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The breaking and mending of porphyrins: reductive coupling of secochlorin bisaldehydes

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ABSTRACT

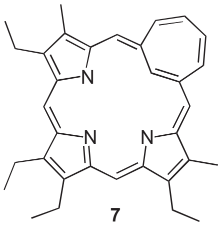
The reaction of free base or Ni(II) complex secochlorin bisaldehydes **$4H_2$** and **4Ni** regenerates the ultimate starting material of the bisaldehydes, *meso*-tetraphenylporphyrin **$2H_2$** and **2Ni**, respectively. Depending on the reaction conditions employed (hydrazine hydrate in pyridine at reflux or hydrazine hydrate activated with sulfur in the presence of aqueous NaOH at ambient temperature), either porphyrin **$2H_2$** is formed together with known dihydroxymorpholinochlorin **$9H_2$** or known 2-hydroxychlorin **$8H_2$**. Two different reaction pathways for the hydrazine reaction can be derived, either involving the formation of a *meso*-tetraphenyl-1,4,5-triazepinoporphyrin that loses spontaneously N_2 or a Wolff–Kishner-type pathway that also involves an intramolecular aldol-type reaction. Neither reaction is synthetically useful but both highlight in an impressive fashion the high thermodynamic stability of porphyrins. They also bring the 'breaking and mending of porphyrin' strategy to its ultimate conclusion by regenerating the starting porphyrin.

The synthesis of porphyrin analogues, such as expanded porphyrins,[1] porphyrin isomers,[2] or porphyrin analogues in which one (or, in selected cases, two) pyrrolic building blocks are replaced by a non-pyrrolic hetero- or carbacycle is one of the key areas of research in current porphyrin chemistry.[3] The desire to gain a deeper understanding of the aromatic nature of porphyrins and the need for fine-tuned chromophores to be used in synthetic light harvesting systems or as photo-chemotherapeutics are some driving forces of this work.[4]

We contributed by synthesizing a range of porphyrinoids containing non-pyrrolic heterocycles such as azetes,[5] oxazoles,[6–8] imidazoles,[9] morpholines,[8,10–12] or pyrazines[13] along a 'porphyrin breaking and mending' pathway.[9] The synthesis of morpholinochlorin **1M** illustrates this approach (Scheme 1). A *meso*-tetraarylporphyrin, **2M**, is converted into the corresponding diolchlorin **3M**.[10] Subsequent diol cleavage generates secochlorin bisaldehyde **4M**,[7,14] that is subjected to a ring-closing reaction.[10,11]

In one particular instance we used a bifunctional nucleophile, hydroxylamine, to ring-close secochlorin **$4H_2$**.[9] However, the anticipated porphyrinoid **$5H_2$** containing a seven-membered ring could not be isolated. Instead, one of the products isolated (in 15%) at that time was novel-imidazoloporphyrin **$6H_2$** (Scheme 2).[9] Its formation was rationalized by the extrusion of CO_2 from **$5H_2$**, thus providing indirect evidence for the existence of oxadiazepinone-derived porphyrinoid **$5H_2$**.

A single class of stable porphyrin analogues containing a seven-membered ring in place of a pyrrole are the known tropiporphyrins, such as example **7**.[15] This carbaporphyrin class was synthesized along a 3+1 pathway, that is along a total synthesis route in which a tripyrromethane and 1,3,5-cycloheptriene-1,6-dicarbaldehyde were condensed to form the macrocycle.



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We showcase here an intriguing reaction that likely involves the intermediacy of a porphyrinoid containing a seven-membered ring that, however, cannot be isolated. Instead, it spontaneously fragments to form a porphyrin. Our findings have no direct preparative significance. However, they contribute to the understanding of the physical and chemical properties of porphyrinoids containing non-pyrrolic heterocycles in general, and nitrogen-rich seven-membered rings in particular.

Following our work on the reaction of secochlorin bisaldehyde **$4H_2$** with hydroxylamine (Scheme 2),[9] it seemed only logical to test the reaction of bisaldehydes **$4H_2$** and **4Ni** with hydrazine. Thus, the bisaldehyde free base and its nickel(II) complex were heated to

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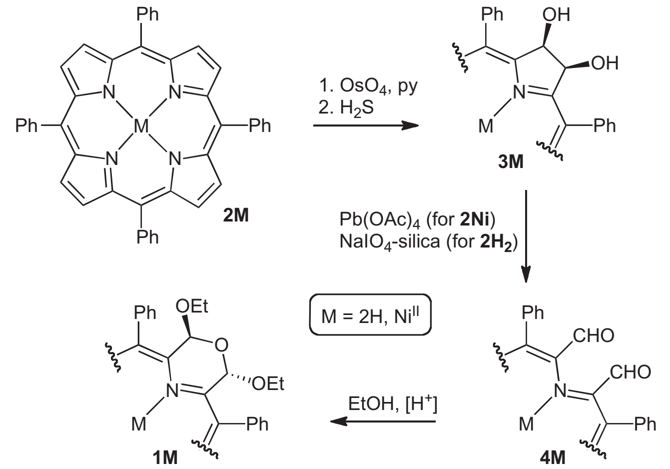
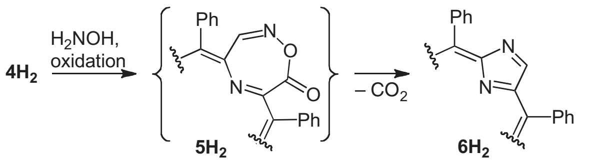


Scheme 1. Synthesis of a morpholinochlorin along the 'breaking and mending of a porphyrin' strategy.



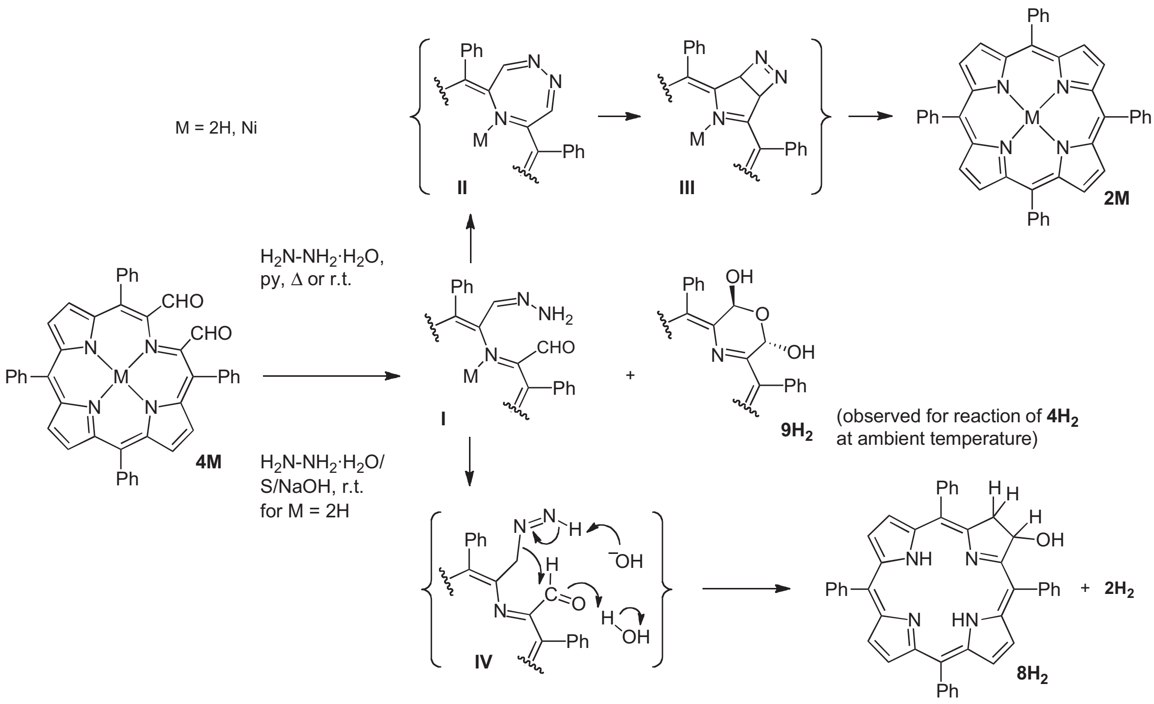
Scheme 2. Synthesis of imidazoloporphyrin $\mathbf{6H_2}$ via putative intermediate $\mathbf{5H_2}$.

reflux with a large stoichiometric excess hydrazine hydrate in pyridine.[16] The reaction produced a single, non-polar product in high (for the Ni(II) complex) and moderate (for the much more labile free base bisaldehyde) yields. Much to our surprise, the products were identified as porphyrins $\mathbf{2H_2}$ and **2Ni**, respectively (Scheme 3).[17]

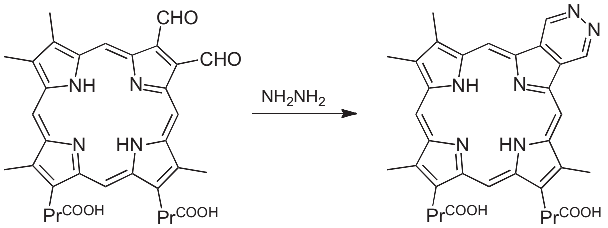
The formation of the porphyrin can be rationalized: the reaction of hydrazine with bisaldehyde **4** under imine-forming conditions likely forms hydrazone **I** and subsequently the 1,4,5-triazepine-containing porphyrinoid **II**. Porphyrin **2M** is subsequently formed by loss of nitrogen from this seven-membered ring intermediate. From a thermodynamic point of view, this reaction certainly possesses a greatly favorable $\Delta H^{\circ}_{\text{reaction}}$ because the likely non-planar porphyrinoid with inherent strain is converted into very stable products, the strain-free, planar porphyrin, and gaseous N_2. Mechanistically, a facile excision of N_2 from 1,4,5-triazepine **II** is not surprising and several pathways are possible. Perhaps the most elegant pathway involves a de facto disrotatory cyclization to form **III** (alas, while electrocyclic reaction pathways are most appealing for this reaction, this is the thermally disallowed reaction pathway),[18] followed by a retro-[2+2] cycloaddition of the rearrangement product (Scheme 3). Interestingly, the analogous inverse reaction steps are frequently utilized in the construction of seven-membered rings.[19] Likewise, porphyrin β,β′-bonds are susceptible to partake in electrocyclic reactions.[20]

In none of the reactions were we able to isolate and directly observe the seven-membered ring product **II**. We reasoned that the loss of nitrogen is assisted by the high temperature of the reaction conditions (pyridine, reflux, 115 °C for several hours). However, a reduction of the reaction temperature to ambient conditions also resulted in the formation of porphyrin $\mathbf{2H_2}$ but accompanied by some of the known dihydroxymorpholinochlorin $\mathbf{9H_2}$, the reaction product of bisaldehyde **4M** with water.[7]

Procedures to activate hydrazine toward hydrazone formation were reported ($H_2N–NH_2·H_2O$ activated with aq NaOH and elemental S at elevated temperature).[21] Using the activated hydrazine, a reaction at room temperature took place over the course of two hours but one of the reaction products still proved to be porphyrin $\mathbf{2H_2}$ (20% isolated yield) plus, much to our surprise, the known β-hydroxylated chlorin $\mathbf{8H_2}$ (in 50% isolated yield).[22] Again, the putative seven-membered ring product could not be directly observed.



Scheme 3. Formation of porphyrin **2M**, β-hydroxychlorin $\mathbf{7H_2}$, and dihydroxymorpholinochlorin $\mathbf{9H_2}$ by reaction of secochlorin **4M** with hydrazine under varying reaction conditions.



10 **11**

Scheme 4. Synthesis of diazine-annulated porphyrin **11**.[25]

The formation of hydroxy-chlorin **$8H_2$** can also be rationalized using a series of known reactions. Again, hydrazone **I** forms as a first step. This undergoes a base-induced tautomerization to form **IV**. Further deprotonation induces the release of N_2 and, in effect, a Wolff–Kishner type reduction of one aldehyde generates an anion that undergoes an intramolecular aldol-type ring-closure reaction with the neighboring aldehyde, thus forming hydroxychlorin **$8H_2$**. Some variations in the order of reactions taking place are conceivable. A loss of a water molecule from **$8H_2$**–thus formally forming the aldol condensation product–generates porphyrin **$2H_2$**.

Of course, we cannot exclude that the porphyrin **$2H_2$** in this reaction was not formed along a competing pathway involving triazepine **II**. On the other hand, we assume that porphyrin **$2H_2$** formed under the pyridine/hydrazine hydrate conditions was formed along the Wolff–Kishner-type pathway as the signature conditions for Wolff–Kishner reductions are generally drastically caustic (KOH, diethylene or ethylene glycol, 180 °C).[23] It thus seems plausible that the two different reaction paths delineated lead to the products observed.

The formation of porphyrins **2** from the aldehydes **4** is formally a reductive coupling. Interestingly, a McMurry reaction[24] on secochlorin bisaldehydes does not lead to the formation of a porphyrin, a circumstance we attribute to steric effects.

Perhaps the closest example of a hydrazine-induced ring-closure reaction of a porphyrin bisaldehyde was presented by Chaudhry and Clezy (Scheme 4).[25] The β,β′-bisaldehyde of the β-octa-substituted porphyrin **$10H_2$** was converted into 1,2-diazine-annulated porphyrin **$11H_2$**, with no report of the loss of nitrogen from this entity.

In summary, the formation of a porphyrinoid containing a seven-membered 1,4,5-triazapine moiety by reaction of a secochlorin bisaldehyde is likely, but the product is unstable with respect to the thermal excision of elemental nitrogen and concomitant formation of a porphyrin. Depending on the reaction conditions employed during the reaction of the bisaldehyde secochlorin with hydrazine, two different reaction pathways that produce some identical products are likely. This reaction highlights the overwhelming stability of the porphyrin framework.

As the original porphyrin starting material was reconstituted, our 'porphyrin breaking and mending' pathway has come to full circle. Or, perhaps more correctly expressing the sentiments of the synthetic chemist aiming at generating novel macrocycles, our efforts were short-circuited.

Acknowledgments

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16. Free base or Ni(II) complex of *meso*-tetraphenylsecochlorin bisaldehyde **$4H_2$** or **4Ni** (~20 mg), prepared according to literature procedures (Ref. 7,10, respectively) was dissolved in pyridine (10 ml) in a round-bottom flask equipped with a magnetic stir bar. To this solution was added $H_2N–NH_2{\cdot}H_2O$ (1.0 ml) and the mixture was heated to reflux for 3 h. When the starting material was consumed (reaction control by TLC and UV–vis), the reaction mixture was evaporated to dryness by rotary evaporation. The resulting mixture was separated on a preparative TLC plate (500 μm silica gel–CH_2Cl_2/petroleum ether 30–60 1:1). Isolated yield for **$2H_2$** and **2Ni** after recrystallization, were up to 50% and 70%, respectively. Their spectroscopic properties were identical to those of independently prepared materials (Ref. 17).
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22. An aqueous suspension of NaOH, sublimed S, and $H_2N–NH_2{\cdot}H_2O$ (1:1:1 molar ratio) was heated to 80–85 °C and stirred for 2 h. The resulting solution was cooled to ambient temperature. *meso*-Tetraphenylsecochlorin bisaldehyde **$4H_2$** (~20 mg), synthesized in THF in a separate flask according to the literature (Ref. 7) shortly prior to when it was needed, was added. The mixture was stirred at ambient temperature for 2 h. The progress of the reaction was monitored using TLC and UV–vis spectroscopy. Once the starting material was consumed, the crude mixture was filtered (glass frit M), the filter cake extracted with CH_2Cl_2, and the combined filtrates were evaporated to dryness using rotary evaporation. The product **$8H_2$** was isolated by preparative TLC (silica–CH_2Cl_2) in 40–50% yields.
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