The Synthesis of Pure 1,11,15,25-Tetrasubstitutedphthalocyanines as Single Isomers Using Bisphthalonitriles

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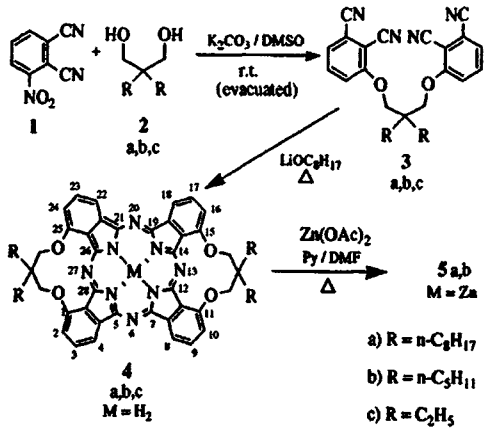
Abstract: Bisphthalonitriles linked by 2,2-disubstitutedpropan-1,3-diol precursors gave pure 1,11,15,25-substituted isomers of mononuclear phthalocyanine derivatives upon homocyclization. Reasonable yields of these phthalocyanines could be obtained with limited polymeric side-products utilizing modified cyclization methods. The ^{1}H NMR spectrum of these phthalocyanines exhibited the discrete doublet-triplet-doublet proton signals expected of a pure isomer.

The cyclotetramerization reaction of monosubstituted phthalonitriles yield phthalocyanine (Pc) derivatives as mixtures of positional isomers.[1,2] Most 3- and 4-substituted phthalonitriles give statistical 1:2:4:1 mixtures of these isomers[1], although a few exceptions exist in which a 2,9,16,23-isomer[3] and a 2,10,17,22-isomer[4] were prepared. Phthalonitriles substituted at the 3-position by large bulky groups can skew the isomer distribution favouring one isomer, the 1,8,15,22-isomer, as a result of steric interactions during the cyclization process.[5] Nevertheless, Pc yields are usually low and purification of the pure pigment isomers impaired due to low solubility of these symmetrical Pcs arising from molecular aggregation. The isolation of these type of pure Pc isomers from a statistical mixture has only recently been achieved for a specific substituent using high performance liquid chromatography (HPLC)[6], and hence direct methods towards the synthesis of a single pure isomer is a desired goal.

Bisphthalonitriles have traditionally been used in preparing binuclear and polynuclear Pcs. Our laboratory has prepared a number of binuclear Pcs containing a wide variety of bridging groups *via* a mixed condensation method involving the cyclization of a bisphthalonitrile with monosubstituted phthalonitriles.[1,7] Others have successfully homocyclized bisphthalonitriles obtaining polymeric Pc derivatives.[8] Our current research has used appropriately linked bisphthalonitriles and modified the cyclization conditions allowing for the preparation of structurally pure mononuclear Pc isomers in reasonable yields. Since some aluminum and zinc metallophthalocyanine (MPc) derivatives have exhibited cytotoxic activity in photodynamic therapy of cancer (PDT)[9], it was of interest to prepare a pure Pc isomer so that PDT activity could be investigated utilizing a pure Pc isomer rather than mixtures. We believe that such investigations are important if Pcs are to be used as photosensitizing drugs.[10]

Nucleophilic substitution of 3-nitrophthalonitrile 1 by 2,2-disubstituted-propan-1,3-diol linking groups 2a-c permitted us to architecturally constrain the subsequent homocyclization of bisphthalonitriles 3a-c[11]. Recently, bisphthalonitriles containing insufficiently constrained bridging groups gave tetrasubstituted phthalocyanines as mixtures of isomers.[12] Our choice of 2,2-disubstitutedpropan-1,3-diols as linking group precursors not only allowed us to utilize commercially available materials, but also custom-made diols obtained from reduction of disubstituted malonic esters. Molecular modeling and *in computo* investigations suggested that the five atom linking group provided by these diols would permit the cyclization of two bisphthalonitriles to a mononuclear phthalocyanine. The short length of the link would also preclude isomer mixtures. It was found that the resulting "*bis*-side-strapped" mononuclear Pc products 4a-c existed as pure isomers.[13]



It is convenient to synthesize metal free Pcs from which a variety of metallophthalocyanine (MPc) derivatives can be prepared. Zinc MPc derivatives 5a,b were readily prepared[14] from the corresponding metal-free Pcs 4a,b. Cyclization of the bisphthalonitriles 3a-c by the 1,3-diiminoisoindole method[1] or via Linstead's method[15] using lithium in amyl alcohol resulted mainly in polymerization even under high dilution conditions. It was found, however, that a high dilution addition of the bisphthalonitrile at a high temperature and short reaction time would yield desired mononuclear Pcs without significant amounts of polymerization products utilizing 1-octanol and the corresponding lithium octoxide at reflux (196°C) for 10 minutes.

Bulky substituents on the linking groups as in 4a,b resulted in enhanced Pc solubility in tetrahydrofuran (THF) and aromatic solvents, ease of purification and higher yields. The isolation of pure Pc isomers is evident by their ^{1}H NMR spectra since Pc macrocycle aromatic protons are observed as discreet doublet-triplet-doublet signals[4,13] in contrast to complex multiplet signals which arise from mixtures of positional isomers.

In conclusion, we have demonstrated that appropriately linked bisphthalonitriles are feasible precursors in preparing structurally pure mononuclear Pc derivatives. Modification of existing cyclization methods by using high dilution, high temperatures and short reaction times have allowed us to synthesize pure mononuclear Pc isomers in reasonable yields.

References and Notes

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(11) **3c**: mp 163-165 °C. EI-MS *m/z* (%): 552 (M+, 4.65), 523 (4.55), 509 (2.8), 495 (2.35), 469 (3.45), 409 (55), 145 (22), 43 (100). ^{1}HMR CD_3CN δ ppm: 7.76 (t, 2H, J=8.2Hz), 7.48 (m, 4H), 4.17 (s, 4H), 1.59 (m, 4H), 1.31 (m, 24H), 0.89 (t, 6H, J=6.5Hz). Anal. calcd. for $C_{30}H_{40}N_4O_2$: C 75.98, H 7.97, N 10.14; Found: C 75.92, H 8.57, N 10.27. **3h**: mp 173-174 °C. EI-MS *m/z* (%): 469 (M+1, 17), 368 (42), 325 (94), 144 (100). ^{1}HMR CD_3CN δ ppm: 7.71 (t, 2H, J=7.8Hz), 7.45 (m, 4H), 4.13 (s, 4H), 1.54 (m, 4H), 1.3 (m, 12H), 0.86 (t, 6H, J=6.7Hz). Anal. calcd. for $C_{30}H_{40}N_4O_2$: C 74.36, H 6.84, N 11.96; Found: C 74.20, H 6.93, N 12.00. **3c**: mp 216-218 °C. EI-MS *m/z* (%): 384 (M+, 3), 259 (4), 241 (58), 145 (38), 97 (80), 55 (100). ^{1}HMR CD_3CN δ ppm: 7.67 (t, 2H, J=8.1Hz), 7.35 (d, 2H, J=7.5Hz), 7.34 (d, 2H, J=8.7Hz), 4.11 (s, 4H), 1.63 (q, 4H, J=15, 7.5Hz), 0.94 (t, 6H, J=7.5Hz). Anal. calcd. for $C_{30}H_{40}O_2N_4$: C 71.88 H 5.21 N 14.58; Found: C 72.24 H 4.78 N 14.99.

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(13) **4a**: Yield 21%. UV-VIS (THF) λ_{max} nm (log ϵ): 352.5 (4.79), 613 (4.58), 646 (4.73), 675 (5.12), 709 (5.17). EI-MS *m/z* (%): 1107 (M+1, 32), 1077 (5), 886 (8), 660 (18), 556 (100). ^{1}HMR C_5D_5 δ ppm: 7.92 (d, 4H, J=6.9Hz), 7.25 (t, 4H, J=7Hz), 6.88 (d, 4H, J=7.2Hz), 4.44 (s, 8H), 1.58-1.88 (m, 64H), 1.15 (t, 12H, J=6.8Hz), -5.99 (s,2H). Anal. calcd. for $C_{70}H_{98}N_8O_4$: C 75.91, H 8.19, N 10.12; Found: C 75.58, H 8.52, N 9.88. **4b**: Yield 16%. UV-VIS (THF) λ_{max} nm (log ϵ): 352.5 (4.76), 614 (4.53), 645 (4.70), 674 (5.10), 709 (5.14). FAB-MS *m/z* (%): 940 (M+, 2), 869 (1.2), 759 (1), 614 (1.5), 460 (5), 307 (34), 154 (100). ^{1}HMR C_5D_5 δ ppm: 8.87 (d, 4H, J=7.7Hz), 8.28 (t, 4H, J=7.9Hz), 7.75 (d, 4H, J=8.83Hz), 4.83 (s, 8H), 1.90 (m, 8H), 1.54 (m, 8h), 1.32 (m, 16H), 0.89 (m, 12H), -4.5 (s, 2H) . Anal. calcd. for $C_{58}H_{66}N_8O_4$: C 76.05 H 8.82 N 10.14; Found: C 75.92 H 8.52 N 10.27. **4c**: yield 7%. UV-Vis (benzene) λ_{max} nm (log ϵ): 352 (4.75), 614 (4.52), 646 (4.70), 672 (5.11), 708 (5.14). EI-MS *m/z* (%): 770 (M+, 35), 211 (10), 145 (31), 55 (100). HRMS required for $C_{46}H_{42}N_8O_4$: 770.33290; Found: 770.33220. ^{1}HMR CF_3COOD δ ppm: 9.05 (d, 4H, J=7.6Hz), 8.49 (t, 4H, J=7.9Hz), 8.03 (d, 4H, J=8.1Hz), 5.10 (s, 8H), 2.13 (q, 8H, J=7Hz), 1.25 (t, 12H, J=7.2Hz).

(14) **8a**: UV-VIS (THF) λ_{max} nm (log ϵ): 356 (4.63), 480 (3.11), 617 (4.49), 655 (4.46), 685.5 (5.17). FAB-MS *m/z* (%): 1171 (M+1, 100), 905 (34), 791 (36), 641 (85), 626 (23), 612 (66). Anal. calcd. for $C_{70}H_{98}N_8O_4Zn$: C 71.81, H 7.58, N 9.57; Found: C 71.53, H 7.11, N 9.93. **8b**: UV-VIS (THF) λ_{max} nm (log ϵ): 356 (4.74), 617 (4.62), 655 (4.56), 686 (5.42). FAB-MS *m/z* (%): 1002 (M+1, 100), 932 (10), 821 (18), 640 (29), 634 (27), 610 (23). Anal. calcd. for $C_{58}H_{66}N_8O_4Zn$: C 69.46, H 6.43, N 11.18; Found: C 69.51, H 6.50, N 10.92.

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