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Oxidation of *meso*-tetraphenyl-2,3-dihydroxychlorin: simplified synthesis of β,β′-dioxochlorins

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Abstract—DDQ Oxidation of *meso*-tetraphenyl-*cis*-2,3-dihydroxychlorins leads to an efficient synthesis of the corresponding 2,3-dioxochlorins. This alternative synthesis of these known chromophores is simple and likely to be more general as compared to established syntheses. A single crystal structure of [*meso*-tetraphenyl-*cis*-2,3-dihydroxychlorinato]Ni(II) proves the ruffled structure of the chromophore. The reduction of the free base dioxochlorin allows the preparation of the *meso*-tetraphenyl-*trans*-2,3-dihydroxychlorin. © 2003 Elsevier Science Ltd. All rights reserved.

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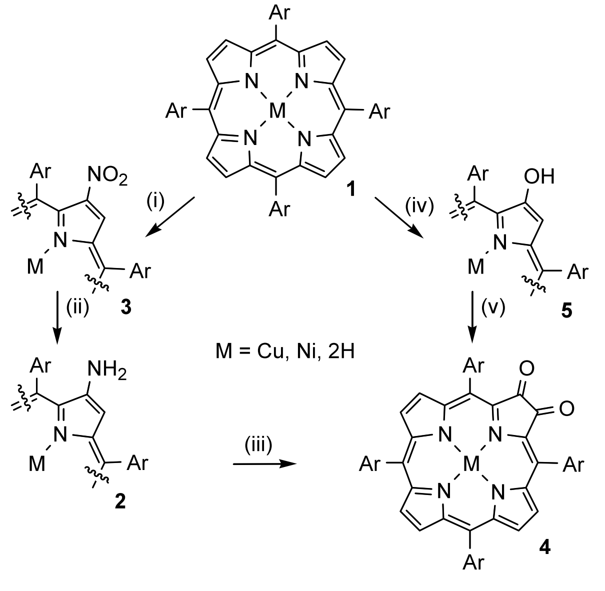
meso-Tetraarylporphyrins (such as TPP, **1**) and their metal complexes are widely used in the design of model compounds of naturally occurring porphyrinic cofactors or light-harvesting systems.[1] The great popularity of TPP (and the closely related 5,10-diphenylporphyrin) arises from the availability of a large number of aryl-functionalized derivatives.[2] The derivatization of the peripheral pyrrolic carbons of TPP, its β-positions, has been studied in depth. Particularly the conversion of TPP into chlorin chromophores (β,β′-dihydroporphyrins)[3] has received special attention because chlorins fulfill the photophysical requirements for drugs to be used in the photodynamic therapy (PDT) of tumors.[4]

Crossley and co-workers reported in 1984 that β-aminoporphyrin **2**, available by reduction from the corresponding β-nitroporphyrin **3**, is susceptible to oxidation to β,β′-dione **4** (Scheme 1).[5] It was later shown that **4** could also be prepared by oxidation of β-hydroxyporphyrin **5**,[6] itself available by a number of routes from TPP.[7] Diones of type **4** have since found wide use in the construction of multi-porphyrin assemblies, porphyrins containing extended π-systems, cavitands, and anion sensors.[7–10]

We have reported the OsO_4-mediated dihydroxylation of TPP to generate diol chlorin **6**[11,12] (Scheme 2) and its utilization in the synthesis of a number of chlorin-like macrocycles.[13,14] We now report the oxidation of



Scheme 1. *Reaction conditions:* (i)[15] NO_2 or $AgNO_3/I_2$; (ii)[16] $NaBH_4$/Pd–C or $SnCl_2/HCl/CH_2Cl_2$; (iii) 1. $h\nu/O_2$, 2. H^+/H_2O or SeO_2, Δ or 1. Dess–Martin periodinane (DMP), 2. H^+/H_2O; (iv) 1. [*E*-benzaldoximato]Na, Me_2SO, 2. H_2O; (v) $h\nu/O_2$/Rose Bengal or SeO_2, Δ.

Keywords: chlorins; 2,3-diolchlorins; 2,3-dioxochlorins; DDQ oxidation.

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diolchlorin **6** to dione **4** using DDQ. This simple method parallels the β-dione- and β-tetraone-porphyrin syntheses described by Starnes and Rebek using IBX as the oxidant,[10] and is believed to be more general as compared to the established Crossley-syntheses. We further report the single crystal structure of **4**, as its Ni^{II} complex **4Ni**, and the reduction of the diones **4H** and **4Ni**.

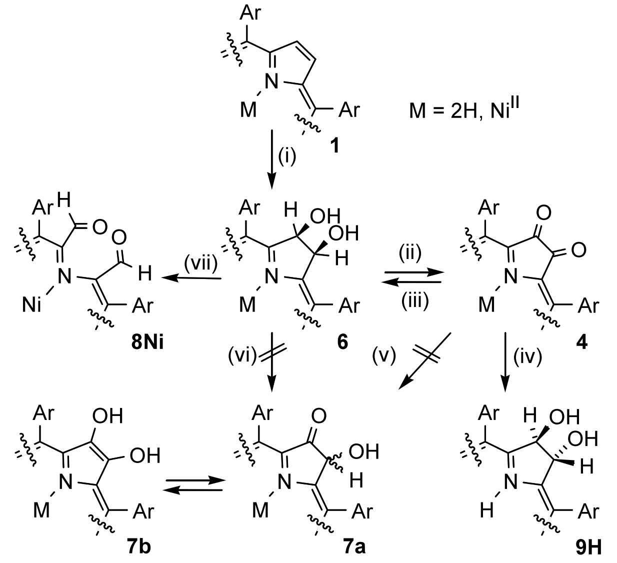
Reaction of polar diol **6**, as its free base or Ni^{II} chelate, with excess DDQ in benzene or toluene under reflux conditions produces low polarity products within 24 h (Scheme 2). Following filtration and chromatographic isolation, diones **4H** and **4Ni** are isolated in up to 70% yield. These products were, based on their diagnostic NMR and UV–vis spectra (vide infra) identified as **4H** or **4Ni**, respectively.[17] Insertion of Zn^{II} into **4H** using standard methodologies (Zn^{II} acetate, MeOH/pyridine/CHCl$_3$, Δ) generates **4Zn**.

The UV–vis spectrum of **4H** in comparison to that of **6H** is shown in Figure 1. While the spectrum of the diol chlorin **6H** exhibits the characteristics of a typical chlorin, the spectrum of dione chlorin **4H** lacks any well-defined side bands above 500 nm. Its slightly hypsochromically shifted Soret band has a much lower extinction coefficient (log $\varepsilon_{404} = 4.87$) as compared to **6H** (log $\varepsilon_{408} = 5.27$). This electronic influence of the carbonyl groups on the π-system is also observed in the UV–vis spectrum of the corresponding Ni^{II} complex **4Ni** as compared to diol **6Ni** (Fig. 2).

Crystals suitable for a single-crystal X-ray diffractometry study of **4Ni** were grown by slow evaporation of a CDCl$_3$ solution.[18] The structure is shown in Figure 3. The structure, the first X-ray structure of a dioxochlorin, confirms the expected connectivity of the macrocycle. A side view of the chromophore shows clearly its ruffled conformation. The root mean square (rms) deviation from planarity of the C$_{20}$N$_4$Ni core in **4Ni** is 0.293 Å).

Secochlorin bisaldehyde **8Ni**, available by diol cleavage of diol chlorin **6Ni**,[13] possesses a chromophore comparable to that of **4Ni** in that both contain two carbonyl groups attached to adjacent α-positions of a chlorin framework. The UV–vis spectrum of **8Ni** (Fig. 2C) shows some similarities with that of **4Ni** (Fig. 2B), particularly with respect to the broad side bands and the two peaks in the region below 500 nm. However, there are significant differences such as the inverted intensity ratio of the two high-energy bands. We attribute these differences to their differing degrees of ruffling.[19] The secochlorin **8Ni** is significantly more ruffled than **4Ni** (rms of the C$_{20}$N$_4$Ni core of **8Ni** = 0.611 Å).[13]

The ruffling effect of Ni(II) on porphyrin chromophores is well known. The coordination interaction of the small ion Ni(II) 'pulls' the ring-nitrogens inward, thereby ruffling the macrocycle. The conformational disparity of the chromophores **4Ni** and **8Ni** is the result



Scheme 2. *Reaction conditions:* (i)[12] 1. OsO$_4$, pyridine, 2. H$_2$S; (ii) 4-fold molar excess DDQ; (iii) Zn–Hg/H$^+$ or Pd–C/H$_2$; (iv) 1-fold molar excess NaBH$_4$, 2. H$^+$/H$_2$O (v) 1. 1 equiv. NaBH$_4$, 2. H$^+$/H$_2$O; (vi) 1 equiv. DDQ; **6H** (purple, $R_f = 0.08$)→**4H** (green–yellow, $R_f = 0.60$); **6Ni** (forest green, $R_f = 0.10$)→**4Ni** (bright yellow–green, $R_f = 0.52$), all R_f measured on silica/CH$_2$Cl$_2$; (vii) Pb(IV) acetate.

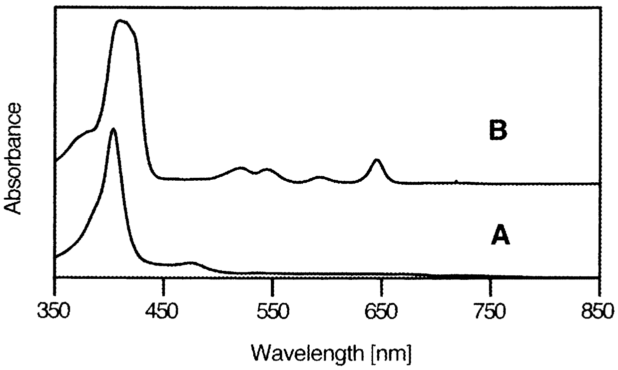


Figure 1. Normalized UV–vis spectra (CH$_2$Cl$_2$) of **4H** (**A**) and **6H** (**B**).

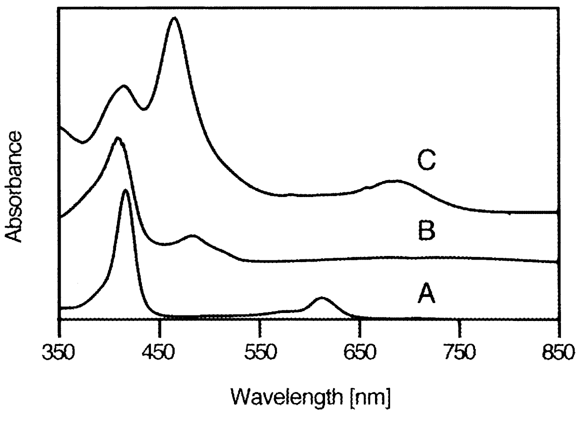


Figure 2. Normalized UV–vis spectra (CH$_2$Cl$_2$) of **6Ni** (**A**), **4Ni** (**B**) and **8Ni** (**C**).

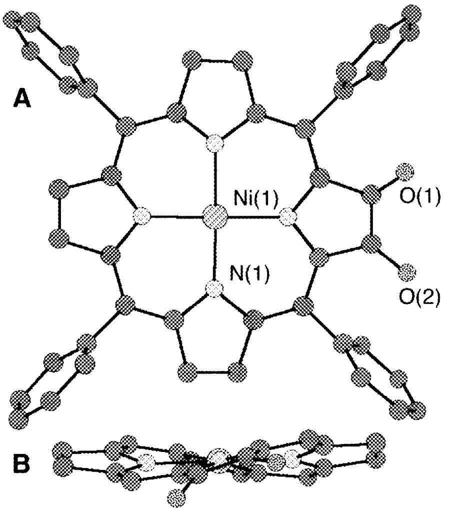


Figure 3. Ball-and-stick model of crystal structure of **4Ni**, hydrogens omitted for clarity.[18] A. top view; B. side view along the N(1)–Ni(1) bond axis, phenyl groups omitted for clarity. Selected bond distances: N(1)–Ni(1) = 1.939(2), C(1)–O(1) = 1.230(9); C(2)–O(2) = 1.250(9).

of the cleavage of the β,β′-bond. The bond cleavage destroys the structural integrity of the rigid porphyrinic framework, allowing for a larger degree of ruffling in **8Ni** and, consequently, for shorter Ni–N bond distances. The average Ni–N bond distance in **8Ni** is 1.892 Å as compared to 1.939(2) Å in **4Ni**.[13] The origin of the influence of the conformation of porphyrinic chromophores on their electronic properties is an issue of current debate.[20] A comparison of the species **4Ni** and **8Ni** which differ in the extent of the ruffling of their otherwise similar chromophores may help to refine the understanding of the electronic effects of distortion of porphyrinic chromophores.

The conversion of diols **6** to diones **4** requires 2 equiv. of DDQ. The first equivalent oxidizes the dione to the corresponding α-hydroxy ketone **7a** which likely exists as its enol tautomer **7b** containing a porphyrin-like π-system. Access to such a catechol-type porphyrinic chromophore is attractive as it might allow the chelation of the porphyrinic chromophore to a variety of metal ions.[21] In due course of the oxidation reaction of **6** to **4** using DDQ, however, no isolable species with an intermediate oxidation state was observed, even under conditions leading to incomplete conversion of the starting material. This indicates that the oxidation of the electron-rich diol porphyrin **7** to the corresponding dione is faster than the oxidation of diol chlorin to **7**. An analogous 2,3-diaminoporphyrin reportedly is also very unstable toward oxidation.[22]

Reduction of dione **4H** and **4Ni** using $LiAlH_4$, Zn–Hg/H^+, and H_2/Pd–C led to the isolation of the *cis*-diol **6H** and **6Ni**, respectively, as the main product. The observed degree of stereoselectivity of the reduction may be an outcome of chelating interactions of the dione with the reductants, favoring *cis*-hydrogenations. Reduction of dione **4H** using $NaBH_4$ in THF/MeOH produces a complex mixture of products from which a main product can be isolated by preparative plate chromatography. It possesses a near-identical UV–vis spectrum and identical mass (APCI-MS of $m/z = 649$ corresponding to MH+) to **6H** but has a lower polarity ($R_f = 0.28$, silica/CH_2Cl_2). Its ^1H and ^{13}C NMR spectra show a two-fold symmetry of the molecule (i.e. the characteristic d-d-s, 2H each, pattern for the β-hydrogen region) and are similar to those of the *cis*-diol **6H**.[23] We thus assign it the structure of the novel *trans*-diol **9H**. We were never able to isolate from these reduction reactions species we could assign the α-hydroxy ketone structure **7a** (or **7b**), even under conditions which resulted in incomplete conversion of the starting material.

In summary, dione **4** is accessible from TPP in two steps (dihydroxylation, diol oxidation). Since both steps proceed under conditions which are compatible with a wide range of potential phenyl-substituents, the synthesis of **4** is regarded as being fairly general. A comparison of the photophysical properties of dione **4Ni** with those of secochlorin **8Ni** is suggested to be a suitable model to gain further information about the influence the conformation of porphyrinic chromophores has on their electronic properties. Neither a two-hydrogen oxidation of diol **6** nor a two-hydrogen reduction of dione **4** allowed access to the intriguing catechol-like diol chlorin **8** but a four-hydrogen reduction of **4** allowed the preparation of the novel *trans*-*vic*-diol **9H**.

Acknowledgements

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17. Though not a novel compound class, the full description of the *meso*-tetraphenylporphyrin-derived dioxochlorins has not appeared in the peer-reviewed literature:
    *2,3-Dioxo-5,10,15,20-tetrakisphenylchlorin (**4**).* A solution of diol **6H** (165 mg, 2.55×10^{-4} mol) in benzene (22 mL) and pyridine (3 mL) was heated to reflux for 36 h during which time DDQ (270 mg, 6.5 equiv.) was added in three equal increments. Caking in the flask during the reaction was removed by sonication. Once all starting material was consumed (TLC control), the solvent was evaporated under vacuum. The residue was taken up in CH_2Cl_2 and filtered through a plug of silica gel. The filtrate was reduced and **4H** was isolated and purified by column chromatography (silica, $CHCl_3$/20% pet ether 30–60). The main brown fractions were combined and evaporated to dryness, depositing a dark blue powder of analytical purity (120 mg, 73%). R_f=0.6 (silica-CH_2Cl_2); UV–vis ($CHCl_3$) λ_{max} (log ε): 403 (4.87), 475 (3.84) nm; Fl ($CHCl_3$, $\lambda_{excitation}$=420 nm) λ_{max} (rel. intensity): 648 (1.0), 708 (0.2) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J=5.0 Hz, 2H), 8.64 (d, J=5.0 Hz, 2H), 8.60 (s, 2H), 8.16 (d, J=7.5, 4H), 7.94 (d, J=7.5, 4H), 7.82–7.70 (m, 12H), −1.9 (br s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 141.0, 140.7, 139.8, 139.2, 138.1, 134.2, 134.1, 132.6, 128.4, 128.2, 128.1, 128.0, 127.1, 126.9, 124.0, 114.0 ppm; IR (KBr): $\nu_{C=O}$=1725 cm^{-1}; MS (APCI+, 100% CH_3CN) m/e=645 (MH+), 683 (MK+); HR-MS (+FAB of MH+) calcd for $C_{44}H_{28}N_4O_2$: 644.2212, found: 644.2220.
    *[2,3 - Dioxo - 5,10,15,20 - tetrakisphenylchlorinato]Ni(II) (**4Ni**)*: Prepared as described for **6H** in benzene or toluene and isolated as dark blue powder in 65% yield by column chromatography (silica, $CHCl_3$). R_f=0.52 (silica-CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J=5.0 Hz, 2H), 8.24 (s, 2H), 8.14 (d, J=5.0 Hz, 2H), 7.80 (br d, J=9.2 Hz, 4H), 7.68–7.54 (m, 16H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.8, 141.0, 140.7, 139.8, 139.2, 138.1, 134.2, 134.1, 132.6, 128.4, 128.2, 128.1, 128.0, 127.1, 126.9, 124.0, 114.0 ppm; UV–vis (CH_2Cl_2) λ_{max} (log ε) 413 (4.89), 482 (4.17), very broad band stretching from 580 to 820 nm, centered ~700 nm; IR (KBr): $\nu_{C=O}$=1722 cm^{-1}; LR-MS (APCI+, 100% CH_3CN) m/e 700 (M+), 741 (M$^{+\bullet}$$CH_3CN$).
    *[2,3 - Dioxo - 5,10,15,20-tetrakisphenylchlorinato]Zn(II) (**4Zn**):* To a solution of **4H** (100 mg, 1.40×10^{-4} mol) in $CHCl_3$ (20 mL) was added a solution of Zn^{II} acetate (66 mg, 3.0×10^{-4} mol) in MeOH (1.0 mL) and the mixture was heated to reflux for 1 h. The cooled mixture was washed several times with H_2O, the organic layer dried (Na_2CO_3) and chromatographed (silica-$CHCl_3$). The main yellow fraction was evaporated to dryness to produce **4Zn** as a brown–blue solid in high yield. R_f=0.8 (silica-CH_2Cl_2/CCl_4 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J=4.4 Hz, 2H), 8.46 (s, 2H), 8.31 (d, J=4.4 Hz, 2H), 8.05 (d, J=6.8, Hz, 4H), 7.78 (dd, J=6.4, Hz, 4H), 7.72–7.53 (m,); UV–vis (CH_2Cl_2) λ_{max} (rel. intensities) 416 (1.0), 496 (0.13), broad, featureless band centered ~650 nm; IR (KBr): $\nu_{C=O}$=1724 cm^{-1}; LR-MS (APCI+, 100% CH_3CN) m/e=706.
18. The X-ray structural data for **4Ni** have been deposited at the Cambridge Crystal Structure Base. CIF files are available free of charge via the Internet at http://www.ccdc.cam.ac.uk. Refer to reference number CCDC-205948.
19. This assessment includes effects such as (a) the differing relative orientation of the carbonyl groups to the chromophore, (b) the possible effects of the π–π-interactions of the stacked carbonyl groups in **8Ni**, (c) the effects of shortened Ni–N bond distances.
20. For an excellent overview over the current debate, see: Haddad, R. E.; Gazeau, S.; Pécaut, J.; Marchon, J.-C.; Medforth, C. J.; Shelnut, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 1253–1268.
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23. *2,3 - trans - Dihydroxy - 5,10,15,20 - tetrakisphenylchlorin (**9H**)*: To a solution of **4H** (50 mg, 7.76×10^{-5} mol) in THF (10 mL) was added $NaBH_4$ (2.9 mg, 1 equiv.). The reaction mixture was allowed to react for 4 h at rt. The reaction was then quenched with dilute aq. HCl and the solvent was evaporated to dryness by rotary evaporation. Preparative chromatography (20×20 cm, 1000 μm silica,

$CHCl_3$) was used to purify the product. The major pink fraction was isolated and crystallized by slow solvent exchange from CH_2Cl_2 to MeOH. Yield: 15 mg (30%). $R_f = 0.28$ (silica, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, $J = 4.8$, 2H), 8.52 (s, 2H), 8.35 (d, $J = 4.8$, 2H), 8.20-8.16, (m, 6H), 8.06 (d, $J = 6.8$, 2H), 7.99 (d, $J = 4.8$, 2H), 7.78-7.70 (m, 12H), 6.22 (d, $J = 3.6$, 2H), 2.32 (d, $J = 4.0$, 2H), −1.91 (br s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 153.9, 142.2, 141.6, 141.3, 136.3, 134.5, 133.8, 133.4, 133.3, 129.0, 128.8, 128.7, 128.3, 128.2, 127.2, 124.8, 123.7, 113.5, 81.6 ppm; LR-MS (APCI+, 100% CH_3CN) $m/e = 649$ (MH+).