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# Synthesis of new porphyrazines with tertiary or quaternized aminoethyl substituents

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**Abstract**

Metal-free and metallo-porphyrazines (M = Mg or Co) carrying eight dimethylaminoethylthia-groups on peripheral positions have been synthesized from the disodium salt of dithiomaleonitrile and the hydrochloride of dimethylaminoethylchloride. The magnesium derivative (MgPza) was converted into quaternized product (MgPzq) by reaction with methyl iodide. The metal-free derivative was obtained by treatment with trifluoroacetic acid and its reaction with cobalt (II) acetate led to the cobalt derivative (CoPza). Aggregation of MgPzq molecules has been observed in aqueous solution by the blue-shift of the Q-band absorption with an accompanying decrease in intensity. The new compounds have been characterized by elemental analysis, IR, NMR and their electronic spectra. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* Porphyrazines; Phthalocyanines; Dithiomaleonitrile; Tetrapyrol derivatives

## 1. Introduction

Intensive research interest in peripherally functionalized porphyrazines during the last decade has shown that these tetrapyrol derivatives should be considered as alternatives to the phthalocyanines that have found extensive applications in many fields. These include material science and the photodynamic therapy of tumors as well as pigments and dyes [1–4]. A range of different substituents provides porphyrazine ligands with interesting new features such as greatly enhanced organic solubility compared to their phthalocyanine counterparts, or additional donor sites to create multinuclear complexes [5–8]. Synthetic methods for a number of unsymmetrically substituted derivatives have also been developed [9,10].

Our previous papers have described a series of phthalocyanines with crown ether moieties. Those products with bulky azacrown ether macrocycles on their periphery had enhanced solubility [11–15]. Quaternizable aza-functions also provided products soluble in aqueous solutions over a wide range of pH [16,17].

It is well known that the addition of bulky substituents on the periphery results in products soluble in apolar solvents, while sulphonium or quaternary ammonium groups lead to water- or polar solvent–soluble derivatives. This paper describes the preparation of novel soluble porphyrazine structures which carry eight 2-dimethyl

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or 2-trimethylaminoethylthio-substituents on the periphery. It is expected that the latter compound will be soluble in water in a wide pH range.

## 2. Results and discussions

The alkylation product of the thiolate groups of disodium salt of dithiomaleonitrile with 2-dimethylaminoethylchloride was chosen as the starting point for a soluble porphyrazine (Fig. 1). The latter compound was obtained as the hydrochloride salt from the chlorination of dimethylaminoethanol with thionyl chloride [18]. During the alkylation process excess $Na_2CO_3$ was added to completely neutralize the amine groups. The oily product was obtained in high yield (85%). In the IR spectrum of bis(dimethylaminoethylthio) maleonitrile stretching vibrations of CN, $CH_3$ and $CH_2$ groups are observed at 2210, 2780 and 2920 $cm^{-1}$. These values comply with those reported in the literature for similar compounds [7,19]. In the $^1$H-NMR spectrum three different types of protons are clearly seen: triplets at 3.24 and 2.64 ppm correspond to neighbouring S–$CH_2$ and N–$CH_2$ groups respectively. The singlet at 2.25 ppm is for N–$CH_3$ protons. The ratio of the integral values (2:2:6) also confirms the proposed structure.

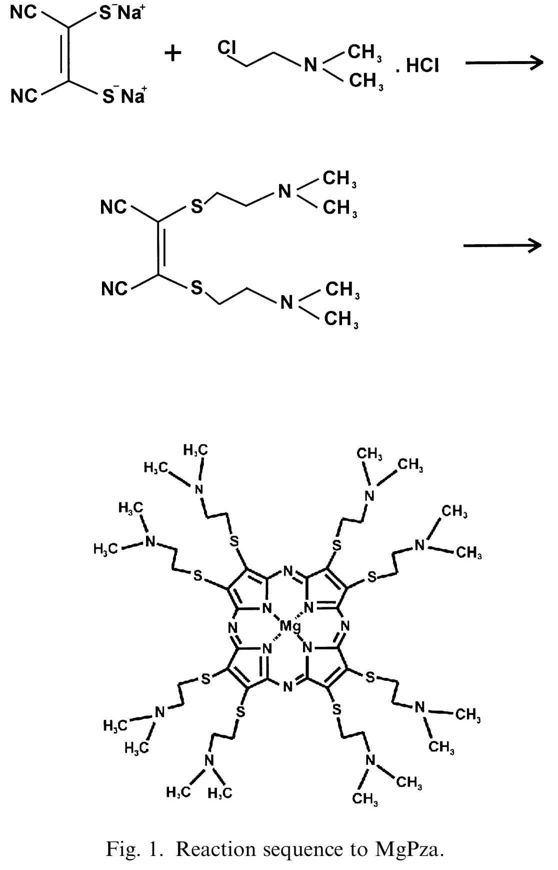

Fig. 1. Reaction sequence to MgPza.

Conversion of bis(2-dimethylaminoethylthio)-maleonitrile into porphyrazine was achieved by the template effect of magnesium butanolate [5–8,19]. The reaction is feasible in propanol, but better yields were obtained in butanol (40%). Cyclotetramerization gave the dark blue octakis(2-dimethylaminoethylthio) porphyrazinatomagnesium (MgPza). It is soluble in ethanol, acetone, methanol, ethylacetate and chloroform and insoluble in apolar hydrocarbon solvents such as hexane and petroleum ether.

Elemental analyses correspond closely with the values calculated for $C_{48}H_{80}N_{16}S_8Mg$. In the $^1$H-NMR spectrum, chemical shifts for S–$CH_2$, N–$CH_2$ and N–$CH_3$ groups appear at 2.66, 2.18 and 2.07 ppm, respectively.

In the IR spectrum $\nu_{CH}$ vibrations of the dimethylaminoethyl groups keep their places around 2760–2940 $cm^{-1}$, but as expected the C≡N stretching vibrations of the starting material are lacking after porphyrazine formation. The fingerprint regions of other divalent metalloporphyrazines are almost identical.

As expected for a porphyrazine of $D_{4h}$ symmetry, there is a single Q band absorption in the low energy region and a single B band. These absorptions correspond to $\pi \rightarrow \pi^*$ transition and are observed around 664–675 and 374–379 nm depending on the polarity and donor properties of the solvents (e.g. acetone, ethanol, methanol, DMF, chloroform and pyridine) at concentrations of approximately $10^{-4}$ M (Table 1).

When water-soluble tetrapyrrol derivatives are required, sulphonium or quaternary ammonium groups are introduced on the periphery. Peripheral dimethylaminoethyl substituents of MgPza, which lead to solubility in common organic solvents, are extremely suitable for conversion into quaternary ammonium groups by alkylation with alkyl

Table 1
Absorption maxima ($\lambda_{max}$, nm) and extinction coefficients ($\varepsilon$, $10^3$ 1 mol$^{-1}$ cm$^{-1}$) for MgPza and MgPzq in different solvents

| Solvents | Compounds [$\lambda_{max}$ ($\varepsilon$)] | |
|---|---|---|
| | MgPza | MgPzq |
| Ethanol | 668 (59.16),<br>374 (56.8) | 667 (38.175),<br>373 (37.825) |
| DMF | 672 (58.52),<br>376 (56.52) | 667 (43.25),<br>379(44.475) |
| Methanol | 664 (70.75),<br>376 (74.55) | – |
| Acetone | 669 (43.32),<br>374 (44.4) | – |
| Chloroform | 671 (49.92),<br>378 (48.48) | – |
| Pyridine | 675 (36.40),<br>379 (35.08) | – |
| Water | – | 660 (17.85),<br>358 (19.9) |
| DMSO | – | 669 (43.45),<br>376 (43.4) |

halides such as $CH_3I$ [17]. When MgPza was treated with methyl iodide the hygroscopic porphyrazine with eight quaternary ammonium groups [$(MgPzq)^{8+}.8I^-$] was obtained (Fig. 2). There are no major changes in the IR spectrum after quaternization. The electronic spectrum in water exhibits absorption maxima at 660 and 358 nm. In polar organic solvents, there is a slight bathochromic shift, but the extinction coefficients are about twice as high (Table 1). These changes can be explained by the higher tendency of porphyrazine molecules to aggregate in aqueous solution [20].

Demetallization of MgPza to metal-free derivative $H_2Pza$ was accomplished in $CF_3COOH$. Since protons in the inner core of porphyrazines are screened by aromatic Π electrons of the macrocycle, they appeared at −1.0 ppm in the $^1$H-NMR. These NO–H groups are also observed through their stretching vibrations at 3280 cm$^{-1}$ in the IR spectrum. Electronic spectra can be used in order simply to differentiate metal-free and metallo-porphyrazines. While Q band absorptions are split into two peaks at around 600–700 nm in the former, the same absorptions appear as a single peak in the latter. Thus the single intense peak at 672 nm for MgPza corresponds with two relatively weak peaks at 638 and 709 nm in the metal-free analogue. The reason for the splitting is the change of symmetry from $D_{4h}$ to $D_{2h}$.

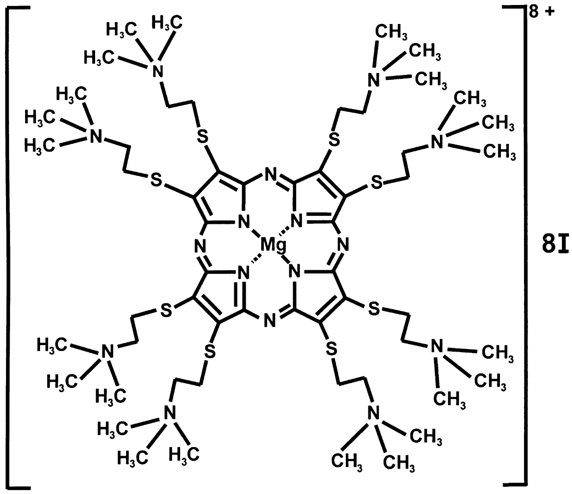

Fig. 2. [Octakis(2-trimethylammoniumethylthio)porphyrazinato-magnesium] octaiodide (MgPzq).

$H_2Pza$ is the starting point for the incorporation of different metal ions into the porphyrazine core. Inner core protons can be exchanged with metal ions. As an example of a divalent metal porphyrazine derivative, CoPza was obtained from $H_2Pza$ and Co-acetate by refluxing in ethanol. The IR spectrum of CoPza is very similar to MgPza and there is a single intense Q band absorption which is at 635 nm while B band absorption is at 326 nm.

## 3. Experimental

IR spectra were recorded on a Mattson 1000 FTIR spectrophotometer as KBr pellets, electronic spectra on a Unicam UV–VIS spectrophotometer. Elemental analysis was performed at the Instrumental Analysis Laboratory of TÜBİTAK Marmara Research Centre. Proton NMR spectra were recorded on a Bruker-Spectrospin 250 MHz spectrometer using $SiMe_4$ as the reference.

### *3.1. Bis(2-dimethylaminoethylthio)maleonitrile*

A suspension of disodium salt of dithiomaleonitrile (0.186 g, 1 mmol), hydrochloride salt of 2-dimethylaminoethylchloride (0.432 g, 3 mmol) and anhydrous sodium carbonate (1.06 g, 10 mmol) in 50 ml of acetone was refluxed under nitrogen for 4 h. The volume of the mixture was then reduced to half by evaporation and the residue was added dropwise into crushed ice (~250 g). The whole mixture was stirred till a clear solution was obtained. This aqueous solution was extracted with chloroform (4×50 ml). After drying the chloroform solution on anhydrous $Na_2SO_4$, the solvent was evaporated under reduced pressure to obtain the product as a waxy residue. Yield: 0.240g (85%). The compound is soluble in chloroform, acetone, ethanol and methanol.

$\nu_{max}$ $(cm)^{-1}$ (KBr pellet): 2920, 2780, 2760, 2210, 1510, 1480, 1260, 1195, 1030, 980, 850, 760. (Found: C, 50.10; H, 7.85; N, 20.11. $C_{12}H_{20}N_4S_2$ requires: C, 50.70; H, 7.04; N, 19.72.) $^1$H-NMR ($CDCl_3$) δ3.24 (t, S-$CH_2$, 2H), 2.64 (t, N-$CH_2$, 2H), 2.25 (S, N-$CH_3$, 6H) ppm.

### *3.2. Octakis(2-dimethylaminoethylthio)porphyrazinatomagnesium (MgPza)*

Mg powder (100 mg, 4.17 mmol) was refluxed overnight in 20 ml of butanol with the addition a few $I_2$ crystals. To this grayish magnesium butanolate suspension, bis(2-dimethylaminoethylthio) maleonitrile (284 mg, 1 mmol) was added as a slurry in a small amount of butanol. After refluxing for 5h, a dark blue suspension was obtained. It was evaporated to dryness to obtain a crude product as a paste that was first washed with *n*-hexane. It was then dissolved in dichloromethane and the magnesium salts were filtered off. After evaporation of the solvent, pure porphyrazine was obtained. Yield: 105 mg (40%). This compound was soluble in ethanol, methanol, acetone, ethylacetate and chloroform.

$\nu_{max}$ ($cm^{-1}$) (KBr pellet) 2940, 2780, 2760, 1460, 1370, 1290, 1215, 1160, 1130, 1090, 1040, 880, 850, 790, 760. $\lambda_{max}$ (nm) (DMF) 672, 376. (Found: C, 50.10; H, 7.21; N, 18.95. $C_{48}H_{80}N_{16}S_8Mg$ requires C, 49.66; H, 6.90; N, 19.31.) $^1$H-NMR ($CDCl_3$) δ 4.05 (s, S-$CH_2$, 2H), 2.66 (s, N-$CH_2$, 2H), 2.18 (s, N-$CH_3$, 6H) ppm.

### *3.3. [Octakis(2-trimethylammoniumethylthio) porphyrazinatomagnesium]-octaiodide (MgPzq)*

MgPza (116 mg, 0.1 mmol) was dissolved in dichloromethane (10 ml) and methyl iodide (1.6 ml, 3.65 g, 25.6 mmol) was added. This mixture was stirred in the dark under $N_2$ at room temperature for 24h. The blue precipitate was filtered, washed with dichloromethane and then with diethylether, and dried in a vacuum desicator over $P_2O_5$ for 12 h. This porphyrazine was soluble in water, ethanol, DMF and DMSO. Yield: 120 mg (52%).

$\nu_{max}$ ($cm^{-1}$) (KBr pellet) 2980, 2920, 1630, 1480, 1330, 1230, 1150, 1020, 980, 910, 795, 750. $\lambda_{max}$ (nm) ($H_2O$) 660, 358. (Found: C, 28.80; H, 4.95; N, 9.44. $C_{56}H_{104}N_{16}S_8I_8Mg$ requires C, 29.27; H, 4.53; N, 9.76.)

### *3.4. Octakis(2-dimethylaminoethylthio)porphyrazine ($H_2$Pza)*

MgPza (116 mg, 0.1 mmol) was treated with $CF_3COOH$ (~1 ml) and mixed at room temperature for 3 h. It was neutralized with aqueous ammonia (10%) and 2 ml NaOH (2M) was then added to raise pH to ~12. This mixture was kept in the refrigerator overnight to complete the precipitation. It was filtered, washed extensively with water and dried in vacuo. Finally, the pure porphyrazine was obtained by column chromatography on silicagel with MeOH/$CHCl_3$ (1:20) as eluent. The dark blue–violet product was soluble in ethanol, acetone, chloroform and dichloromethane. Yield: 80 mg (70%).

$\nu_{max}$ ($cm^{-1}$) (KBr pellet) 3280, 2940, 2760, 1600, 1460, 1390, 1290, 1120, 1040, 810, 740. $\lambda_{max}$ (nm) (EtOH) 709, 638, 343. (Found: C, 50.21; H, 7.65; N, 19.23. $C_{48}H_{82}N_{16}S_8$ requires C, 50.62; H, 7.21; N, 19.68.) $^1$H-NMR ($CDCl_3$) δ 4.10 (s, S-$CH_2$, 2H), 2.74 (s, N-$CH_2$, 2H), 2.20 (s, N-$CH_3$, 6H), −1.0 (broad s, NH) ppm.

### *3.5. Octakis(2-dimethylaminoethylthio)porphyrazinatocobalt (CoPza)*

To a solution of $Co(CH_3COO)_2.4H_2O$ (250 mg, 1 mmol) in 15 ml ethanol was added $H_2$Pza (114 mg, 0.1 mmol) in 10 ml ethanol. The mixture was refluxed with stirring for 18 h. After cooling to room temperature a precipitate, consisting essentially of the product and unreacted metal salt was formed. It was filtered, washed with cold ethanol and dried. This crude product was dissolved in chloroform, filtered, and the filtrate evaporated to dryness to obtain the pure dark blue porphyrazine. This porphyrazine was soluble in ethanol, acetone, chloroform and dichloromethane. Yield: 90 mg (75%).

$\nu_{max}$ (cm$^{-1}$) (KBr pellet) 2940, 2780, 1550, 1420, 1040, 925, 800, 670, 625. $\lambda_{max}$ (nm) (EtOH) 635, 326. (Found: C, 47.85; H, 7.13; N, 18.33. $C_{48}H_{80}N_{16}S_8Co$ requires C, 48.20; H, 6.70; N, 18.75.)

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