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Synthesis of Novel Unsymmetrical Monoaminated Phthalocyanines

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Abstract: Metal-free monoaminophthalocyanine 3 was synthesised by reacting of subphthalocyanine 1 with 5-amino-1,3-diiminoisoindoline 2. Alternatively, compound 3 was prepared from octadecylaminodiiminoisoindoline 6 by reaction with 1 to give 7 followed by acidic hydrolisis. The zinc complex 8 was obtained from 3 by treatment with anhydrous zinc acetate. The preparation of 8 by template condensation of subphthalocyanine 1 with aminodiiminoisoindoline 2 and zinc acetate was unsuccessful. In this case, a mixture of statistical distribution compounds was obtained. A tentative reaction pathway for the condensation between subphthalocyanines and diiminoisoindolines is also given.

The interest in phthalocyanines (Pcs),¹ in addition to basic research, has been recently expanding also in applied fields such as xerography, photovoltaics, electrochromism, optical disc, laser dyes, liquid crystals, molecular metals, electrocatalysis, chemical sensors and photodynamic cancer therapy (PDT).²

Hydrophilic phthalocyanines and naphthalocyanines (Ncs) are being extensively studied as photosensitizers for PDT.³ On the other hand, Pc derivatives with chelated diamagnetic metals, such as Zn^{2+} , Al^{3+} , and Ga^{3+} , are of special interest because they enhance this photodynamic activity.⁴

Although the synthesis of tetrasubstituted hydrophilic Pcs are well documented,¹ there have been few reports on mono- or disubstituted unsymmetrical amphiphilic Pcs mainly because of their preparative difficulty.^{1c, 5} Recently, a selective synthetic strategy to produce unsymmetrical Pcs by condensation of a subphthalocyanine (SubPc) with different substituted diiminoisoindolines has been published.⁶ However, the most usual method to obtain unsymmetrically substituted Pcs is the statistical condensation of two different dinitriles^{5c-d} or diiminoisoindolines.^{5a-b}

Our current interest in monofunctionalised Pcs in order to bond them to biomolecules like monoclonal antibodies, without the disadvantage of crosslinking reactions, prompted us to prepare a novel amphiphilic phthalocyanine 3, monofunctionalised with an amino group, through a ring enlargement reaction of unsubstituted subphthalocyanine 1,⁷ and its zinc (II) complex 8.



The SubPc 1 was prepared according to a modified fashion of the procedure reported by Meller and Ossko,⁹ previously described by us.¹⁰

Heating of a solution of subphthalocyanine 1 and 5-amino-1,3-diiminoisoindoline $(2)^{11}$ in a 1:4 molar ratio in N,N-dimethylaminoethanol affords a mixture of monoaminophthalocyanine 3 and unsubstituted Pc (H₂Pc) (Scheme 1). Compound 3 was isolated in a 60% yield by extraction with glacial acetic acid.¹³

Self-condensation products of diiminoisoindoline 2 were not observed, even being it in a molar excess, thus indicating the low reactivity of the compound under the employed reaction conditions.

It is reasonable to assume (Scheme 2) that diminoisoindoline 2 reacts with subphthalocyanine 1 to give an open four-unit compound (A), which cyclises to give 3 or alternatively undergoes a cleavage, either thermal or promoted by attack of diminoisoindoline 2, or even of a solvent molecule, affording one or two diminoisoindoline- dimers (B) and (C) among other possible products. Self-condensation of two units of (B) would lead to the isolated unsubstituted phthalocyanine (H_2Pc), whereas condensation of (B) with (C) would lead also to 3.



Scheme 2

This scheme should be general for the reactions of subphthalocyanines and diiminoisoindolines. The relative importance of the pathways, represented in **Scheme 2**, and other possible routes of evolution (not appreciable in this particular case), such as further condensation of two units of type (C) or eventual reactions of a substituted tetramer of type (A) with dimers of type (B) or (C), would depend on the substituents of the reactants and on the reaction conditions.^{1b}

An alternative way to obtain aminophthalocyanine **3** would be the reduction of the mononitrophthalocyanine **5**. However, reaction of subphthalocyanine **1** with 5-nitro-1,3-diiminoisoindoline $(4)^{14}$ under the same conditions described above or in other solvents used in this kind of reactions⁶ such as mixtures of dichlorobenzene-dimethyl sulfoxide, employing different molar ratios of the reactants (from 4:1 to 1:4) affords, besides **5**, the other four statistical distribution phthalocyanines with two, three, four and no nitro groups in variable ratio as an intractable mixture.¹⁵ The higher reactivity of **4** in comparison with **2** would promote its autocondensation. This fact together with a reaction pathway similar to that depicted above (**Scheme 2**) would explain the different compounds obtained in the reaction. Surprisingly, the few reports on synthesis of unsymmetrically substituted phthalocyanines via subphthalocyanines described in the literature do not refer to the mechanism of this reaction and they do not mention any kind of statistical distribution products.⁶

A third alternative method for the preparation of 3 was developed. Thus diiminoisoindoline 6^{16} was reacted with subphthalocyanine 1 in similar conditions to those described above to yield a mixture of phthalocyanine 7^{17} and H₂Pc. In this case, the compounds were separated by column chromatography. Compound 7 was converted to the monoaminoderivative 3 by acid hydrolysis with HCl.⁸ The overall reaction yield in this case was 15 %, lower than that obtained by direct reaction of 1 and 2.

The zinc metal complex 8 was prepared from the metal-free phthalocyanine 3 by reaction with anhydrous zinc acetate in DMF at reflux temperature for 3 h.¹⁸ The preparation of 8 by template condensation of SubPc 1 with aminodiiminoisoindoline 2 and zinc acetate was unsuccessful. In this case, a mixture of statistical distribution compounds was obtained. The presence of the zinc (II) ion would facilitate the ring opening of 1 and the cleavage of the open tetramer A (Scheme 2) giving rise to a statistical pathway. This is probably the reason why no examples of reactions of subphthalocyanines with iminoisoindolines templated by metal ions have been described in the literature.

In conclusion, we have synthesised two novel species of unsymmetrical phthalocyanines, the metalfree monoaminophthalocyanine 3 and its zinc complex 5,¹⁹ which are interesting candidates for photodynamic sensitization and have proposed a reaction pathway for the formation of Pcs via subphthalocyanines. Work is in progress in both areas and will be reported in due course.

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- 7. Recently, the synthesis of the zinc tri-*tert*-butyl-4-aminophthalocyanine (mixture of four isomers)⁸ has been described by reduction of the corresponding mononitrophthalocyanine obtained by condensation of the appropriate phthalonitriles. This two-step statistical method could not be applied to the preparation of 8 because the reaction between 4-nitro- and unsubstituted phthalonitriles in a molar ratio 1:3 in the presence of Zn(OAc)₂·2H₂O afforded in our hands an intractable mixture of statistical distribution products, with a large amount of ZnPc, which could not be separated.
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- Procedure for the preparation of 2 : 4-aminophthalonitrile¹² (2 g,14 mmol), sodium methylate (0.2 g) and methanol (150 ml) were stirred together at room temperature for 1 hour while bubbling a rapid stream of ammonia gas through the system. The temperature was raised to reflux with continuous passage of ammonia for 20 hours. After cooling, the solvent was eliminated at low presure and then 30 ml of a saturated solution of amonium chloride was added thus precipitating a light brown solid. The solid was filtered, washed several times with water and dried to obtain 2 g (90% yield) of 2. mp 245-255°C (dec.); MS (EI) m/z 160 (M⁺, 100), 144 (47), 143 (58). H-NMR (CD₃OD) δ 7.65 (1H, d, J=8 Hz, arom H), 7.20 (1H, d, J=2.5 Hz, arom H), 6.78 ppm (1H, dd, J=8, 2.5 Hz, arom H); ¹³C-NMR (CD₃OD) δ 178.6 (CNH₂), 168.6 (C=N), 165.9 (C=N), 156.3 (CC=N), 139.0 (CC=N), 126.3 (arom CH), 116.4 (arom CH), 109.9 ppm (arom CH).
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- **13. 3:** mp >300°C; MS (FAB) m/z 529, 530 [M⁺, (M+H)⁺]; IR (KBr) υ 3420, 3354, 3288 (NH₂), 1610 cm⁻¹ (C=N); UV (TFA) λ_{max} (log ε) 731 (5.18), 688 (5.00), 644 (sh), 631 (sh), 319 (5.08).
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- 15. The mono- (5), di-, tri- and tetranitrophthalocyanines were characterized by MS (FAB) using concentrated sulphuric acid as matrix, m/z 559, 604, 649, 694, respectively. Furthermore, the mixture was reduced with Na₂S to obtain a crude which was analyzed by field desorption mass spectrometry (FD-MS) showing to be a mixture of mono- (3), di-, tri-, and tetraaminophthalocyanines.
- 16. 6: mp 150-165°C (dec.); H-NMR (TFA-d₁) δ 9.60 (1H, d, J=2.5 Hz, arom H), 8.60 (1H, d, J=8 Hz, arom H), 8.00 ppm (1H, dd, J=8, 2.5 Hz, arom H).
- 17. 7: mp >300°C; MS (FAB) m/z 796 (M⁺); IR (KBr) υ 3280 (NH), 2910, 2840, 1660 (CON), 1610 cm⁻¹; UV (CHCl₃) λ_{max} (log ε) 696 (5.03), 660 (5.00), 640 (sh), 607 (sh), 335 (5.00).
- **18.** 8: mp >300°C; MS (FAB) m/z 591, 593, 595 (M⁺); IR (KBr) \cup 3420, 3354, 3288 (NH₂), 1580 cm⁻¹ (C=N); UV (DMF) λ_{max} (log ε) 665 (5.20), 614 (3.10), 346 (3.70).
- 19. Satisfactory elemental analytical data were obtained for compounds 3, 7 and 8 and their precursors.