

Towards N-alkylated phthalocyanines using 2,3,9,10,16,17,23,24-octaneopentoxypthalocyanine

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ABSTRACT: 4,5-Dineopentoxypthalonitrile was prepared from catechol and neopentyl tosylate in three steps. Condensation of this substituted phthalonitrile with lithium metal in 1-pentanol led to 2,3,9,10,16,17,23,24-octaneopentoxypthalocyanine. Lithiation in tetrahydrofuran gave the dilithium phthalocyanine which on methylation did not give the expected N-methylated product 29,31-dimethylphthalocyanine. The precipitate formed on methylation appeared to be the N⁺-CH₃ derivative in which one of the peripheral nitrogens was N-methylated. Methylation with ¹³CH₃I likely yielded an N⁺-methylated phthalocyanine having the requisite increased mass in its mass spectrum. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: 4,5-dineopentoxypthalonitrile; 2,3,9,10,16,17,23,24-octaneopentoxypthalocyanine; 2,3,9,10,16,17,23,24-octaneopentoxypthalocyanine nickel(II); N-methylation

INTRODUCTION

The existence of N-substituted porphyrins, both as natural products [1] and obtained through synthesis [1–5], has been known for some time. Attempts to prepare N-alkylated phthalocyanines as early as Linstead's time [6] failed and produced only metal-free phthalocyanine (Pc). For example, dilithium phthalocyanine (**1**) on attempted methylation with iodomethane in methanol gave only metal-free phthalocyanine (**2a**) and none of the desired *N,N*-dimethylphthalocyanine (**2b**) or *N*-methylphthalocyanine (**2c**) (Scheme 1). Perhaps this early failure and the recognition that phthalocyanines (Pcs) are very much more planar than porphyrins, show less tendency towards deformation and have a smaller central cavity than porphyrins have inhibited further research in this area. Despite this, internal N-alkylation of Pcs would be desirable, if possible, as it would provide a means of preventing aggregation in metal-free Pcs, a goal mainly achieved in metallated phthalocyanines containing axial ligands [7, 8].

In some early experiments we repeated Linstead's work but used aprotic solvents such as tetrahydrofuran (THF) to carry out the alkylations. In all cases only metal-free non-alkylated Pcs were recovered. We reasoned that the electron charge on the internal nitrogen of the unsubstituted lithiated phthalocyanine (**1**) was too delocalized to act as an effective nucleophile in alkylation reactions. An effective strategy would entail a method to increase the electron density on the internal nitrogens of the phthalocyanine. Hence we believed

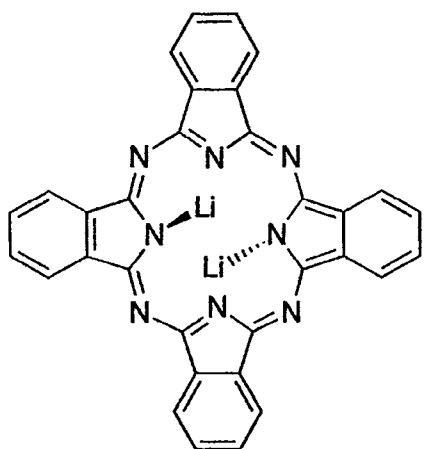
that a dilithium phthalocyanine containing electron-donating groups would be more effective in undergoing internal N-alkylation. The neopentoxo group is an ideal electron-donating substituent for increasing the solubility of the phthalocyanines and has been widely used in our group [9–11]. Phthalocyanines containing eight symmetrically disposed neopentoxo groups about a phthalocyanine ring have not been previously prepared and became the first necessary step in the ultimate N-methylation experiments.

RESULTS AND DISCUSSION

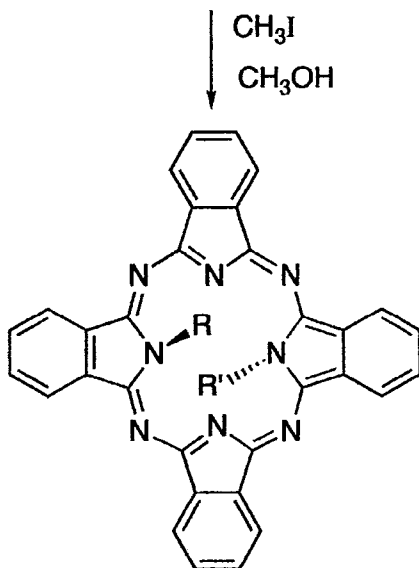
Dialkoxypthalonitriles have been prepared from catechol before by the following route [11–14]. Thus treatment of catechol (**3**) in hexamethylphosphoramide (HMPA) with KOH, Aliquat 336 and neopentyl iodide (**4a**) or neopentyl tosylate (**4b**) at 90 °C for 4–6 days gave 1,2-dineopentoxybenzene (**5**) in 70% and 91% yields respectively. Bromination of **5** with bromine in acetic acid produced the desired dibromo derivative 1,2-dibromo-4,5-dineopentoxybenzene (**6**) in 87% yield. Conversion of **6** to the dinitrile with CuCN in *N,N*-dimethylformamide (DMF) gave 4,5-dineopentoxypthalonitrile (**7**) in 61% yield (Scheme 2). Heating **7** with NiCl₂ in 2-*N,N*-dimethylaminoethanol (DMAE) readily yielded 2,3,9,10,16,17,23,24-octaneopentoxypthalocyanine nickel(II) (**8**) in 28% yield. On the other hand, conversion of **7** with lithium 1-pentanol in 1-pentanol gave, upon acidic work-up, the metal-free **9**.

Since Linstead had already tried to methylate directly in a protic solvent, we decided to first treat metal-free **9** with molten lithium to afford 2,3,9,10,16,17,23,24-octaneopentoxypthalocyanine dilithium (**10**) in the aprotic solvent tetrahydrofuran. We were hopeful that subsequent methylation of the electron-rich **10** would provide a desired *N,N*-

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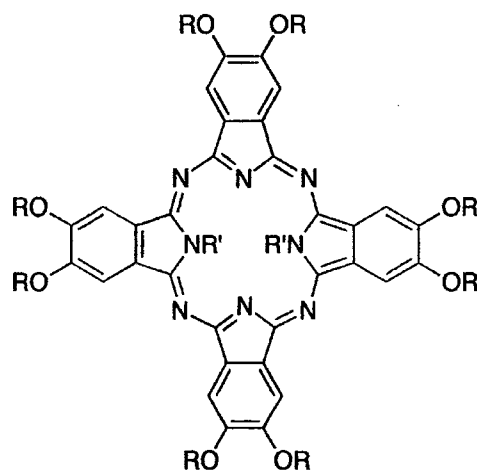
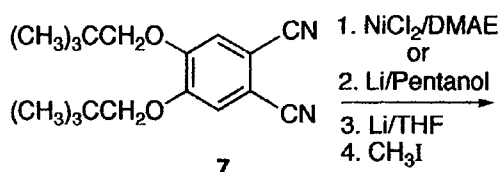
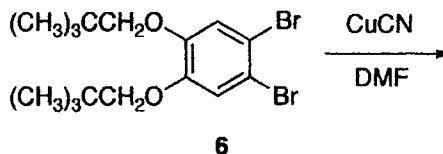
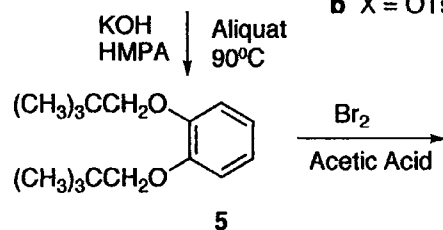
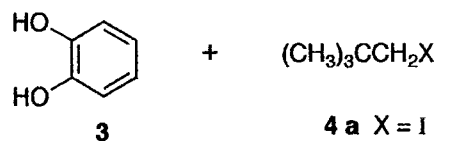
1



- 2 a R = R' = H
 b R = R' = CH₃
 c R = CH₃, R' = H

Scheme 1.

dimethylphthalocyanine such as 29,31-dimethyl-2,3,9,10,16,17,23,24-octaneopentoxypthalocyanine (**11**) (Scheme 2). We also hypothesized that if an N-methylated phthalocyanine were to form, then the liberated iodide ion would be a good nucleophile which would cause the reverse reaction in an S_N2 type reaction to regenerate the original lithium Pc. To prevent this, we used methyl tosylate as the alkylating agent, since the tosyl anion that is formed would be a poor nucleophile. In the event, treatment of **10** with either methyl tosylate or iodomethane in THF resulted in a change in the UV-vis spectrum of the resulting solution, reminiscent in fact of peripheral *N*-protonated phthalocyanines [15, 16]. When this solution was quenched with water, a product was

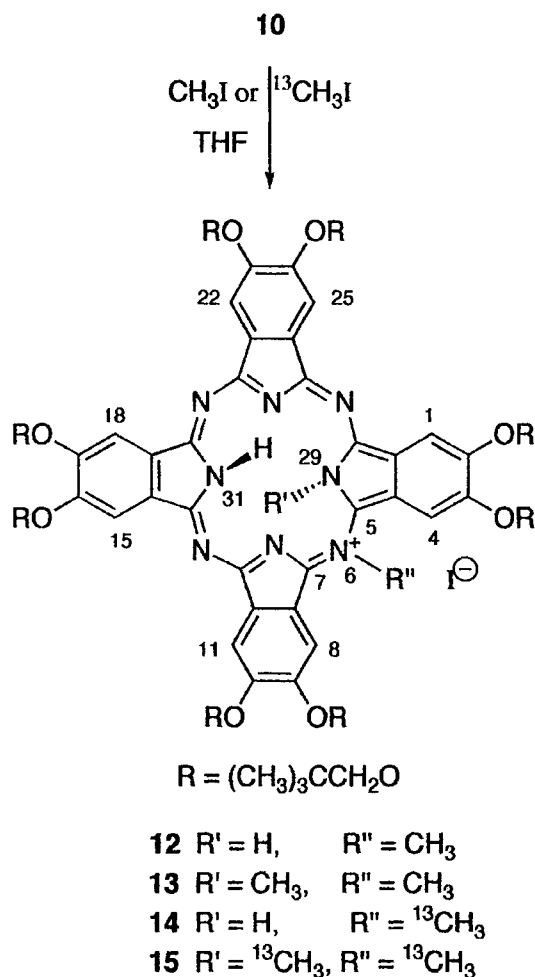


R = (CH₃)₃CCH₂O

- 8 R' = Ni
 9 R' = H
 10 R' = Li
 11 R' = CH₃

Scheme 2.

isolated which, on purification by column chromatography, proved to be identical to non-methylated, metal-free **9**. Control experiments showed that quenching with water resulted in a solution having a UV-vis spectrum identical with **9**. Thus it appeared that a reaction occurred in solution which gave a product which was moisture-sensitive and regenerated the metal-free **9**. These initial experiments convinced us that studies directed towards N-methylated



Scheme 3.

phthalocyanines should be performed under anhydrous conditions in aprotic solvents.

Finally, treatment of **10** with CH_3I in refluxing THF for 8 h resulted in a reaction as indicated by a change in the UV-vis spectrum of the solution. Upon cooling, a green precipitate appeared. This precipitate could be filtered under dry argon and its FAB mass spectrum obtained immediately. FAB mass spectral analysis using the aprotic *o*-nitrophenyl octyl ether as solvent exhibits a strong molecular ion cluster at 1217 amu, which would be typical of an N-methylated phthalocyanine. There appeared to be a small additional peak at 1232 amu indicative of an *N,N*-dimethylphthalocyanine. The sensitive nature of the products precluded further purification at this stage, but it is suggested that the major product is in fact the peripheral N-methylated phthalocyanine 6-methyl-2,3,9,10,16,17,23,24-octaneopentoxophthalocyanine iodide (**12**), while a minor product is 6,29-dimethyl-2,3,9,10,16,17,23,24-octaneopentoxophthalocyanine iodide (**13**) (Scheme 3). It should be noted that this unique peripheral N-methylation is different from the known N-methylation of pyridino moieties in tetraazaphthalocyanines (tetrapyridinoporphyrazines) [17–19]. The fact that the products precipitated from THF at room temperature indicated salt formation as the parent compound **9**, and a presumed internal N-alkylated product

such as **11** would be expected to be very soluble in THF. The UV-vis data on the crude mixture (Fig. 1) are similar to those for N-protonated phthalocyanines [15, 16] and are consistent with structures **12** and **13**. Mass spectral analysis of the presumed mixture of **12** and **13** did not exhibit any peaks consistent with dipositive species (~ 609 amu) and therefore we believe that only mono N-peripheral alkylation has occurred. Although attempts were made to obtain NMR spectra of the crude mixture of **12** and **13**, even under conditions where the mixture was filtered and partially dissolved in $\text{THF-}d_8$, the insolubility and sensitivity to moisture prevented the acquisition of adequate data. Thus in the end the very simple NMR spectrum of **9** did not aid in the final characterization of **12** and **13**. Since the FAB mass spectral data were obtainable, we repeated the methylation using iodomethane- ^{13}C . Thus methylation of **10** with $^{13}\text{CH}_3\text{I}$ gave precipitates showing molecular ion clusters centered at 1219 and 1234 amu, consistent with the N-methylated phthalocyanines **14** and **15** containing the heavier isotope (Fig. 2). Another possibility for the structures of the dimethylated phthalocyanines **13** and **15** is for peripheral dimethylation to have occurred and internal proton removal to give a dication monoanion zwitterion species. We were concerned that the molecular ion cluster at 1217 amu might be simply some unreacted dilithium phthalocyanine **10** or its $\text{M}^+ + 1$ peak, but all attempts to obtain a FAB mass spectrum of **10** failed and the increased amu of the products obtained using the $^{13}\text{CH}_3\text{I}$ obviates this possibility. Finally, since methylation occurred most likely at a peripheral nitrogen, we were curious as to whether we could effect N-peripheral methylation using metal-free **9** rather than the dilithium **10**. In the event, no reaction took place with **9** and CH_3I under identical conditions as before. Thus the increased electron density of the dilithium **10** is perhaps essential for possible N-alkylation, even of the peripheral nitrogen.

CONCLUSION

Attempts to prepare an internal N-methylated phthalocyanine led most likely to previously unknown peripherally substituted N-methylated phthalocyanines. There was some indication by mass spectral data that exclusive internal N-methylation might be possible if phthalocyanine systems could be designed to block peripheral N-alkylation. These studies provide some experience that, although peripheral N-alkylation may become more routine, further experiments must be introduced to definitively demonstrate internal N-alkylation.

EXPERIMENTAL

Inert atmosphere conditions were maintained using Praxair high-purity argon. Magnetic stirring methods were utilized during reaction processes. Flash chromatography was performed using silica gel of particle size 40–63 μm . Melting points (m.p.) were determined using a Kofler hot stage or a Fisher Johns melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectroscopy for proton and carbon was performed using a Bruker ARX 400 high-field Fourier transform instrument at room temperature, unless noted otherwise. Chemical shifts are

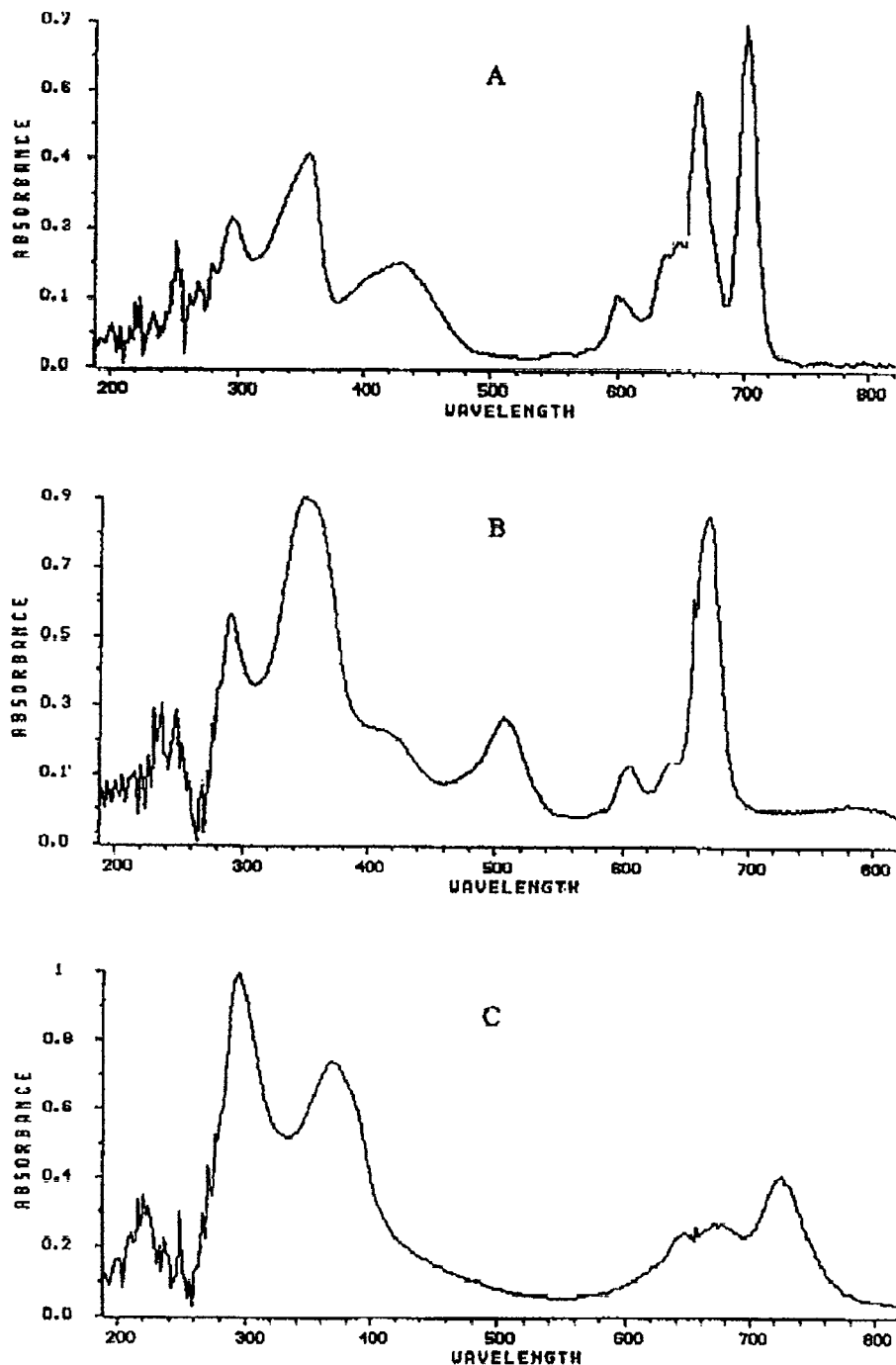


Fig. 1. UV-vis spectra of 9 (A), 10 (B) and 12 + 13 (C) (identical for 14 + 15).

reported in parts per million (δ). The splitting patterns of proton resonances are described as singlets (s), doublets (d) or triplets (t). Coupling constants are reported in hertz for signals. Proton-decoupled chemical shifts are reported for the ^{13}C NMR resonances. Infrared (IR) spectra were recorded on a Unicam Mattson 3000 FT-IR spectrometer using KBr discs for solid samples and NaCl discs for liquid samples. Ultraviolet-visible (UV-vis) spectra were recorded

on a Hewlett-Packard HP8451A diode array spectrophotometer. Mass spectra (MS) were recorded at 70 eV on a Kratos Profile Mass Spectrometer in the EI mode for lower-molecular-weight molecules and in the FAB mode for higher-molecular-weight molecules. Microanalyses were performed by Guelph Chemical Laboratory Ltd, Guelph, Ontario.

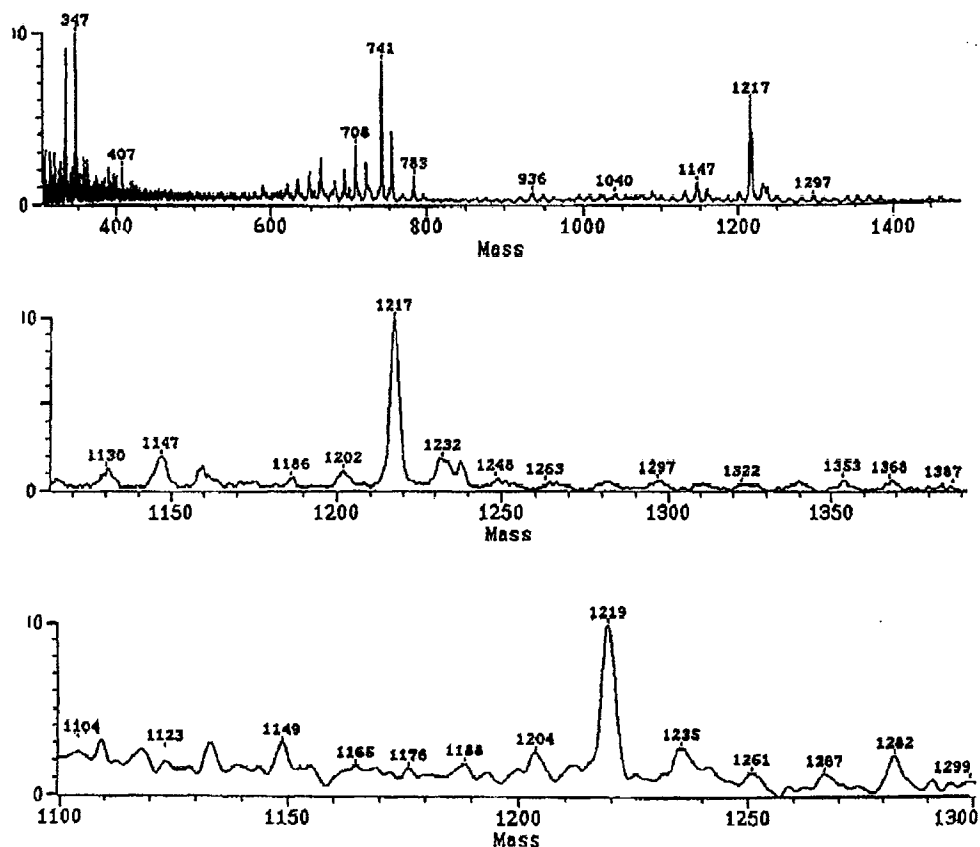


Fig. 2. FAB mass spectra of 12 + 13 (full mass range) (top), 12 + 13 (high mass range) (middle) and 14 + 15 (high mass range) (bottom).

Neopentyl Tosylate (4b)

Compound **4b**, m.p. 44–45°C, was synthesized according to a known procedure [20, 21].

1,2-Dineopentoxybenzene (5)

To 15.5 mL of HMPA were added 2.7 g (41 mmol) of KOH, 2.3 g (21 mmol) of catechol, 10.0 g (41 mmol) of neopentyl tosylate and 0.1 mL of Aliquat 336. This mixture was stirred under an argon atmosphere while being heated at 90°C for 6 days. After this time the reaction mixture was cooled to room temperature and poured onto 100 mL of water. The mixture was extracted using 3 × 100 mL portions of ether. The combined ether extracts were washed with 100 mL of water followed by 100 mL of brine and dried over MgSO₄. The ether was removed under vacuum. Chromatography on a flash silica gel column using 95% hexane and 5% ether as the eluting solvents gave the product as a clear, colourless liquid in 91% yield: ¹H NMR (CDCl₃) δ 6.95 (s, 4H), 3.71 (s, 4H), 1.17 (s, 18H); ¹³C NMR (CDCl₃) δ 149.8, 120.8, 113.5, 78.8, 26.8, 23.2; IR (KBr) 3038, 1227 cm⁻¹; MS *m/z* (relative intensity) 250 (M⁺, 80), 180 (62), 110 (100), 71 (57). Anal. calc. for C₁₆H₂₆O₂: C, 76.75; H, 10.45. Found: C, 76.73; H, 10.87.

1,2-Dineopentoxybenzene (5) (Alternative Method)

To 2 mL of HMPA were added 0.17 g (2.5 mmol) of KOH, 0.28 g (2.5 mmol) of catechol, 0.67 mL (5.0 mmol) of neopentyl iodide and 0.1 mL of Aliquat 336. This mixture was stirred under an argon atmosphere while being heated at 90°C for 4 days and then worked up as above. Chromatography on a flash silica gel column using 95% hexane and 5% ether as the eluting solvents gave the product as a clear, colourless liquid in 64% (0.4 g) yield.

1,2-Dibromo-4,5-dineopentoxybenzene (6)

A stirred solution containing 1.0 g (4.0 mmol) of 1,2-dineopentoxybenzene in 1.6 mL of acetic acid was cooled to 5°C. To this solution, 0.4 mL (8.0 mmol) of bromine dissolved in 1 mL of acetic acid was added dropwise over a period of 1 h. Bromination was induced by the addition of a crystal of iodine. After the addition of bromine was complete, the mixture was allowed to stir for an additional 20 min in the ice-water bath. After this time the ice bath was removed and stirring was continued for another 1 h as the mixture warmed up to room temperature. The reaction mixture was partitioned using 100 mL of 1% NaHSO₃ solution and 100 mL of ether. Successive washings of the ether layer were carried out with 100 mL portions of 1% NaHSO₃ solution until the water layer was colourless. The

ether layer was further washed with 100 mL of 5% NaOH solution, 100 mL of H₂O and 100 mL of brine and then dried over MgSO₄. The solvent was removed under vacuum and the product was obtained as a clear, colourless liquid which crystallized to a white solid in 87% yield: m.p. 48–49°C; ¹H NMR (CDCl₃) δ 7.03 (s, 2H), 3.57 (s, 4H), 1.05 (s, 18H); ¹³C NMR (CDCl₃) δ 149.5, 117.4, 114.3, 79.0, 32.1, 26.6; IR (KBr) 650, 1250 cm⁻¹; MS *m/z* (relative intensity) 408 (M⁺, 10), 268 (100), 71 (34). Anal. calc. for C₁₆H₂₄Br₂O₂: C, 47.08; H, 5.93. Found: C, 47.17; H, 6.13.

4,5-Dineopentoxyphthalonitrile (7)

A stirred mixture containing 0.50 g (1.7 mmol) of 1,2-dibromo-4,5-dineopentoxybenzene and 0.45 g (5.0 mmol) of CuCN in 6.8 mL of DMF was refluxed for 5 h under an argon atmosphere. After this time the reaction mixture was cooled to room temperature and 17 mL of concentrated ammonium hydroxide solution was added. The suspension was allowed to stir for an additional 15 min and then the precipitate was filtered and washed with water until the filtrate was neutral. Chromatography on a flash silica gel column using 3% ether and 97% toluene as the eluting solvents gave the product as a white solid in 61% (0.30 g) yield: m.p. 201–202°C; ¹H NMR (CDCl₃) δ 7.08 (s, 2H), 3.66 (s, 4H), 1.07 (s, 18H); ¹³C NMR (CDCl₃) δ 152.8, 116.1, 115.3, 108.2, 78.9, 32.1, 26.4; IR (KBr) 2229, 1230 cm⁻¹; MS *m/z* (relative intensity) 300 (M⁺, 87), 71 (57). Anal. calc. for C₁₈H₂₄N₂O₂: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.24; H, 7.88; N, 9.39.

2,3,9,10,16,17,23,24-Octaneopentoxypthalocyanine Nickel (8)

A mixture containing 0.200 g (0.667 mmol) of 4,5-dineopentoxypthalonitrile and 0.053 g (0.111 mmol) of NiCl₂ in 6.6 mL of DMAE was heated to reflux for 48 h. After cooling to room temperature, the reaction mixture was transferred to test tubes. Precipitation of the nickel Pc was carried out by adding a 90% methanol and 10% water solution. The precipitate was collected by centrifugation and washed twice with methanol. Further purification of the phthalocyanine was carried out by flash silica gel column chromatography using 20% hexane and 80% toluene as the eluting solvents. Final purification of the nickel Pc involved precipitation using toluene/hexane. The desired nickel Pc was obtained as a green solid in 28% (59 mg) yield: m.p. > 300°C; ¹H NMR (benzene-*d*₆) δ 8.93 (s, 8H), 3.88 (s, 16H), 1.26 (s, 72H); UV-vis λ_{max} (toluene) (log ε) 672 (5.17), 640 (4.52), 604 (4.46), 416 (4.37), 336 (4.59), 314 (4.73), 288 (4.78) nm; FABMS 1260 (M+1). Anal. calc. for C₇₂H₉₆N₈O₈Ni: C, 68.62; H, 7.68; N, 8.89. Found: C, 69.09; H, 8.08; N, 8.56.

2,3,9,10,16,17,23,24-Octaneopentoxypthalocyanine (9)

Under an argon atmosphere, 0.0115 g (1.665 mmol) of lithium metal was added to 1 mL of 1-pentanol and heated to 80°C until all the lithium had reacted. To this alkoxide solution, 0.100 g (0.333 mmol) of 4,5-dineopentoxypthalonitrile was added as the temperature was raised to 100°C. The reaction mixture was stirred overnight at this temperature. After this time the resulting dark green mixture was cooled to room temperature and transferred to test tubes.

Precipitation of the metal-free Pc was carried out by adding a 10% water and 90% ethanol solution along with a few drops of concentrated HCl solution to the test tubes. The precipitate was collected by centrifugation and washed twice with methanol. The Pc was further purified by silica gel column chromatography using 5% hexane and 95% toluene as the eluting solvents. Final purification involved the reprecipitation of the Pc from toluene and ethanol. The desired Pc 9 (22 mg) was obtained as a green solid in 22% yield: m.p. >300°C; ¹H NMR (benzene-*d*₆, 300 K) δ 9.10 (s, 8H), 3.88 (s, 16H), 1.24 (s, 72H), -0.71 (s, 2H); UV-vis λ_{max} (toluene) (log ε) 702 (4.94), 662 (4.87), 648 (4.55), 636 (4.50), 598 (4.29), 432 (4.46), 354 (4.78), 294 (4.61) nm; FABMS 1202 (M⁺); Anal. calc. for C₇₂H₉₈N₈O₈: C, 71.85; H, 8.21; N, 9.31. Found: C, 70.85; H, 8.28; N, 8.70.

2,3,9,10,16,17,23,24-Octaneopentoxypthalocyanine Dilithium (10)

In a separate flask a small piece of lithium wire (2–3 mg) was washed in dry THF which was decanted and dried under argon. The lithium was melted with hot air to give a drop of molten lithium freed from adhering impurities. This drop was added to a solution of 5 mg (4.2 × 10⁻³ mmol) of 2,3,9,10,16,17,23,24-octaneopentoxypthalocyanine (9) in 3 mL of dry THF. The reaction mixture was heated at 70°C for 8 h under dry argon. The UV-vis spectrum is shown in Fig. 1.

Methylation of 10 with CH₃I or ¹³CH₃I

Dilithium 10 was filtered under argon and transferred to a small pressure ampoule containing 1 mL of dry CH₃I or ¹³CH₃I. The ampoule was sealed and heated at 90°C for 6 h, during which time the dark green solution was homogeneous. The ampoule was allowed to cool to room temperature, during which time a precipitate formed. The precipitates, suggested to be 12 + 13 or 14 + 15, were filtered under dry argon and their UV-vis spectra (THF) (Fig. 1) and FAB mass spectra (*o*-nitrophenyl octyl ether) (Fig. 2) were taken.

Acknowledgements

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