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Polysubstituted phthalocyanines by nucleophilic substitution reactions on hexadecafluorophthalocyanines

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Nucleophilic substitution reactions on hexadecafluorophthalocyaninato zinc(II) with a variety of O, N, C, and S nucleophiles led to narrowly defined mixtures of polysubstituted phthalocyanines, some of which are completely inaccessible by classical phthalonitrile condensation reactions.

The use of the phthalocyanine (Pc) moiety in materials having technological applications has been demonstrated over the years.[1] Most of the current research in phthalocyanine chemistry emphasizes the usefulness of Pc materials that stems from their characteristic properties.[2] Nevertheless in the most recently discovered applications of economic relevance[1,2] good solubility of the Pc material is a necessary requirement.

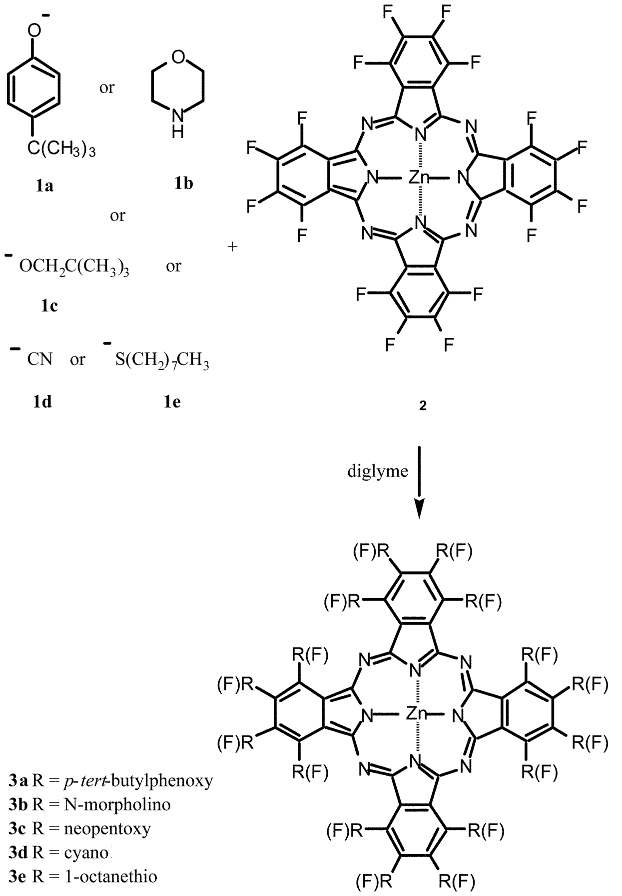
So far, two main strategies have been followed to obtain novel mononuclear Pc compounds with increased solublity. In the first, condensation of a substituted phthalonitrile precursor leads to a Pc product functionalized on the peripheral and/or non-peripheral positions around the macrocycle. Another strategy is the possibility of starting with a pre-formed easily prepared substituted Pc and functionalizing the substituents afterwards.

For metallophthalocyanines (MPcs) with central elements with valence states higher than two, axial substitution with bulky ligands has been used as well, as a method to obtain a more soluble product.[3] From our experience, starting from a preformed Pc precursor would be more advantageous since suitable phthalonitrile precursors are not always readily available and in other instances do not always yield Pc compounds.[4]

Only two previous examples of solubilizing Pcs by substitution of the benzo sites have been found in the patent literature. In one report a rather unreactive starting material was used and therefore quite stringent reaction conditions were used.[5] In the second report, hexadecasubstituted Pcs[6] were prepared by nucleophilic substitution of hexadecachlorophthalocyanines.[7] Here the complete lack of solubility of the Pc precursor makes nucleophilic substitution reactions unreliable. Since hexadecafluorophthalocyanines are readily made and even commercially available we conceived of a more direct way to obtain new soluble Pcs by nucleophilic substitution reactions as described in Scheme 1.

In a general synthesis twenty equivalents per fluoro group of the nucleophile precursors **1a–e** reacted with an equimolar amount of n-butyllithium under an argon atmosphere in diglyme at a suitable temperature. Then one equiv. of hexadecafluorophthalocyaninato zinc (**2**) is added and the reaction mixture is heated to around 100 °C for 8 h. In an alternative method, when the nucleophile by itself is reactive enough, the activation step using n-butyllithium can be eliminated and the Pc starting material can react with a solution of this nucleophile (**1b**) alone, either neat or in an appropriate solvent. In another synthesis, when KCN (**1d**) is used as the nucleophile, a cyclic polyether, *e.g.* 18-crown-6, can be used to activate the nucleophilic species as a naked ion. This reaction allowed us to obtain a mixture of tetradeca- and hexadecacyano phthalocyanines as identified by MALDI-TOF analysis. Although the yield of this particular reaction was low, the alternative approach starting from a hexacyanobenzene derivative has never been accomplished. Reactions of **1a–e** with **2** gave phthalocyanines **3a–e** in which, on average, 12, 8, 12, 14, and 16 fluoro groups had been replaced, respectively.

For all the examples above, the benefit of using a relatively soluble starting Pc material (**2**) became apparent. Relatively low temperatures between 65–120 °C could be used depending on the degree of substitution expected and on the nature of the solvent. Former investigations using a pre-formed Pc precursor had a more limited scope due to the extremely low solubility of the starting material (MPc or $Cl_{16}MPc$). In addition, it has been established that fluoroaryl compounds undergo nucleophilic substitution with different nucleophiles at an increased rate in the order of 10^2 to 10^3 times faster than other halogen analogs.[8] Therefore the use of hexadecafluorophthalocyanines as starting materials seemed a good choice for the substitution reaction using different nucleophiles. In this respect, the fact that a broad range of nucleophilic reagents with O, N, C and S atoms could be used was, by itself an attractive feature to follow this new approach. Many Pc compounds that cannot be prepared from a phthalonitrile or other known precursors could be obtained.[4] Moreover, for one nucleophile that works well with this new method a series of compounds with



3a R = *p-tert*-butylphenoxy
3b R = N-morpholino
3c R = neopentoxy
3d R = cyano
3e R = 1-octanethio

Scheme 1

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similar structure can be prepared for correlation studies such as the application of ligand electrochemical parameters[9] to the design of new MPcs for a particular technological use. An apparent drawback of this new methodology that is anticipated is that, since there is a possibility of substitution on sixteen different sites on the Pc macrocycle, there is a possibility of obtaining mixtures of products. For nucleophiles having medium steric effects, as many as 12 substituents (**3a,c**), other than fluoro, can be found in the product, but for highly hindered nucleophiles (**3b**) between 8–10 morpholino groups can be identified in the final products. The similarity of physical properties of the products obtained in these mixtures does not allow, at present, for isolation of a single pure compound.

There is some spectroscopic evidence of what seems to be a different pattern of sequential substitution of the Pc precursor compared to that of a phthalonitrile. When tetrafluorophthalonitrile is subjected to a nucleophilic substitution under basic conditions, positions 4 and 5 (that correspond to the peripheral sites on the Pc after condensation) are substituted first.[4] In the case of the hexadecafluorophthalocyanines, the non-peripheral positions appear to be substituted first. This fact was inferred from the observation of the ^{1}H NMR and UV-Vis spectra of **3c** in which twelve fluorine atoms have been substituted by neopentoxy groups. The NMR spectrum shows the singlets expected for the alkoxy $-OCH_2$ protons at 4.85 ppm for the non-peripheral and at 4.30 ppm for the peripheral neopentoxy groups. These assignments are made based on some previous NMR studies of hexadeca- and octaneopentoxy phthalocyanines.[10] The integral ratio of 2 : 1 for non-peripheral *versus* peripheral protons supports the idea of having two substituents on the non-peripheral positions and only one substituent on a peripheral site of each benzo ring of the Pc product. A comparison of the Q-band absorptions in the UV-Vis spectra of different polyneopentoxyphthalocyanine derivatives and that of the tetrafluorododecaneopentoxyphthalocyanine (**3c**) reported here seems to support the idea of the non-peripheral substitution occurring first. The λ_{max} for the latter lies at around 750–752 nm just between the corresponding maxima for a peripheral octaneopentoxyphthalocyanine (λ_{max} = 672 nm) or a non-peripheral octaneopentoxy phthalocyanine (λ_{max} = 748 nm) and that of a hexadecaneopentoxy derivative (λ_{max} = 758 nm).[10]

Fortunately, the distribution of polysubstituted compounds obtained after completion of the reaction is narrow‡. It is important to mention here that for certain technological applications where the solubility is important, the latter fact is beneficial. It is well known that a mixture of different Pc compounds of similar structure is more soluble than a pure Pc material, due to disruption of aggregation phenomena.

MALDI analysis of all the products obtained shows that a mixture of at least three polysubstituted products is obtained after the reaction is completed (Fig. 1, for MALDI of **3b**). Most importantly, MALDI-TOF analysis has proven to be indispensable in following the extent of the substitution reactions. The degree of substitution depends markedly on the steric effect of the nucleophile as well as on the nucleophilicity, the temperature and the time required to complete the reaction. For nucleophiles with a low steric effect or high nucleophilic capabilities, the maximum degree of substitution is 16 ($^-$CN and $^-S(CH_2)_7CH_3$) in 6% and 41% yields respectively.

In summary, we have developed a more direct synthetic route to polysubstituted Pc materials of enhanced solubility using as starting material a commercially available pre-formed Pc precursor. Multisubstituted phthalocyanines can be tailor-made, having the appropriate solubility, electrochemical, photochemical and medical parameters necessary for a wide variety of applications.

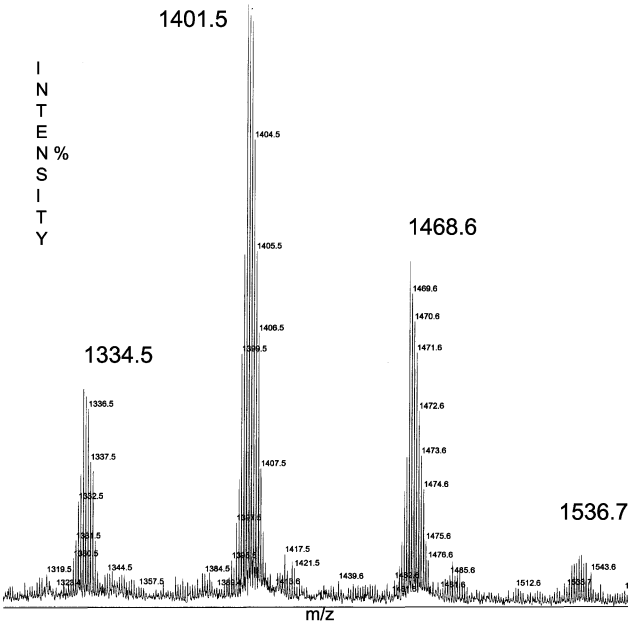

Fig. 1 MALDI of **3b**, having 7–10 morpholino groups.

Notes and references

‡ Synthesis of tetrafluorododecaneopentoxyphthalocyanine zinc is described below. In a 100 mL Schlenk type flask fitted with a condenser, 40 mL of diglyme were placed under an argon atmosphere. Then 811 mg (9.2 mmol) of neopentyl alcohol were introduced. When all alcohol had dissolved, 4.3 mL of 1.6 M n-BuLi in hexane were added. To this 20 mg (0.023 mmol) of F_{16}ZnPc were added and heated to 110–130 °C. After 8 h the crude product was isolated by precipitation into water and subsequent neutralization of the aqueous suspension. The final product was obtained after chromatographic purification using flash silica-gel and a mixture of toluene–ethyl acetate 20 : 1 as eluent to give **3c** in 53% yield based on a dodecasubstituted product; MALDI-MS for $C_{92}H_{132}F_4N_8O_{12}Zn$ (*m/z* intensity, %) (M^+ 1682.0, 100); for $C_{87}H_{121}F_5N_8O_{11}Zn$ (M^+ 1614.9, 37).

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