Photochemical preparation of pyrrole ring-contracted chlorins by the Wolff rearrangement†

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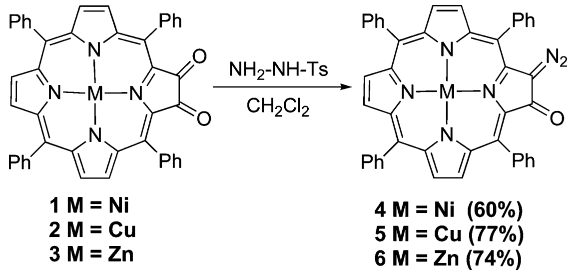
Photolysis of the Ni(II), Cu(II), and Zn(II) 2-diazo-3-oxochlorins generates 4-membered rings containing azeteoporphyrins.

Porphyrins and chlorins, by virtue of their unique electronic properties have been evolved as key components of artificial photosynthetic devices[1] and molecular materials,[2] as well as effective agents in medical applications such as photodynamic therapy (PDT).[3] The latter area utilizes low energy photoexcitation at tissue transparent wavelengths in the near infrared spectral region to form toxic "diradical-like" species such as $^1O_2$ from $^3O_2$ *via* annihilation of the photogenerated $^3\pi\pi^*$ state.

In a chemically related arena, valence deficient carbene diradicals produced by loss of dinitrogen from diazoketones are known to undergo H-atom abstraction (triplet) or insertion (singlet) reactions with external substrates.[4] They also facilitate complex internal transformations[5] such as the Wolff rearrangement of the ketocarbene to form a ketene that subsequently reacts with nucleophiles.[6] Photochemically, diazoketones are quite reactive, making them intriguing candidates for chromophore-based photo-therapeutic applications (*e.g.* PDT), especially in hypoxic environments. Moreover, since unusual and effective chromophore periphery modification[2,7] is also important for nearly all porphyrinoid-based applications, diazoketone reactivity may have considerable potential in this area as well.

Current literature provides only one synthetic route to 2-diazo-3-oxochlorins; the reaction of aminoporphyrins with $NaNO_2$ in THF.[8] This is an established method to diazonium salts,[9] but in the presence of trace peroxides in THF, it fortuitously generates the Cu(II) and Ni(II) 2-diazo-3-oxochlorins in 54% and 30% yields, respectively.[8] Our previous work on photochemical diradical generating systems,[10–12] and those conjugated to strong chromophores,[13,14] prompted our interest in the syntheses and photoreactivities of 2-diazo-3-oxochlorins.

The accessibility of 2,3-dioxochlorins[15,16] and the well known conversion of α-dioxo functionalities to α-diazo-oxo systems in high yields by reaction with *p*-toluenesulfonylhydrazine,[17–19] especially in π-electron conjugated backbones,[18] inspired our synthetic approach to these targets (Scheme 1). The 2,3-dioxochlorins precursors (**1–3**)[15,16] are readily prepared by a literature procedure.[15] The desired (2-diazo-3-oxochlorinato)nickel(II) (**4**), copper(II) (**5**), and zinc(II) (**6**) compounds are then obtained by reaction of **1**–**3** with 20 equiv. of *p*-toluenesulfonylhydrazine under reflux in dichloromethane for 9 h, 6 h, and 3 h, respectively. Separation by column chromatography yielded **4** (60%), **5** (77%), and **6** (74%) in markedly better yields than previously reported.[8] Use of Zn(II) as a co-reagent can reduce these reaction times by as much as a factor of six.[20]



Scheme 1 Synthesis of 2-diazo-3-oxochlorins.

Photolysis of **4** and **5** in a 1 : 1 mixture of $CHCl_3$–MeOH was previously reported to yield photoproducts involving substitution on the periphery of the π-electron conjugated macrocycle. These products are the hydroxy porphyrin (**4a**, **5a**: trace, 25%), the methoxy porphyrin (Ni(II): 8%, Cu(II): 28%) and two MeOH insertion oxochlorin products, the methoxy (**4b**, **5b**: 10%, 5%) and dimethoxy (**4c**, **5c**: 14%, 11%) species.[21] The latter products suggest involvement by carbene intermediates, the precise natures of which were not determined.

Carbene intermediates in heterocyclic ring systems can also undergo the Wolff rearrangement.[6,22] To date, only two examples of pyrrole ring-contracted porphyrinoid constructs featuring a 4-membered azete moiety have been reported, and both were obtained by thermal oxidation.[23,24] We postulated that such an azeteoporphyrin should be accessible *via* the photoinduced Wolff rearrangement. One may also expect other periphery modification such as radical or nucleophile addition products resulting from unimolecular or bimolecular reactions.

Toward these goals, a 0.7 mM solution of **4** in a 1.67 : 1 solution of dried, degassed CH_2Cl_2 : MeOH (40 mL) was irradiated with a 200 W HgXe lamp in a Pyrex vessel ($\lambda > 300$ nm) under nitrogen for 6 h at 10 °C. The photoreaction generated two major and two minor molecular products that were completely characterized, as well as black residue that is insoluble in standard organic solvents. Analogous to the previous report, we also obtain (2-hydroxy-5,10,15,20-tetraphenylporphyrinato)nickel(II) **4a** (3%) and (2-methoxy-3-oxo-5,10,15,20-tetraphenylchlorinato)nickel(II), **4b** (5%), but in low yields. We observe in much better yield, the dimethoxychlorin (2,2-dimethoxy-3-oxo-5,10,15,20-tetraphenyl-chlorinato)nickel(II) **4c** (32%), as well as the unusual pyrrole ring-contracted target azeteoporphyrin

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† Electronic supplementary information (ESI) available: Synthesis and characterization of **4**, **4a–e**, **5**, **5a–d**, **6**, and **6a–d**, as well as X-ray crystallographic data for **4d**, **4e**, and **5d**. See DOI: 10.1039/b612776m

compound **4d**[25] (16%) derived from the Wolff rearrangement and quenching by MeOH (Fig. 1).

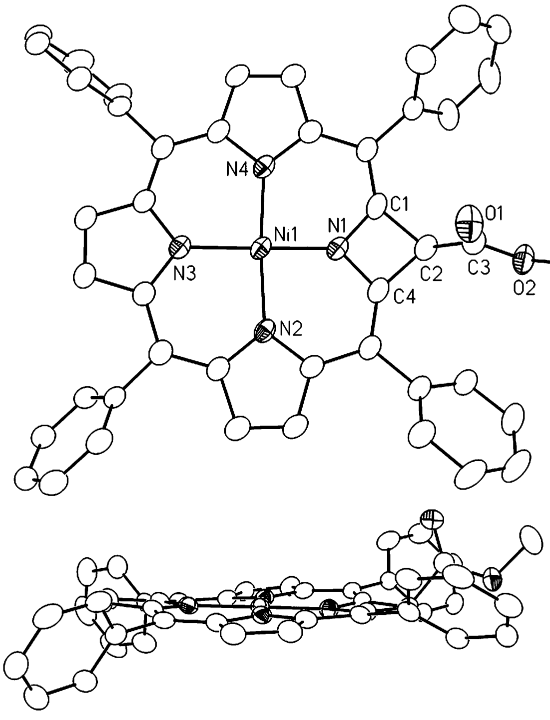
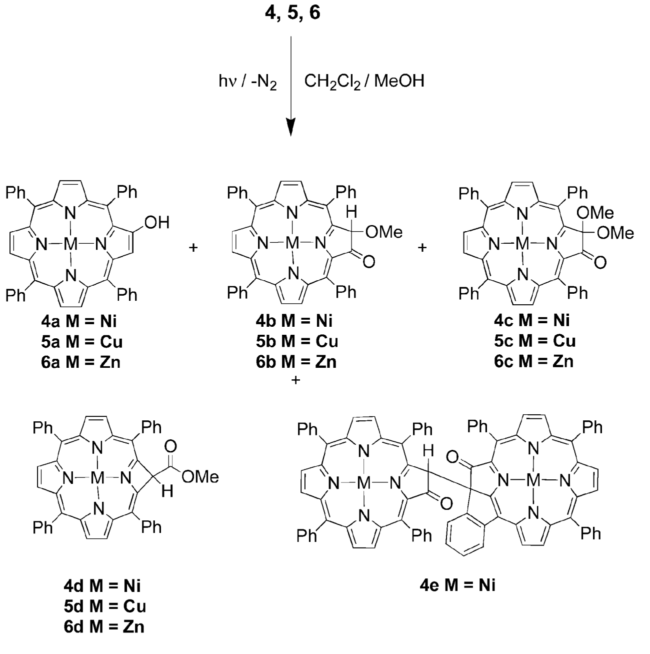


Fig. 1 X-Ray structure of photoproduct **4d**. Upper: front view, Lower: side view along N2–Ni1–N4 axis; Thermal ellipsoids are illustrated at 50% probability; H-atoms are omitted for clarity.

Photolysis of the Cu(II) 2-diazo-3-oxochlorin **5** under the same conditions generates chemically similar photoproducts, including the 4-membered ring-containing Cu(II) azeteoporphyrin, **5d**[26] (7%) (Scheme 2). Isolation of **4d** and **5d** led us to conclude that **4** and **5** traverse similar reaction pathways, which are analogous to the one proposed by Meinwald[27] where methanol addition to the ketene generates a methoxy ester.



Scheme 2 Photoreaction products obtained upon irradiation of **4**, **5**, and **6**.

Due to multiple product formation, a single quantum yield for the overall photoreaction was obtained by monitoring the photobleaching of the Soret band at $\lambda_{max} = 430$ nm.[28] The quantum yield for the decay of **5** in CH_2Cl_2 at $\lambda = 365$ nm irradiation wavelength was measured to be $\Phi_{365} = 0.13$, which is in accordance with published values for UV-excitation of diazoketones.[29]

One additional photoproduct was also detected in trace amounts; the dimerization product of two Ni(II) 2-diazo-3-oxochlorins, which are fused at the 2-position upon loss of N_2 **4e**[30] (Fig. 2). The X-ray structure of the dimer also reveals formation of an exocyclic ring, suggesting that the mechanism for dimerization first involves radical addition to the *meso*-phenyl ring.[14] Although mechanistically speculative, the dimer is a glimpse into the nature of the black residue formed upon photolysis of **4** and **5**, suggesting formation of high molecular weight species. Efforts to reduce the yield of that material by dilution have thus far been unsuccessful, indicating that the bimolecular aggregation kinetics compete favorably with substrate addition and the Wolff rearrangement.

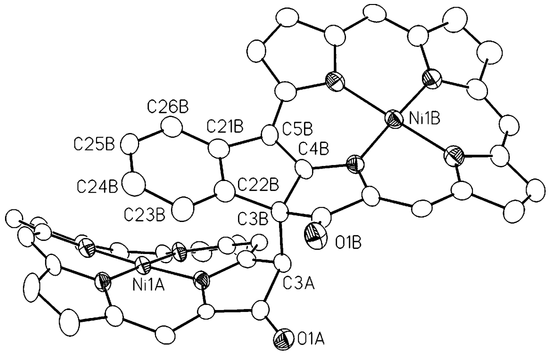


Fig. 2 X-Ray structure of photoproduct **4e**. Thermal ellipsoids are illustrated at 50% probability; H-Atoms and spectator phenyl rings are omitted for clarity.

To determine whether the unfilled d-shell of the central metal influences the photochemical reactivity and product yields, (2-diazo-3-oxochlorinato)zinc(II) **6** was prepared using the synthetic method described above. When a 0.7 mM solution of **6** in a 1.6 : 1 solution of dried, degassed CH_2Cl_2 : MeOH was irradiated (200 W HgXe, $\lambda > 300$ nm) for 6 h at 10 °C, the analogous products (**6a–d**) to those isolated upon photoreaction of **4** and **5** were obtained in similar quantities. This indicates limited influence of charge transfer or ligand field excited states in the excited state reaction dynamics.

The unique X-ray structures of **4d** and **5d** are isomorphous and reveal that the macrocycles are both planar with remarkably short $M–N_{azete}$ distances (**4d**: 1.83 Å, **5d**: 1.89 Å). Typically, metal ions with small radii compensate for the larger porphyrin core size by drawing in the pyrrole nitrogens, resulting in puckering of the backbone.[31,32] For **4d** and **5d** this is not the case as the rigidity of the smaller macrocycle enforces a planar structure, despite the short $M–N_{azete}$ bonds. The result is unusual considering the highly ruffled/saddled nature of many Ni(II) porphyrins.[13,33]

The Wolff photoproducts **4d** and **5d** can be considered as a type of chlorin since they possess an electronic structure with the requisite 20π electron macrocycle. This assumption is supported by the chlorin-like electronic absorption spectra of these compounds (*e.g.* **4d**, Fig. 3), which show a prominent Q_x band as the lowest energy feature. Relative to the starting diazo-oxochlorin **4**, the absorption profile of **4d** exhibits a modest blue-shift, likely due to reduction of the conjugation length and pronounced planarity of the macrocycle.[33]

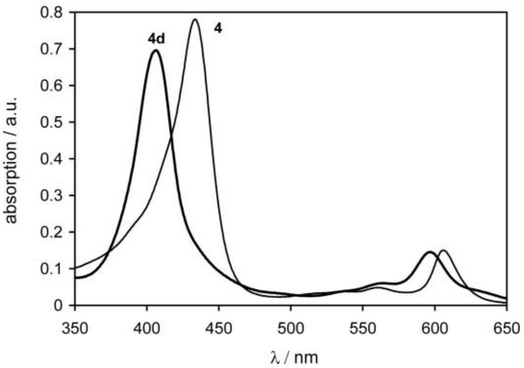


Fig. 3 Electronic absorption spectra for **4** and **4d** in CH_2Cl_2.

To probe whether visible region photolysis could generate the Wolff product, **4** and **5** were irradiated with a HgXe lamp (200 W, $\lambda \geq 395$ nm) for 48 h at 10 °C in a Pyrex vessel under nitrogen. Although the photolysis times were increased, Wolff products **4d** and **5d** are still obtained in 6% and 8% isolated yields, respectively, due to conjugation of the diazo unit into the visible region ππ* transitions of the macrocycle.

The formation of Wolff products **4d–6d** and C–C bond coupling species **4e** derive from carbene insertion, suggesting formation of a singlet carbene intermediate. Indeed, photolysis (Hg arc lamp; 100 W, 5 h) of a frozen solution of **4** and **5** at 5 K within an EPR cavity (X-band) yields no new EPR signals between 500–7000 G characteristic of a triplet carbene, despite detection of photoproduct by TLC upon thawing. Our experience in detecting carbene and triplet diradical intermediates by frozen solution photolysis/EPR at 5 K[11,34] leads us to conclude that the carbene intermediates of both **4** and **5** are likely singlet in nature. This is consistent with their ability to effectively participate in the Wolff rearrangement and C–C bond coupling rather than olefin or azine formation.[35] Herein we demonstrate a new synthetic approach to 2-diazo-3-oxochlorins and the unprecedented photochemical formation of azeteoporphyrins *via* the Wolff ring contraction. Photoproduct analysis and low-temperature EPR measurements suggest that singlet carbene intermediates are formed, leading to insertion reactions, as well as formation of the ketene intermediate of the Wolff pathway. In a general sense, our synthetic strategy allows selective installation of a photo-labile fragment on the periphery of a chlorin macrocycle and can therefore be seen as a synthetic tool for future periphery modifications on porphyrinic heterocycles. Overall, both carbene and ketene intermediates of this type may find potential as *in situ* alkylating agents in photo-therapeutic applications in hypoxic environments.

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25 CCDC reference numbers 605756 (**4d**), 605758 (**4e**), and 605757 (**5d**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b612776m. Crystal data for **4d**: brown block, 0.25 × 0.23 × 0.18 mm^3, $C_{45}H_{30}N_4NiO_2$, M = 717.44, orthorhombic, a = 17.0768(12) Å, b = 14.1377(10) Å, c = 27.7514(19) Å, V = 6699.9(8) Å^3, T = 130(2) K, space group *Pbcn*, Z = 8, ρ_{calcd} = 1.423 Mg m^{-3}, μ = 0.627 mm^{-1}, $2\theta_{\max}$ = 50°, Mo$_{K\alpha}$ (λ = 0.71073). A total of 78224 reflections were measured, of which 5956 (R_{int} = 0.0526) were unique. Final residuals were R = 0.0441 and $wR2$ = 0.1025 (for 5104 observed reflections with $I > 2\sigma(I)$, 500 parameters) with GOF 1.231 and largest residual peak 0.322 e Å^{-3} and hole −0.405 e Å^{-3}. $R1$ = 0.0533 and $wR2$ = 0.1073 for all data.
26 Crystal data for **5d**: dark blue block, 0.15 × 0.11 × 0.10 mm^3, $C_{45}H_{30}CuN_4O_2$, M = 722.27, orthorhombic, a = 17.074(3) Å, b = 14.209(2) Å, c = 27.882(4) Å, V = 6764.3(19) Å^3, T = 130(2) K, space group *Pbcn*, Z = 8, ρ_{calcd} = 1.418 Mg m^{-3}, μ = 0.693 mm^{-1}, $2\theta_{\max}$ = 52°, Mo$_{K\alpha}$ (λ = 0.71073). A total of 72376 reflections were measured, of which 6870 (R_{int} = 0.1183) were unique. Final residuals were R = 0.0522 and $wR2$ = 0.1064 (for 4587 observed reflections with $I > 2\sigma(I)$, 470 parameters) with GOF 1.047 and largest residual peak 0.306 e Å^{-3} and hole −0.572 e Å^{-3}. $R1$ = 0.0926 and $wR2$ = 0.1233 for all data.
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