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Surprising Outcomes of Classic Ring Expansion Conditions Applied to Octaethyloxochlorin. 3. Schmidt Reaction Conditions

Ruoshi Li,[a] Mathias Zeller,[b,c] Torsten Bruhn,[d] and Christian Brückner*[a]

Abstract: The Schmidt reaction (treatment of a ketone with sodium azide and a mineral acid) is an alternative to the Beckmann rearrangement to expand a cyclic ketone to a lactam. However, when applied toward the conversion of a synthetic porphyrin to a derivative containing a non-pyrrolic building block this approach failed to generate the expected lactam. Instead, using sulfuric acid as a catalyst, a novel heptaethyl-2-hydroxy-chlorin-3-one was formed, structurally characterized, and its mechanism of formation deduced. The work demonstrates how the extraordinary structural stability of the porphyrin macrocycle redirects the reactivity of classic ring expansion reactions. Using hydrochloric acid as a catalyst, a somewhat regioselective chlorination of the *meso*-positions of the oxochlorin was observed. The halogenation sites were determined spectroscopically and by X-ray crystallography of select derivatives. The regioselectivity of the halogenation was computationally rationalized. This method to generate regioselectively 5-chloro-, 10-chloro-, and 5,10-dichlorooxochlorins is superior over alternative halogenation methods.

Introduction

In the foregoing contributions, we illustrated to which extent classic ring-expansion reaction conditions (Baeyer-Villiger oxidation and Beckmann rearrangement conditions) applied to octaethyloxochlorin did – or did not – lead to the desired ring-expanded products.[1] The work aimed at developing novel methodologies to convert a pyrrole in a porphyrin to a non-pyrrolic heterocycle. The study of this class of porphyrinoids, the so-called pyrrole-modified porphyrins (PMPs), is valuable for a number of fundamental and practical purposes.[2] For instance, the non-pyrrolic building block(s) may possess functional groups that are in direct conjugation with the chromophore and that enable their utilization in sensing applications.[3]

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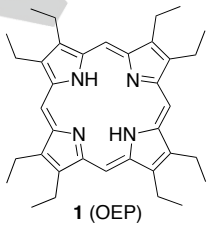
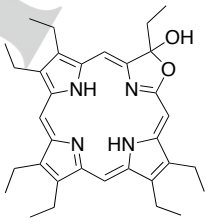
Multiple precedents for the conversion of *meso*-tetraaryl-porphyrins to PMPs are known.[2, 4] Most β-alkylporphyrin-derived PMPs were prepared by total synthesis,[2d, 2f, 5] but some have also been synthesized by conversion of octaethylporphyrin (OEP, **1**). Examples include oxazolochlorin **2**,[6] or the PMPs **3**[1a, 7] and **4**[8] containing six-membered rings. Other exotic pathways towards PMPs have also become known; for instance, chlorophin **5** was formed by serendipity as the product of an oxidation and subsequent rearrangement of a [hydrocorrinato]Ni(II) complex.[9]



1 (OEP)



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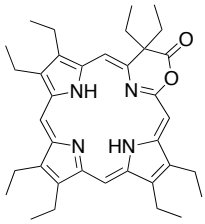

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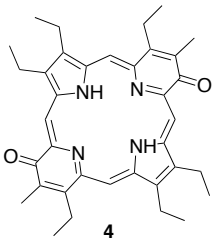

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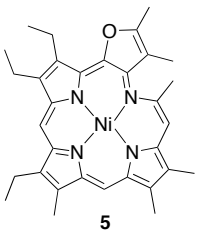
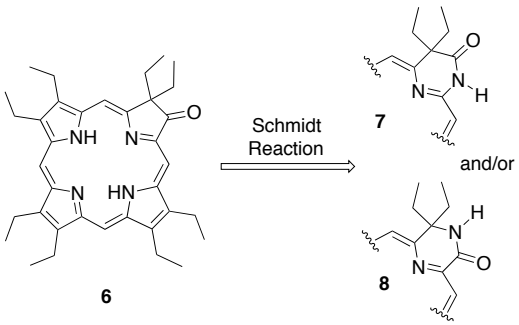


5

Among the classic reactions known to expand a ring by a nitrogen atom is the Schmidt reaction.[10] This reaction is an acid-catalyzed reaction of hydrazoic acid (HN_3), generated *in situ* from sodium or potassium azide and a strong acid, with a ketone to form an amide/lactam.[11] This reaction is mechanistically similar to the Beckmann and Hofmann reactions and the Curtius rearrangement in that an electropositive nitrogen is formed that initiates a carbon fragment migration of a neighboring group, whereby the carbocation intermediate formed is then stabilized by uptake of water.[12]

Well-known OEP-derived ketone **6** is readily accessible via two complimentary routes,[13] and its regular ketone reactivity was demonstrated.[13c, 14] We thus identified oxochlorin **6** as being potentially susceptible to a ring-expansion reaction under Schmidt conditions (Scheme 1). Parallel to the mechanistic considerations controlling the Beckmann reactions,[1a] product **8**

(over **7**) is also the more likely product of a Schmidt reaction pathway.[15] However, as multiple examples have shown, the steric restrictions imposed by the porphyrin ring can alter the expected outcomes of classic reactions.[1, 8]



Scheme 1. Planned ring-expansion reaction under Schmidt reaction conditions.

Indeed, we will present here another set of unexpected reaction outcomes when applying Schmidt reaction conditions to oxochlorin **6**. In short, none of the reactions led to the formation of the target lactams but generated, depending on the particular reaction conditions chosen, an α-hydroxyoxochlorin derivative or led to the formation of *meso*-chlorinated products. In fact, the methodology discovered for the step-wise and regioselective *meso*-chlorination methodology is in some respects superior to established methods.

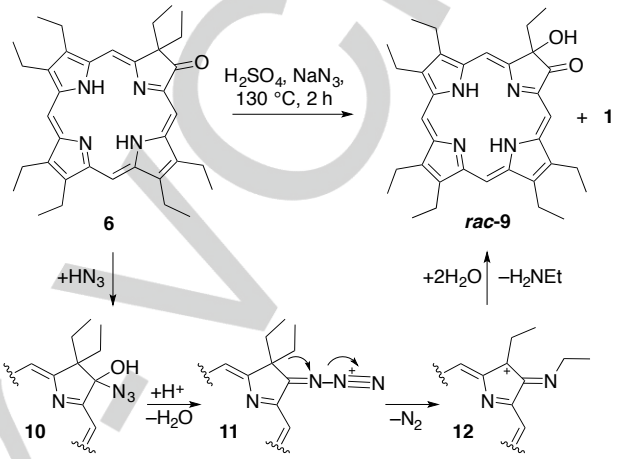
Results and Discussion

Reaction of Oxochlorin under Sulfuric Acid-catalyzed Schmidt Reaction Conditions

SAFETY NOTICE: *NaN_3 as well as the volatile and toxic HN_3 are potentially explosive! All experiments using azides/hydrozoic acid are only to be performed on small scales, in a fume hood, and using a blast shield. Following recent recommendations,[16] we eliminated the use of CH_2Cl_2 or $CHCl_3$ as reaction solvents to prevent the formation of explosive azidomethanes.*

Treatment of oxochlorin **6** under a number of Schmidt reaction conditions (NaN_3/TFA, NaN_3/H_2SO_4 at r.t.) only recovered the starting material. Using a 30-fold molar excess of NaN_3 in hot conc. H_2SO_4 (130 °C, 2 h), a single, dark green polar product **9** (as a racemic mixture, ***rac*-9**) formed in 23% yield, along with 16% OEP **1** and 22% recovered **6** (Scheme 2).

Product **9** possesses a chlorin-like UV-vis spectrum that is similar to that of the starting oxochlorin **6** (Figure 1). Its composition as determined by HR ESI+ MS ($C_{34}H_{43}N_4O_2$ for $[M{\cdot}H]^+$) showed that no additional nitrogen was incorporated into the molecule; instead an OH-group was taken up and an ethyl group was lost. The ketone functionality was preserved, as seen by the presence of a $\nu_{C=O}$ stretch (at 1694 cm^{-1}) in its IR spectrum. Thus, the α-hydroxy ketone (acyloin) structure **9** seemed possible, and was confirmed by single crystal X-ray diffraction (Figure 2). Not surprisingly, the replacement of an ethyl group at the *gem*-diethyl portion of the molecule by a hydroxy group does not perturb the near-planar conformation of the chromophore.[1a] The deviations from planarity within the pyrrolinone moiety are so small as to be readily crystal-packing-induced.



Scheme 2. Reaction of oxochlorin **6** under Schmidt reaction conditions and putative reaction mechanism for the formation of product ***rac*-9**.

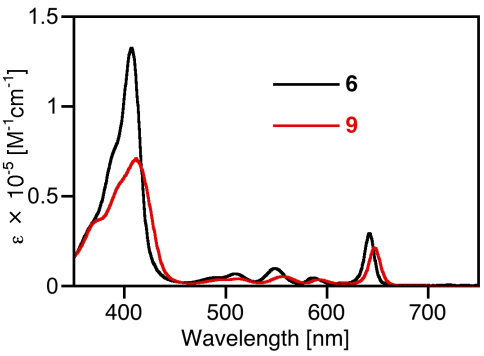


Figure 1. UV-vis spectra ($CHCl_3$) of the compounds indicated.

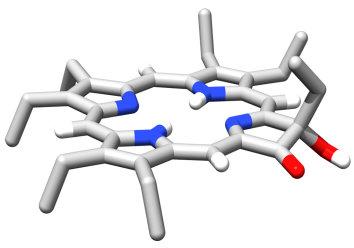


Figure 2. Stick representation of the X-ray single crystal structure of 3-hydroxy-2-oxochlorin ***rac*-9**, oblique view. All disorder and hydrogen atoms bonded to sp^3-carbons removed for clarity. For details to the X-ray structure analysis, see SI.

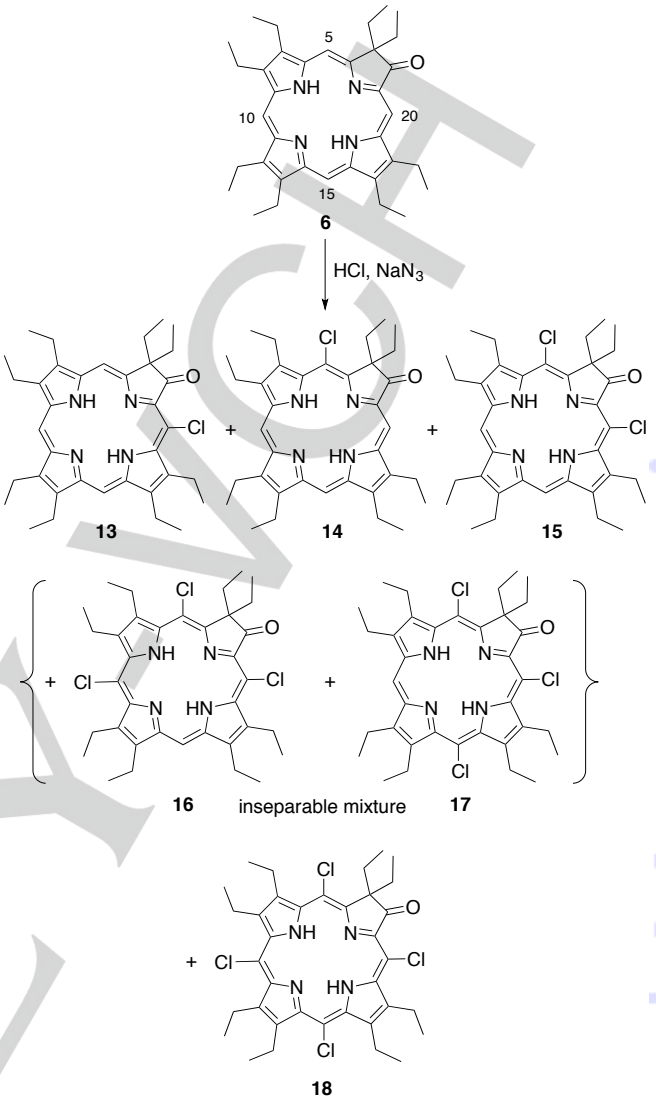
The presumed mechanism of formation of **9** is straight forward. Assuming the Schmidt reaction initiated in the standard way, forming azidohydrin intermediate **10** that subsequently dehydrated to form **11**, it set the stage for the (formal) formation of the nitrene by loss of N_2.[11] The nitrene is then stabilized by a 1,3-migration of a single ethyl group, forming ethylimine **12**. Hydrolysis of the ethylimine functionality upon aqueous work-up would generate ***rac*-9**. The facile hydrolysis of imines of type **12** was observed before.[1a]

The mechanism for the formation of OEP **1**, amounting to a formal reduction, is less clear. Perceivably, azidohydrin **10** can be protonated/dehydrated and one of the adjacent ethyl groups migrates back to this position, followed by a reduction/nitrogen elimination event. We note that azide is a strong reducing agent ($E°$ = -3.09 V).[17] However, we are not aware of any reaction in which azide/hydrazoic acid were utilized to accomplish a comparable 2-electron reduction as required for the above reaction mechanism.

Thus overall, the prerequisite for the Schmidt reaction, namely the migration of the quarternary benzylic pyrrolidine carbon, did not take place. Instead an ethyl group of relative lower migratory aptitude migrated. This likely indicates that the expansion of the five-membered pyrrolinone to a six-membered pyrazine is sterically too demanding. The finding that the steric restrictions imposed by the porphyrin framework redirect the expected reaction into alternate reaction channels is similar to the observation that the oxime of oxochlorin **6** undergoes an abnormal Beckmann reaction instead of the anticipated regular Beckmann rearrangement.[1a]

Reaction of Oxochlorin under Hydrochloric Acid-catalyzed Schmidt Reaction Conditions

The use of conc. aqueous HCl as the mineral acid in a biphasic system with 1,2-dichlorobenzene (ODCB) and using a large excess of azide in the attempted Schmidt reaction of **6** resulted, as per ESI+ MS and ^{1}H NMR (details provided below), in the formation of successively *meso*-chlorinated oxochlorins (Scheme 3). Since all four *meso*-positions are non-equivalent, a number of mono-, di-, and tri-halogenated products could be expected, but the reaction is well-controlled and subject to a degree of regioselectivity: At first, the two readily separable mono-chlorinated products **13** and **14** are formed, with a 3.5-fold larger amount of the 20-substitued product **13** formed over the 5-substituted isomer **14** (see below for a rationalization of the reaction mechanism and the regioselectivity). No other single halogenation products were detected. The relative higher reactivity of the 20-position of oxochlorin **6** was also observed in a number of oxidation reactions.[1b] The next product to form is the 5,20-dichlorinated species **15**, also readily isolable by plate chromatography. As the reaction times are extended and the starting material gets fully consumed, higher chlorinated products become the major products. However, we could not separate the two trichlorinated isomers **16** and **17** and thus isolated them as a mixture. The terminal product, *meso*-tetrachlorooxochlorin **18** is a yellow-green compound that can be isolated in up to 77% yield when the reaction times is extended to 24 h.



Scheme 3. *meso*-Halogenation of oxochlorin **6** under NaN_3/HCl-induced Schmidt reaction conditions.

The selectivity of this halogenation reaction of oxochlorin **6** is superior to that of the NCS-mediated chlorination of **6**. NCS was used in the past to achieve *meso*-chlorination of OEP (**1**).[18] Oxochlorin **6** is also susceptible to a NCS-mediated halogenation, but it furnishes rapidly (1 h, rt) a complex mixture of all isomers of the mono- and dichlorinated oxochlorins (as per ESI+ MS and TLC), with no perceivable preference for the formation of any single product.

The UV-vis spectra of the lower halogenated products are regular chlorin-type spectra that may be slightly red-shifted compared to the spectrum of the parent ketone **6** (Figure 3A). Increasing halogenation also affects the optical spectra, as seen for the significantly red-shifted and generally broadened spectrum of the tetrahalogenated species **18** (Figure 3B). This observation is typical for per-halogenated porphyrins.[19]

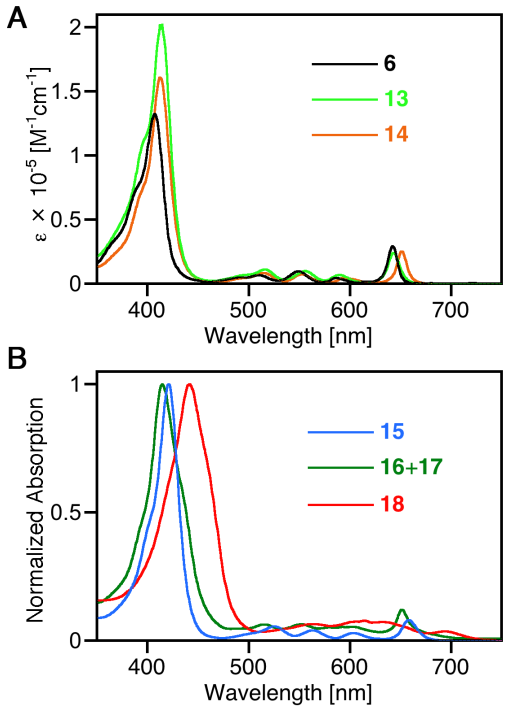


Figure 3. UV-vis spectra ($CHCl_3$) of the compounds indicated.

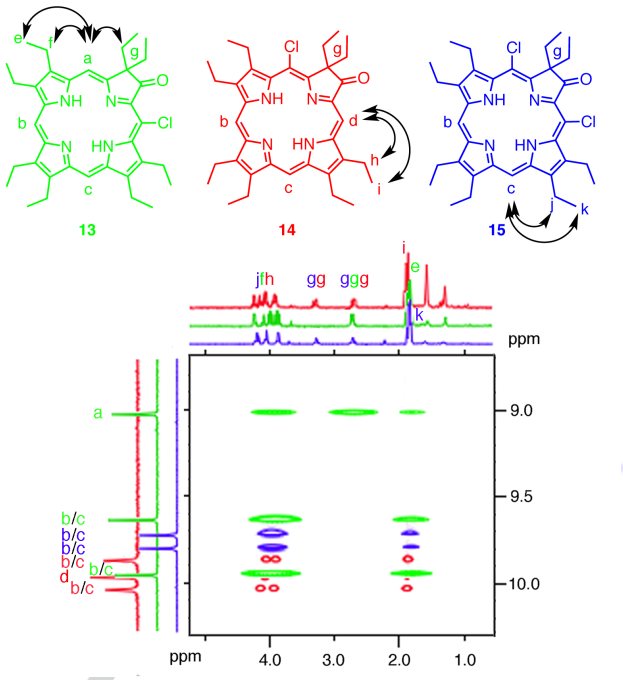


Figure 4. Partial $^1H,^1H$-NOESY spectra of **13** (green),**14** (red) and **15** (blue); arrows indicate some of the diagnostic correlations.

The 1D and 2D NMR ^1H NMR spectra of the mono- and di-halogenated products allow their unambiguous identification. This is accomplished by $^1H,^1H$-NOESY spectroscopy (Figure 4). Key to this is the facile identification of the *meso*-groups adjacent to the *gem*-diethyl groups and the ketone group. The two diastereotopic CH_2-protons of the *gem*-diethyl groups are readily recognized. Their correlation to a neighboring *meso*-group identifies the most high-field shifted *meso*-H atom signal as the 5-position. All other *meso*-proton signals correlate each to two other CH_2-groups, thus identifying mono-chlorinated product **13**. Similarly, the *meso*-group at the 20-position correlates to only one β-ethyl group while the CH_2-groups of the *gem*-diethyl groups do not possess any correlation (and the high-field *meso*-proton signal has vanished). This identifies mono-chlorinated isomer **14**. 5,20-Bischlorinated product **15** shows the spectroscopic signatures of both **13** and **14**.

Further proof for these assignments were provided by the single crystal X-ray crystal structures of 20-chlorooxochlorin **13** and 5,20-dichlorooxochlorin **15** (Figure 5). The mono-halogenated compound **13** is nearly as planar as the parent oxochlorin **6**,[1b] with only a 7° torsion angle between the C_{meso}-Cl and C=O bonds. Dihalogenation of both *meso*-positions adjacent to the carbonyl group results in a larger distortion (25°) of this angle, but this translates only into a 10° out-of-plane distortion of the pyrrolinone moiety plane from the mean plane of the macrocycle.

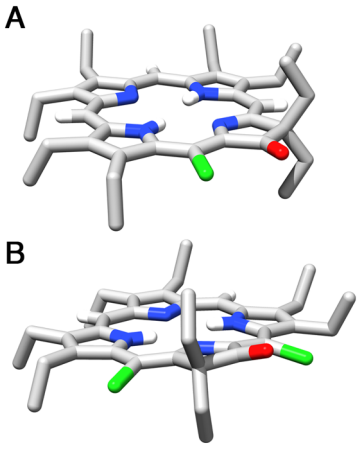


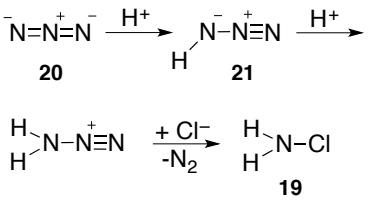
Figure 5. Stick representation of the X-ray single crystal structures of (A) 20-chlorooctaethyloxochlorin **13** and (B) 5,20-dichlorooctaethyloxochlorin **15**, oblique views. All disorder and hydrogen atoms bonded to sp^3-carbons removed for clarity. For details to the X-ray structure analyses, see SI.

While aryl-chlorides can be used for further manipulations,[20] aryl-bromides are potentially more useful in, for example, cross-coupling reactions.[20c, 21] We therefore replaced the conc aq HCl with aq HBr or HBr in acetic acid in the reaction of **6** with NaN_3. However, both acids resulted in the formation of complex reaction mixtures. Partial bromination of the ethyl groups could be recognized in some products.[18a] We abandoned the investigation of this reaction.

OEP is also susceptible to this *meso*-chlorination reaction. However, due to the low solubility of OEP **1** in ODCB, only a small amount of OEP was converted to 5-chloro-octaethylporphyrin under the biphasic conditions. However, OEP in conc aq HCl/NaN_3 reaction generated the known products 5-chloro- and 5,15-dichloro-octaethylporphyrin in respectable yields within 2 h.[18b, 19a]

Mechanistic Consideration of the *meso*-Chlorination of Oxochlorin using HCl/NaN_3

We are not aware that the combination of aq HCl/NaN_3 has been described as a halogenation method.[22] Computations detailed below will provide some support that the halogenation is an electrophilic aromatic substitution reaction on mono-protonated dioxochlorin **6**·H^+. But what might be a reasonable electrophile? We suspect it is chloramine. Its high reactivity with respect to halogenation reactions is well-known.[23] The formation of chloramine can be rationalized (Scheme 4). The protonation of azide **20** produces azoic acid **21**. This may be protonated again, followed by nucleophilic attack by Cl^- and loss of N_2, thus generating chloramine **19**.



Scheme 4. Proposed formation of chloramine **19** from azide **20** in conc aq HCl.

Assuming an electrophilic aromatic substitution reaction also rationalizes the pronounced effects the choice of organic solvents have on the outcome of the reaction. When using toluene, very little consumption of **6** is observed and chlorinated toluene was observed by MS. No reaction was observed in 1,2,4-trimethylbenzene that is even more susceptible to chlorination. $CHCl_3$ leads to a high reactivity of **6**, but was dismissed for safety reasons.

Having identified a potential electrophile and likely chlorination mechanism, this raises the question whether (protonated) oxochlorin **6** is susceptible to an electrophilic aromatic substitution, and whether the observed regioselectivity of the reaction can be rationalized. Computations provide insight into both aspects of this halogenation reaction.

The computed average local ionization energies (ALIEs) were shown to be simple quantitative reactivity predictors of the nucleophilicities of aromatic molecules in cases where steric influences are low,[24] including in porphyrins.[25] Ignoring steric effects, this is because the ionization energies approximate the electronic energy change accompanying the rate-determining step in the reactions of electrophiles with aromatic molecules. Hence, a plot of the ALIE surfaces allows the direct visualization of the predicted sites of reactivity toward an electrophilic attack.

We computed the ALIE surfaces of octaethyloxoporphyrin **6** in the neutral, mono-, and diprotonated states (Figure 6). In the neutral state, none of the *meso*-positions show a significantly lower ionization potential (i.e., higher reactivity) that could rationalize our experimental findings. In the monoprotonated state **6**·H^+, however, the reactivity of the 5- and 20-positions are significantly increased, with the position adjacent to the oxo-group being the most reactive. From a purely electronic point of view, mono-chlorination would be predicted to produce a mixture of the 20- and 5-chloro isomers in a ratio of 1.8:1 in favour of 20-chloro compound **13**. Considering steric effects, the 20-position is also slightly preferred, because it has only one flanking ethyl group (instead of three for the 5-position), this finding matches the experimental findings very well. The diprotonated molecule **6**·$2H^{2+}$ still shows an increased reactivity of the 5- and 20-positions, but the relative difference in reactivity between them and the other *meso*-positions is washed out.

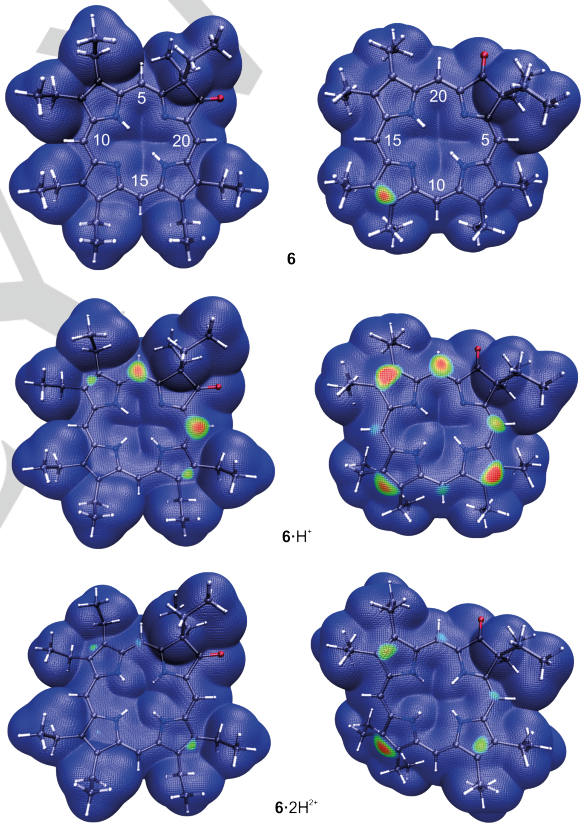


Figure 6. ALIE surfaces with an energy range from 0 to 0.4 eV (lowest absolute values: 8.12 eV, 11.66 eV, 14.79 eV for **6**, **6**·H^+, and **6**·H^{2+}) of the species indicated, highlighting the sites of highest nucleophilicity. Left column: top view; right column: rear view. The red color in the ALIE surfaces shows the area of lowest ionization energy = highest reactivity toward electrophilic substitution.

The ALIEs accurately predict also the regioselectivity of the subsequent chlorinations (see ESI): The ALIEs of the mono-protonated compounds **13**·H^+ and **14**·H^+ correctly predict that dichlorination will take place solely at the 5- or 20 position, respectively. Interestingly, for monoprotonated dichloro-oxochlorin **15**·H^+, the ALIEs predict a chlorination selectively at

the 10-position (ratio of **16** to **17** would be 12:1). However, it seems that the pronounced distortion in **15**·H^+ as the result of the combination of halogenation and protonation also enables diprotonation (forming **15**·$2H^{2+}$) to take place. In accordance with the experiment, the ALIEs of **15**·$2H^{2+}$ shows no preference for the third halogenation of the 10- or 15-position.

Base Properties of Oxochlorin 6

The match of the experimental results with the ALIE computations for mono-protonated **6**·H^+ suggest that **6** is, under the reaction conditions of the halogenation reaction, mono-protonated and not, as generally observed for porphyrins, diprotonated. In fact, the protonation state of oxochlorin **6** was much debated, with conflicting arguments presented for the presence of mono-, di-, and even tricationic species under a variety of protonation conditions.[26]

Oxochlorin **6** exhibits solvatochromism (Figure 7). Its UV-vis spectrum in $CHCl_3$ is 10 nm red-shifted compared to its spectrum in toluene (or ODCB). But when washed with 12 M aq HCl, both solvents show the formation of the identical species, characterized by a λ_{max} band at 622 nm and a split Soret band. Consistent with Stolzenberg's report,[26a] but contrary to Papkovsky's reports,[26b, 26d, 27] we interpret the species with the λ_{max} = 622 nm as the mono-protonated species **6**·H^+. We base this on the results of UV-vis titrations that provided only indications for the formation of a mono-protonated species under the conditions tested (see ESI).

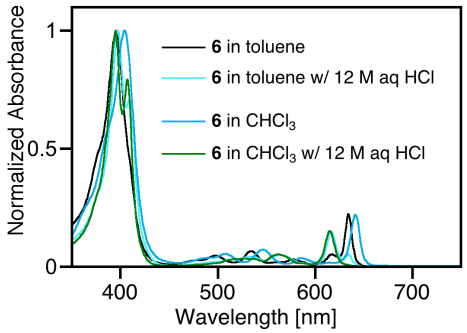


Figure 7. UV-vis spectrum of **6** in the solvents indicated.

The computations provided additional insight and support for this. ALIE surfaces for neutral **6** species show an area of high nucleophilicity at the inner nitrogen opposite of the oxopyrroline (see ESI), suggestive of the first site of protonation. The mono-protonated species, on the other hand, does only show a very small nucleophilicity at the inner nitrogens. Correspondingly, ΔG for the mono-protonation is calculated to be -16 kcal/mol, but is only -4 kcal/mol for the diprotonation. Considering that the oxo-functionality of **6** is in conjugation with the imine within the pyrrolinone, thus drastically reducing its basicity, these findings are reasonable. Also, the crystal structure reported for an imine derivative of **6** also shows selective mono-protonation at this site.[1a]

Conclusions

In conclusion, standard Schmidt reaction conditions (H_2SO_4/NaN_3) applied to oxochlorin **6** did not proceed to form the expected lactam, but the α-hydroxyketone **9** was isolated. This suggested that a nitrene intermediate had formed, but that it did not rearrange to form a ring-expanded product. Instead, a substituent of generally lower migratory aptitude rearranged allowing the retention of the stable and strain-free planar conformation of the starting tetrapyrrolic framework.

Using HCl/NaN_3, the reaction led to a controlled, stepwise and somewhat regioselective chlorination of the 20-(preferred) or the 5-position, followed by the formation of the 5,20-dichlorinated product, followed by an inseparable mixture of the 5,10,20- and 5,15,20-trichlorinated products, and eventually to the tetrachlorinated 5,10,15,20-tetrachlorinated oxochlorin **11**. We are not aware that the use of aq HCl/NaN_3 was ever reported to lead to a chlorination reaction. We suggest that an electrophilic aromatic substitution by an *in situ* formed chloramine species had taken place. Mono-protonated oxochlorin **6**·H^+ was predicted to be the key species to be halogenated as only this species was predicted to possess the prerequisites for the observed regioselectivity. A number of computational and experimental findings further support this supposition. The *meso*-halogenation reaction was demonstrated to be more regioselective and better yielding than the corresponding traditional halogenation reaction using NCS.

Experimental Section

Materials and Instrumentation: Solvents and reagents were used as received. OEP **1**[28] was converted to oxochlorin **6** using either the procedures described by Chang *et al*. or Inhoffen *et al*.[13a, 13b] Aluminum-backed, silica gel 60, 250 µm thickness analytical plates, 20 × 20 cm, glass-backed, silica gel 60, 500 µm thickness preparative TLC plates, and standard grade, 60 Å, 32-63 µm flash column silica gel were used. Alternatively, flash column chromatography was performed on an automated flash chromatography system, on normal-phase silica gel columns. The fluorescence yields (ϕ were determined relative to that of octaethylporphyrin of 0.13 (benzene).[29]

^1H and ^{13}C NMR spectra were recorded with Bruker 300, 400 and 500 MHz instruments in the solvents indicated and are referenced to residual solvent peaks. UV/Vis spectra were recorded with a Cary 50 spectrophotometer, fluorescence spectra with a Cary Eclipse fluorimeter, both Varian, Inc. High- and low-resolution mass spectra were provided by the Mass Spectrometry Facility, Department of Chemistry, University of Connecticut.

Single Crystal X-ray Diffractometry: CCDC-1475300 (**9-rac**), CCDC-1516013 (**13**), and CCDC-1516012 (**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Further information is also provided in the SI.

Details to the Computations: As reported previously,[25] all calculations have been done using Gaussian09[30] using B3LYP-D3/def2-SVP for the

optimizations and a combination of multiwfn,[31] VMD,[32] and PovRay was used to graph the ALIE surfaces.

SAFETY NOTICE: In reaction with water or Brønsted acids, NaN_3 forms the volatile, highly toxic, and explosive hydrogen azide (HN_3).[22] The use of a well-ventilated fume hood is mandatory for the reaction and the initial work-up. The amount of azide used should be limited. Also note that because of the potential for the formation of the explosive azidomethanes CH_2Cl_2/$CHCl_3$ should be avoided when working with azides.[16]

Heptaethyl-3-hydroxy-2-oxochlorin (9-*rac*). Oxochlorin **6** (28.9 mg, 5.25×10^{-5} mol) was placed in a 25 mL round-bottom flask equipped with a reflux condenser and dissolved in conc sulfuric acid (95-98% H_2SO_4, 10 mL). Sodium azide (108 mg, 1.61×10^{-3} mol, 30 eq) was added and the reaction was heated to 130 °C for 2 h. The reaction mixture was allowed to cool to r.t. and was poured over crushed ice (100 g). The crude product mixture was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were washed with a sat'd aq $NaHCO_3$ solution (× 3), dried over anhyd Na_2SO_4, and the solvent was removed by rotary evaporation. The residue was separated by preparative TLC (silica-$CHCl_3$) to afford starting material **6** (6.5 mg, 22%), OEP **1** (4.4 mg, 16%), and product **9-*rac*** as a dark green powder (6.2 mg, 23%). **9-*rac***: MW = 538.7 g/mol; R_f = 0.13 (silica-100% $CHCl_3$); IR (neat): $\nu_{C=O}$ = 1695 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} (log ε): 412 (4.85), 512 (3.60), 556 (3.72), 591 (3.55), 646 (4.31) nm; Fluorescence λ_{max} (C_6H_6, λ_{exc} = 402 nm): 650 nm, ϕ = 0.08; ^{1}H NMR (400 MHz, $CDCl_3$, 40 °C): δ 9.98 (s, 1H, *meso*-CH), 9.85 (s, 1H, *meso*-CH), 9.71 (s, 1H, *meso*-CH), 9.33 (s, 1H, *meso*-CH), 4.08-3.94 (m, 12H, β-CH_2), 3.35 (br s, 1H, exchangeable with D_2O, 3-OH), 2.73-2.62 (m, 2H, 3-CH_2), 1.93-1.84 (m, 18H, β-CH_3), 0.67 (t, ^3J = 7.3 Hz, 3H, 3-CH_3), -2.75 (br s, 1H, exchangeable with D_2O, NH), -2.87 (br s, 1H, exchangeable with D_2O, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 40 °C): δ 209.1, 160.7, 153.3, 144.7, 143.7, 143.4, 143.0, 139.1, 138.1, 138.0, 137.9, 135.5, 134.8, 133.7, 100.1, 98.1, 92.6, 91.3, 80.8, 32.4, 19.7, 19.4, 19.3, 19.2, 18.4, 18.3, 18.2, 18.0, 17.9, 7.3 ppm; HR-MS (ESI^+, 100% CH_3CN, TOF): *m*/*z* calc'd. for $C_{34}H_{43}N_4O_2$ 539.3381 (for $M{\cdot}H^+$); found 539.3389.

***meso*-Chlorination of Oxochlorin 6.** Reagent quantities, times, products, and yields isolated are specified in Table 1. Oxochlorin **6** was dissolved in 1,2-dichlorobenzene in a 100 mL round-bottom flask equipped with a magnetic stir bar. Conc. aq HCl was added to the stirring solution, followed by solid NaN_3, and the mixture was stirred at ambient temperature, followed by an additional batch of NaN_3. During this time, the color of the solution changed from sky blue to greenish blue then yellowish green. The reaction mixture was poured onto crushed ice (250 g) and then extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with satd. aq. $NaHCO_3$ (3 × 10 mL), brine, dried over Na_2SO_4, and evaporated to dryness by rotary evaporation. The mixture was separated by preparative TLC (silica–50% CH_2Cl_2/hexanes).

Table 1. Specific Reaction Conditions for the *meso*-Chlorination of Oxochlorin **6** in a Bisphasic 1,2-dichlorobenzene/aq. HCl Systems.

Oxochlorin **6** (× 10^{-5} mol)	Solvents[a]	NaN_3 [mg]	Time [b]	Products (isolated yields)
31 mg (5.6)	ODCB: 10 mL HCl: 30 mL	170 + 170 after 1 h	2 h	**6** (13.3 mg, 43%) **13** (8.2 mg, 25%) **14** (2.5 mg, 8%) **15** (2.5 mg, 7%)
38 mg (6.8)	ODCB: 10 mL HCl: 30 mL	170 + 170 after 1 h	5 h	**13** (11.4 mg, 24%) **14** (3.2mg, 8%) **15** (7.6 mg, 17%) **16**+**17** (10.5 mg, 26%)
15 mg (2.7)	ODCB: 4 mL HCl: 12 mL	170 + 170 after 1h	18 h	**16**+**17** (4.4 mg, 25%) **18** (10.3 mg, 48 %)
15 mg (2.7)	ODCB: 4 mL HCl: 12 mL	170 + 170 after 1 h	24 h	**18** (14.2 mg, 77%)

[a] ODCB: 99% pure 1,2-dichlorobenzene; 37% aq HCl; [b] Total reaction time before ice quench; all reactions at ambient temperature

20-Chlorooctaethyl-2-oxochlorin 13: MW= 585.2 g/mol, R_f = 0.25 (silica–50% hexanes/CH_2Cl_2); IR (neat): $\nu_{C=O}$ = 1713 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} (log ε): 412 (5.30), 516 (4.05), 555 (3.99), 589 (3.84), 643 (4.38) nm; Fluorescence λ_{max} (C_6H_6, λ_{exc} = 412 nm): 646 nm, ϕ = 0.014; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 9.94 (s, 1H, *meso*-CH), 9.62 (s, 1H, *meso*-CH), 9.01 (s, 1H, *meso*-CH), 4.26-4.19 (q, 2H, β-CH_2), 4.13-4.05 (q, 2H, β-CH_2), 4.01-3.91 (m, 4H, β-CH_2), 3.88-3.82 (m, 4H, β-CH_2), 2.73-2.70 (m, 4H, 3-CH_2), 1.90-1.78 (m, 18H, β-CH_3), 0.37 (t, 6H, ^3J = 7.4 Hz, 3-CH_3), -2.05 (br s, 1H, NH), -2.39 (br, s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 208.9, 161.6, 155.5, 150.3, 145.5, 143.2, 141.3, 140.0, 139.0, 138.4, 137.7, 137.5, 132.3, 131.1, 108.6, 100.9, 96.8, 90.9, 61.8, 22.2, 19.7, 19.6, 19.5, 19.4, 18.5, 18.3, 18.2, 18.1, 17.9, 17.2, 8.4 ppm; HR-MS (ESI+, 100% CH_3CN, TOF): *m*/*z* calc'd for 585.3355 $C_{36}H_{46}ClN_4O$ (for $M{\cdot}H^+$), found 585.3348.

5-Chlorooctaethyl-2-oxochlorin 14: MW= 585.2 g/mol, R_f = 0.33 (silica–50% hexanes/CH_2Cl_2); IR (neat): $\nu_{C=O}$ = 1715 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} (log ε): 412 (5.21), 514 (3.93), 552 (3.87), 593 (3.65), 651 (4.40) nm; Fluorescence λ_{max} (C_6H_6, λ_{exc} = 412 nm): 653 nm, ϕ = 0.023; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 10.01 (s, 1H, *meso*-CH), 9.94 (s, 1H, *meso*-CH), 9.84 (s, 1H, *meso*-CH), 4.29-4.22 (m, 4H, β-CH_2), 4.18-4.12 (m, 4H, β-CH_2), 4.09-4.04 (m, 4H, β-CH_2), 3.97-3.87 (m, 4H, β-CH_2), 3.34-3.25 (m, 2H, 3-CH_2), 2.74-2.65 (m, 2H, 3-CH_2), 1.90-1.81 (m, 18H, β-CH_3), 0.36-0.32 (t, 6H, 3-CH_3), -2.48 (br s, 1H, NH), -2.88 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 212.7, 160.5, 153.4, 151.7, 146.4, 144.6, 144.2, 142.3, 139.42, 139.36, 138.1, 135.8, 135.0, 134.4, 132.4, 107.3, 98.98, 98.90, 91.9, 63.8, 31.3, 22.4, 19.7, 19.6, 19.5, 19.3, 18.5, 18.3, 18.2, 18.1, 17.3, 8.8 ppm; HR-MS (ESI+, 100% CH_3CN, TOF): *m*/*z* calc'd for $C_{36}H_{46}ClN_4O$ 585.3355 (for $M{\cdot}H^+$), found 585.3353.

5,20-Dichlorooctaethyl-2-oxochlorin 15: MW = 619.7 g/mol; R_f = 0.35 (silica–50% CH_2Cl_2/hexanes); IR (neat): $\nu_{C=O}$ = 1714 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} (log ε): 421 (5.34), 525 (4.09), 562 (3.96), 603 (3.83), 658 (4.25) nm; Fluorescence λ_{max} (C_6H_6, λ_{exc} = 421 nm): 661 nm, ϕ = 0.004; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 9.80 (s, 1H, *meso*-CH), 9.72 (s, 1H, *meso*-CH), 4.23-4.16 (m, 4H, β-CH_2), 4.06 (m, 4H, β-CH_2), 3.89-3.85 (m, 4H, β-CH_2), 3.32-3.24 (m, 2H), 2.75-2.68 (m, 2H, 3-CH_2), 1.84 (m, 18H, β-CH_3), 0.43 (t, ^3J = 7.5 Hz, 6H, 3-CH_3), -2.48 (br, s, 2H, NH) ppm; ^{13}C NMR (125MHz, $CDCl_3$, 25 °C): δ 209.3, 158.3, 154.2, 152.5, 145.2, 144.3, 142.7, 141.6, 139.7, 134.4, 132.9, 132.4, 109.0, 107.2, 100.2, 98.1, 65.9, 31.8, 22.6, 22.5, 19.58, 19.56, 19.4, 18.4, 18.3, 18.2, 18.0, 17.1, 17.0, 9.0 ppm; HR-MS (ESI+, 100% CH_3CN, TOF): *m*/*z* calc'd for $C_{36}H_{45}Cl_2N_4O$ 619.2965 (for $M{\cdot}H^+$), found 619.2960.

Inseparable mixture of 5,10,20-trichlorooctaethyl-2-oxochlorins 16 and 5,15,20-trichlorooctaethyl-2-oxochlorins 17: MW = 654.1 g/mol; R_r = 0.38; IR (neat) $\nu_{C=O}$ = 1717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): compound A: δ 9.13 (s, 1H, *meso*-CH), 3.96-3.78 (m, 12H, β-CH_2), 3.12-

3.05 (m, 2H, 3-CH_2), 2.61-2.54 (m, 2H, 3-CH_2), 1.76-1.62 (m, 18H, β-CH_3), 0.49-0.46 (t, 6H, 3-CH_3), -0.24 (br s, 1H, NH), -0.43 (br s, 1H, NH) ppm; Compound B: δ 9.48 (s, 1H, *meso*-CH) ppm; HR-MS (TOF, 100% CH_3CN): *m*/*z* calc'd for $C_{36}H_{43}Cl_4N_4O$ (for $M{\cdot}H^+$) 653.2575, found 653.2559.

5,10,15,20-tetrachlorooctaethyl-2-oxochlorin 18: MW = 688.6 g/mol; R_f = 0.21 (silica-50% CH_2Cl_2/hexanes); IR (neat): $\nu_{C=O}$ = 1714 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} (log ε): 421 (5.34), 525 (4.09), 562 (3.96), 603 (3.83), 658 (4.25) nm; Fluorescence λ_{max} (C_6H_6, λ_{exc} = 410 nm): 653 nm, ϕ = 0.003; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 3.74-3.65 (m, 8H, β-CH_2), 3.51-3.42 (m, 4H, β-CH_2), 3.00-2.91 (m, 2H, 3-CH_2), 2.51-2.39 (m, 2H, 3-CH_2), 1.59-1.44 (m, 18H, β-CH_3), 0.45 (t, *J* = 7.5 Hz, 6H, 3-CH_2), -0.32 (br, s, 2H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 208.7, 159.9, 151.5, 149.3, 145.5, 144.8, 143.9, 143.4, 141.6, 140.3, 139.4, 135.2, 132.4, 131.7, 130.5, 120.9, 117.1, 108.7, 107.0, 64.7, 30.9, 21.2, 21.0, 20.8, 20.6, 16.4, 16.3, 16.2, 16.0, 9.1 ppm; HR-MS (TOF, 100% CH_3CN): *m*/*z* calc'd for $C_{36}H_{43}Cl_4N_4O$ (for $M{\cdot}H^+$) 687.2185, found 687.2166.

OEP **1** (53.3 mg, 6.6×10^{-5} mol) was suspended in conc. aq HCl (80 mL) in a 100 mL round-bottom flask equipped with a coated magnetic stir bar. Then solid NaN_3 (170 mg, 2.61×10^{-3} mol, 25 eq) was added, and the mixture was stirred vigorously at ambient temperature, followed by an additional batch of NaN_3 (170 mg, 2.61×10^{-3} mol, 25 eq) after 1 h. Stirring was continued for another 1 h. During this time, the color of the solution changed from pink to purple pink then reddish pink. The reaction mixture was poured onto crushed ice (250 g) and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic fractions were washed with satd. aq. $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated to dryness by rotary evaporation. The mixture was separated by preparative TLC (silica–$CHCl_3$). 5,15-dichlorooctaethylporphyrin[18b, 19a] (10%) was eluted first and followed by 5-chlorooctaethylporphyrin[18b, 19a] (20%); 60 % of the starting material **1** were recovered.

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Keywords: porphyrinoids • Schmidt reaction • halogenations • heterocycles • synthetic methodology

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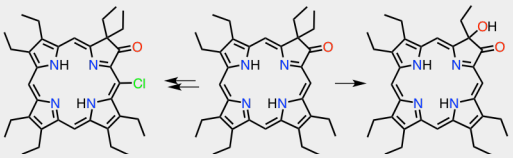

Application of Schmidt reaction conditions to octaethyloxochlorin led, depending on the mineral acid used, to either a loss of an ethyl group and the formation of an α-OH-ketochlorin, or the step-wise and controlled chlorination of the *meso*-positions.

Porphyrinoid chemistry

*Ruoshi Li, Mathias Zeller, Torsten Bruhn, and Christian Brückner**

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Surprising Outcomes of Classic Ring Expansion Conditions Applied to Octaethyloxochlorin. 3. Schmidt Reaction Conditions