A convenient synthesis of functionalized tetraphenylchlorins

Laurent Jaquinod, Claude Gros, Richard G. Khoury and Kevin M. Smith*†

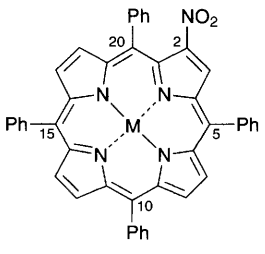
Department of Chemistry, University of California, Davis, CA 95616, USA

Reaction of metallo-2-nitro-5,10,15,20-tetraphenylporphyrins with 'active-methylene' compounds (*e.g.* malonates, malononitriles) in the presence of base gives access to novel cyclopropachlorins or functionalized *trans*-chlorins (both characterized by X-ray crystallography) by way of a sequential Michael addition and rare nucleophilic displacement of a secondary nitro group.

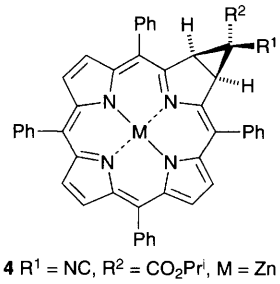
Relatively few methods have been developed which permit generation of *meso*-tetraarylchlorins (*e.g.* 5,10,15,20-tetraphenylchlorin, TPC) from *meso*-tetraphenylporphyrins (TPP) since the diimide reduction introduced in 1969 by Whitlock *et al.*;[1] this method has recently been used by Berenbaum *et al.* to prepare a series of *meso*-tetra(hydroxyphenyl)chlorins which are promising candidates as second generation photodynamic therapy (PDT) sensitizers.[2] Other functionalizations of the TPP macrocycle have involved reactions with carbenes to afford cyclopropyl annulated TPC,[3] and in a series of publications, Crossley and co-workers have stressed that readily accessible 2-nitro-5,10,15,20-tetraphenylporphyrin (2-NO_2TPP) metal complexes **1–3** provide a versatile starting material for functionalization of the porphyrin periphery *via* chlorin intermediates.[4] For example, copper(II) 2-NO_2TPP **2** reacts with sodium methoxide to afford the corresponding 2,2-dimethoxy-3-nitrochlorin *via* a nucleophilic substitution–nucleophilic addition sequence. Denitration yielded the blue–green 2,2-dimethoxychlorin which eliminated methanol to give the corresponding 2-methoxyporphyrin.[5] Conjugate addition of alkyl Grignard reagents to 2-NO_2TPP also yielded unstable chlorins which readily underwent elimination of nitrous acid to yield 2-alkyl-TPPs.[6] 2-Nitroporphyrins were also reduced with $NaBH_4$ to give NO_2-TPCs which were converted into the denitrated chlorin by treatment with tributyltin hydride and AIBN.[7] Fused naphthochlorins have been obtained from the acid-catalysed intramolecular cyclization of Ni^{II} 2-vinyl-TPP.[8] Although recent work has focused on vicinal β,β′-dihydroxylation of TPC and TPP,[9] this approach is hindered by the stoichiometric use of expensive (and toxic) OsO_4, as well as the low reactivity of TPPs.

In the course of our work on the syntheses of pyrroloporphyrins *via* the condensation of nickel(II) or copper(II) 2-NO_2TPP **1–2** with isocyanoacetates,[10] it occurred to us that the conjugate addition of carbon-centred nucleophiles to nitroalkenes should represent a versatile method for new C–C bond formation that might be used to advantage in the preparation of novel chlorin and/or cyclopropyl-annulated chlorins for PDT. Indeed, we have already shown[10] that subjecting **3** to the Barton–Zard pyrrole synthesis[11] conditions ($CNCH_2CO_2Et$–THF–Pr^iOH–DBU), affords a new green compound **4** possessing a cyclopropyl-annulated chlorin with an *exo* configuration with regard to the isopropyl ester function. Since it was recently reported that cyclopropanation proceeds when α-nitroalkenes react with methyl cyanoacetate and malononitrile,[12] we decided to further extend the use of 2-NO_2TPP to prepare cyclopropylchlorins by reaction of this porphyrin with other stabilized carbanions derived from 'active methylene' compounds.

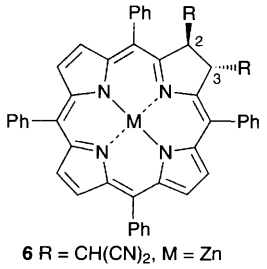
When Ni^{II} 2-NO_2TPP **1** (100 mg scale) was heated with 20 equiv. of dimethyl malonate in the presence of 20 equiv. of NaOMe in refluxing THF–MeOH, the nickel(II) cyclopropanylchlorin **5**‡ was obtained in 12% yield [λ_{max} 416 nm (ε 201,000), 508 (14,000), 516 (13,500), 570 (15,000), 602 (35,500); δ_H ($CDCl_3$) 4.71 (s, 2H), 3.84 (s, Me_{exo}), 2.36 (s, Me_{endo})]. The structure of **5** was confirmed by X-ray crystallography (Fig. 1).§ However, when malononitrile (2 equiv.) was allowed to react with zinc(II) 2-NO_2TPP **3** in refluxing THF–Pr^iOH in the presence of DBU (4 equiv.), quite unexpectedly, the bis(acetonitrile) adduct **6** was obtained in 14% yield [λ_{max}



1 M = Ni
2 M = Cu
3 M = Zn



4 R^1 = NC, R^2 = CO_2Pr^i, M = Zn
5 R^1 = R^2 = CO_2Me, M = Ni



6 R = $CH(CN)_2$, M = Zn
7 R = $CH(CN)_2$, M = 2H
8 R = $CH(CN)_2$, M = Cu
9 R = $CH(CO_2Me)(CN)$, M = Ni
10 R = CH_2CN, M = Ni

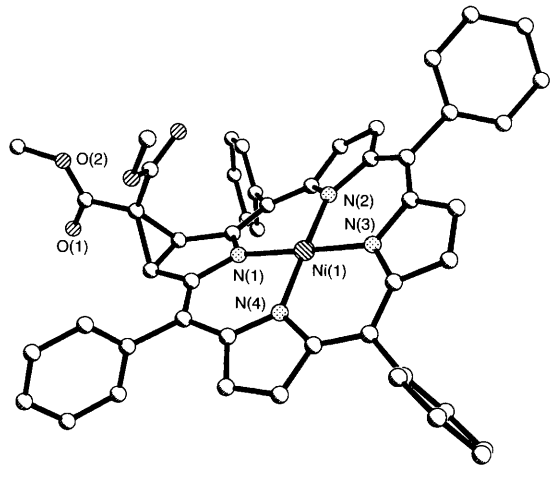


Fig. 1 Molecular structure of **5**. Atomic positions are represented with 50% probability thermal ellipsoids.

414 nm (ε 245,000), 510 (9,500), 582 (15,000), 608 (44,500)]. The overall outcome of the reaction (intermolecular *vs.* intramolecular substitution), was deduced from the ^{1}H NMR spectrum, which featured reduced pyrrolic and acetonitrile hydrogens as two doublets at δ 5.25 and 4.37 (*J* 4.1 Hz, 2H each), respectively. Demetallation in CH_2Cl_2 containing 5% TFA gave the metal free compound **7** [Q band shifted to 642 nm; δ_H −1.87 (s, 2H, NH)]. Similar treatment of Cu^{II} 2-NO_2TPP **2** (400 mg scale) with malononitrile (2 equiv.) yielded only the bis(adduct) **8** (40% yield), shown by X-ray crystallography (Fig. 2) to possess the *trans* arrangement of the two malononitrile moieties on the reduced ring.§ Examination of the crystal packing of compound **8** indicates the presence of a racemic mixture.

Our data suggest a reaction mechanism involving addition of the carbanion at the β-pyrrolic carbon adjacent to that bearing the nitro group, as shown previously by labelling experiments with deuteriated borohydride,[7] leading to a planar nitronate. The nitronate is presumably protonated at the α-carbon from the less crowded face, leading to preferential formation of the *cis*-nitrochlorin (least stable stereoisomer); with trigonal hybridization, the nitro group does not compete sterically leaving prototopic attack as the controlling factor.[13] The nitro group of this intermediate, being secondary and pseudobenzylic, functions as an electrophile to yield the *trans*-chlorin **8** (as a racemic mixture). It is very unusual for a secondary nitro group to serve as an electrophile in a substitution reaction since the reaction of primary and secondary nitroalkanes with base invariably results in the formation of the nitronate anions. Displacement of aliphatic nitro compounds by nucleophiles has mainly been achieved in the presence of palladium(0) phosphine complexes.[14]

Stereochemical control was completely absent upon addition of methyl cyanoacetate (4 equiv.) to **1** (100 mg scale) in refluxing THF–Pr^iOH–DBU. The chlorin, obtained with a 45% yield, was identified as the bis(cyanoacetate) adduct **9** based on its molecular mass peak at *m/z* = 866. The proton NMR spectrum indicated a mixture of four pairs of enantiomers (2,3-pyrrole protons as four independent doublets between δ 5.05 and 5.45). De-methoxycarbonylation of this mixture was smoothly accomplished by heating with NaCl in wet Me_2SO at 140 °C for 15 h, to yield quantitatively **10** as a racemate [λ_{max} 414 nm (ε 152,000), 504 (7,000), 566 (10,500), 608 (30,000)]. The reduced pyrrole and its acetonitrile substituents exhibited an ABX proton system in the NMR [δ_H ($CDCl_3$) 4.57 (dd, X part, J_{A-X} 9.8, J_{B-X} 4.8 Hz, 2H), 2.54 (dd, AB part, J_{A-B} 17.3, J_{B-X} 4.8 Hz, 2H), 2.38 (dd, AB part, J_{A-B} 17.3, J_{A-X} 9.6 Hz, 2H)] indicating that **10** is both chiral and C_2 symmetric. This compound can be conveniently prepared (in 68% yield) by carrying out a one-pot sequential Michael addition, nitro substitution and de-methoxycarbonylation in Me_2SO (with NaH as base). Indeed, addition of a number of different 'active methylene' compounds to 2-NO_2-TPP (in Me_2SO–NaH) gives good yields of the corresponding metal-free chlorins.[15]

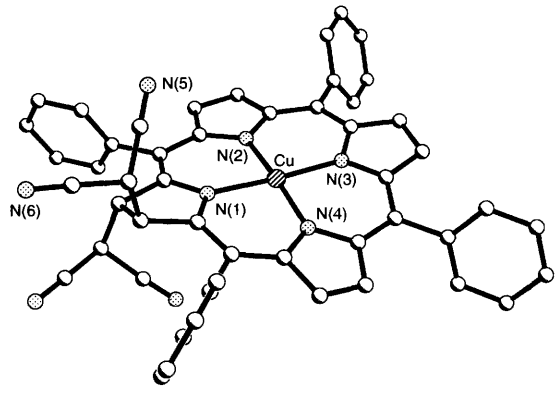


Fig. 2 Molecular structure of **8**. Atomic positions are represented with 50% probability thermal ellipsoids.

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Footnotes

† E-mail: smith@chem.ucdavis.edu

‡ All new compounds gave satisfactory mass spectra, elemental analyses and proton NMR spectra (where appropriate).

§ *Crystal Data* for $C_{49}H_{34}N_4O_4Ni{\cdot}H_2O$ **5**: *M* = 819.56, monoclinic, *a* = 20.089(4), *b* = 15.446(3), *c* = 26.842(5) Å, *U* = 8052(4) Å^3 (by least-squares refinement on diffractometer angles for 42 centred reflections), λ = 1.54178 Å, space group *C*2/*c*, *Z* = 8, D_c = 1.352 g cm^{-3}, *F*(000) = 3408; purple rectangular crystals; crystal dimensions 0.50 × 0.19 × 0.15, μ(Cu-Kα) = 1.20 mm^{-1}, Syntex $P2_1$ diffractometer, scan type 2θ–θ, *T* = 130(2) K, $2\theta_{max}$ = 114°, 5842 data, 5427 unique [*R*(int) = 0.054], 3261 > 2σ(*I*), XABS2 absorption correction, solution and refinement used Siemens SHELXTL ver. 5, refinement based on F^2, *wR* (all data) = 0.3276, *R* (obs. data) = 0.113, largest peak in final difference Fourier map = 1.257 eÅ^{-3}.

For $C_{50}H_{30}CuN_8{\cdot}CH_3OH$ **8**: *M* = 838.17, triclinic, *a* = 12.794(3), *b* = 13.502(3), *c* = 14.406(3) Å, *U* = 2051.9(9) Å^3 (by least-squares refinement on diffractometer angles for 44 centred reflections), λ = 1.54178 Å, space group $P\bar{1}$, *Z* = 2, D_c = 1.357 g cm^{-3}, *F*(000) = 858; red rectangular crystals; crystal dimensions 0.63 × 0.38 × 0.23, μ(Cu-Kα) = 1.20 mm^{-1}, Syntex $P2_1$ diffractometer, scan type 2θ–θ, *T* = 130(2) K, $2\theta_{max}$ = 114°, 5550 data, 5525 unique [*R*(int) = 0.025], 4868 > 2σ(*I*), XABS2 absorption correction, solution and refinement used Siemens SHELXTL ver. 5, refinement based on F^2, *wR* (all data) = 0.1662, *R*(obs. data) = 0.0574, largest peak in final difference Fourier map = 0.664 eÅ^{-3}.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/267.

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