (**3**): $ZnCl_2$, DBU, n-hexanol, 24 h, reflux.

The novel unsymmetric Pc compound (**3**) was characterized by using NMR, FT-IR, UV-Vis and mass spectroscopic methods. In the FT-IR spectrum, aromatic and aliphatic C-H vibrations were observed at 3071 cm^{-1} and 2953 cm^{-1}, C-N and C-O-C vibrations were observed at 1240 and 1100 cm^{-1}, respectively. The ^1H NMR spectrum of **3** in $CDCl_3$ indicated the Pc protons between 7.63-6.61 ppm, the aliphatic protons of morpholine group at 4.74 ($O–CH_2$), 3. 88 ($O–CH_2$), 3.19 ($N–CH_2$), and 2.83 ppm ($N–CH_2$), respectively. The SCH_2, $SCCH_2$, and CH_3 protons were observed at 2.05, 1.73-1.42, and 1.02 ppm, respectively. The ^{13}C NMR spectrum of **3** is compatible with the structure. While the carbons of the phthalocyanine ring were observed between 186-119 ppm, aliphatic carbons were detected between 68-14 ppm. The molecular ion peak observed at m/z = 1404.5 $[M]^+$ for compound **3** confirms the proposed structure.

The simplest Pc unit is the 18-π electron system giving electronic spectra with two absorption regions. These are the B band in the UV region at about 300–400 nm and the Q band in the visible region ranging between 600–700 nm, both correlating to π-π* transitions. UV-Vis spectrum of **3** recorded in THF exhibits an intense single Q band absorption at 699 nm and B band at 363 nm. The spectrum shows the typical pattern of metallo-phthalocyanine complexes (29, 30). When the electronic absorption spectrum of **3** is compared with its derivatives in the literature, the Q band of **3** was shifted to 5 nm blue according to octakis(hexylthio)-substituted ZnPc and 22 nm red according to tetrakis(morpholinoetoxy)-substituted ZnPc.

Upon excitation at 615 nm, fluorescence measurements and fluorescent quenching tests of compound **3** were carried out in THF. The fluorescent emission, excitation, and absorption spectra of compound **3** are as in Figure 1. The fluorescence emission of **3** was found to be at 719 nm. The Stokes shift value calculated as 20 nm for compound **3** is consistent with the Stokes shift of Pcs calculated as 20-30 nm (41). The absorption and excitation spectra of **3** were similar and also observed as a mirror image of the fluorescent spectrum (30, 31).

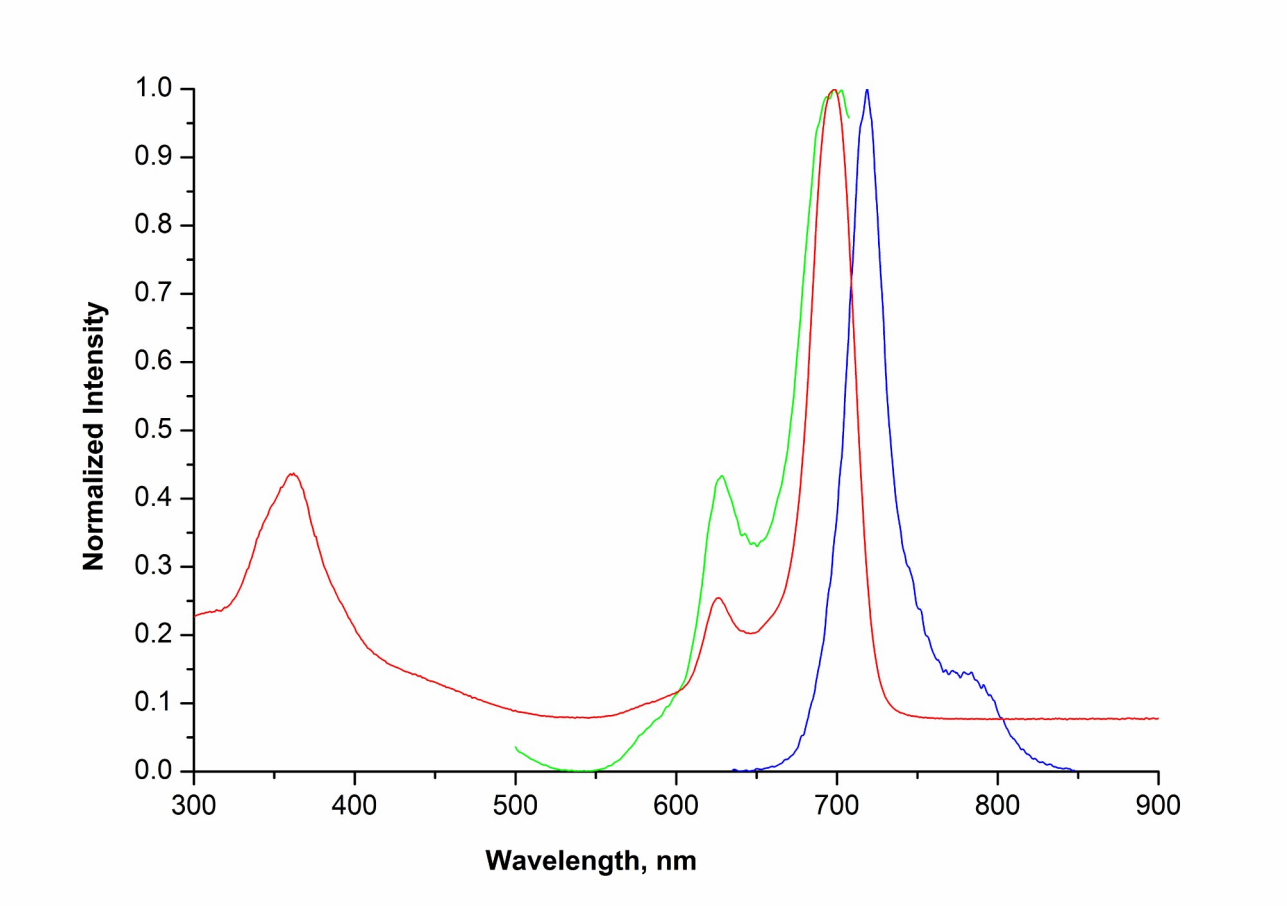


Figure 1: Absorption (red), excitation (blue) and emission (green) spectra of **3** in THF (4×10^{-6} M).

The fluorescence quantum yield (Φ_F) of unsubstituted ZnPc is 0.17 in DMF and was used as a reference in calculating the Φ_F value of compound **3**. The Φ_F value of **3** in the THF has been determined as 0.21, and this value is greater than the Φ_F value of the reference ZnPc (30, 31, 42). According to the literature, Dinçer and coworkers synthesized symmetric and unsymmetric Pcs bearing dipentoxymalonyl, chloro, and hexylthio units. They studied their photophysical properties and reported that the unsymmetric Pc (Φ_F = 0.13) exhibited a greater fluorescence quantum yield in $CHCl_3$ than the symmetric analog (Φ_F = 0.072) (12). In this study, the fluorescence quantum yield of morpholine substituted unsymmetric Pc (**3**) was found to be greater than the value of the symmetric and unsymmetric derivatives in the literature (12).

The natural radiation life (τ_o) and fluorescence life (τ_F) of compound **3** were determined as 6.34 ns and 1.33 ns, respectively. When the calculated values were compared with the values of the unsubstituted ZnPc (τ_o = 6.05, k_F = 1.03 ns), it was found that compound **3** have higher τ_o and k_F values (30, 31).

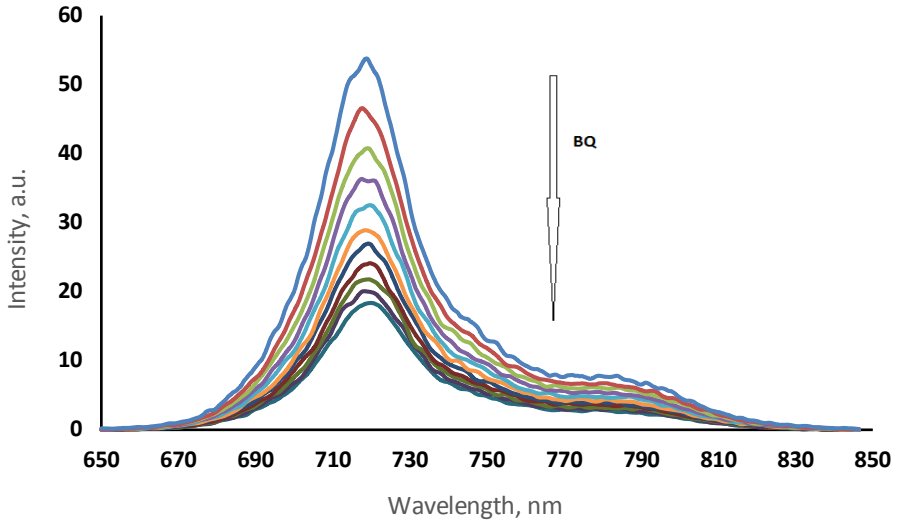


Figure 2: Fluorescent emission spectral changes of **3** (4 x 10^{-6} M) in THF in which different concentrations of hydroquinone in THF was added as quencher. [BQ] = 0.000, 0.008, 0.016, 0.024, 0.032, 0.040 M.

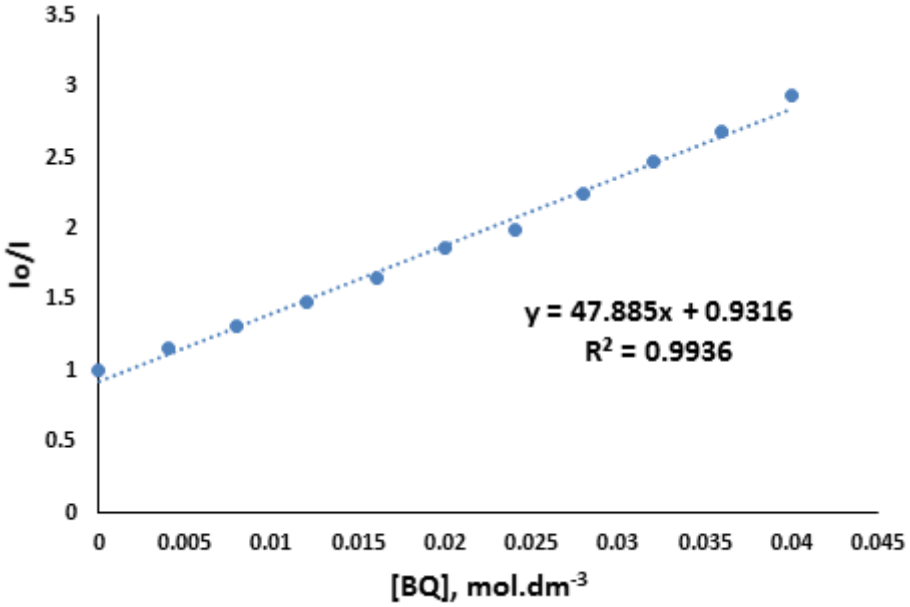


Figure 3: Stern-Volmer plot of **3** for BQ ([BQ] = 0.000, 0.008, 0.016, 0.024, 0.032, 0.040 M).

Fluorescent quenching studies of compound **3** were done by adding benzoquinone at different concentrations in THF, and it was observed that it complied with Stren-Volmer kinetics. The emission plots recorded after adding different concentrations of BQ to compound **3** are given in Figure 2. As the concentration of the BQ increases, the intensity of the emission peak appears to decrease. In addition, as seen in Figure 3, as a result of the diffusion-controlled quenching mechanism, the slope is linear, and the K_{SV} value was calculated as 47.89 M^{-1} (32, 33). kq (bimolecular quenching constant) value of compound **3** was calculated as 3.60x10^{10} s^{-1}. The K_{SV} and k_q values of compound **3** are smaller than the reference unsubstituted ZnPc (K_{sv} = 57.60 M^{-1}, k_q = 5.59x10^{10} s^{-1}).

CONCLUSION

It is reported from studies in the literature that morpholine groups positively change the biological activity of phthalocyanines. In addition, due to the electron donor feature of the sulfur atom, the hexylthio groups shift the Q band of phthalocyanines to the near IR region. Therefore, the synthesis of zinc phthalocyanine carrying hexylthio and morpholinoethoxy groups was thought to be a suitable candidate for biological applications. In this study, a novel peripherally substituted unsymmetric ZnPc (**3**) containing six hexylthio units, and a morpholine group was synthesized. The compound's characterization was successfully performed using various spectroscopic methods and

supported the accuracy of the proposed structure. Photophysical measurements of **3** were examined in THF. The fluorescence quantum yield and fluorescence lifetime for **3** were calculated and compared with the unsubstituted reference ZnPc, and octakis hexylthio substituted ZnPc and found to be greater than both unsubstituted and octa-substituted ZnPcs. Fluorescence quenching studies for compound **3** were performed in THF and with the addition of various concentrations of BQ. K_{SV} and kq values were calculated as a result of the fluorescence quenching studies. In comparison with unsubstituted zinc phthalocyanine, compound **3** showed lower Ksv and kq values. Compound **3** is a good candidate for biological applications due to its absorption in the near IR region and its higher fluorescence quantum yield than its derivatives in the literature.

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