HIGHLIGHTED ARTICLE

Tweaking the Pigments of Life: Conversion of Porphyrins to Pyrrole-Modified Porphyrins

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Keywords: Porphyrins, chlorins, porphyrin analogues, heterocycles, synthetic methodology, structure-function relationships.

This achievement report is a brief summary of what we learned about the conversion of one or two pyrroles within a porphyrin to a non-pyrrolic heterocycle in the 20 years since our first publication in the field [1]; more comprehensive overviews are available [2, 3]. The report is a celebration of the undergraduate and graduate students and postdocs that were involved in the work – and with whom it continues to be exciting to learn more about pyrrole-modified porphyrins (PMPs). The report is also a nod to my scientific mentors that encouraged the pursuit of curiosity-driven work and taught me scientific rigor. Lastly, this report is written with the student looking for an independent career in mind and who wonders how creative research programs emerge from seemingly nowhere. They don’t. What makes a compelling and compact story here, took many decades of (wo)man-years of hard deliberate work and many fortuitous turns.

1. THE BEGINNINGS

I was firstly exposed to porphyrin chemistry as a graduate student with Professor David Dolphin at the University of British Columbia. As part of a project that required the introduction of substituents to β-octaalkylporphyrins [4], we utilized a well-known OsO4-mediated dihydroxylation reaction to generate the corresponding dihydroxochlorins. Having previously worked with the more readily prepared meso-tetraarylporphyrins, the question arose why this most useful dihydroxylation reaction had never been applied to this class of porphyrins. Hence, we set out to test this. Soon we found out that it was possible, indeed. The osmylation/reduction of porphyrin 1 generated the stable chlorin diol 2 and corresponding bacteriochlorin tetaols 3 (Scheme 1) [1, 5]. Initially, the reaction was fickle and exceedingly slow (requiring week-long reaction times), but we optimized the reaction conditions until this transformation became practical (albeit rarely rapid), reliable, and versatile [1, 5]. The risks of working with OsO4 can be minimized using engineering controls and regular personal protective equipment; the cost of OsO4 is routinely much lower than that of almost any meso-arylporphyrin to be dihydroxylated.

Once we had multi-gram quantities of the diols and tetaols in hand, the next question beckoning for experimental verification was whether the standard reactions known to convert a diol functionality into bisaldehydes or biscalboxylic acids were also applicable to these diols. If so, we hypothesized, the resulting oxidation products might be utilized in subsequent reactions to generate novel porphyrinoids. Two examples among the chemistry of β-octaethylporphyrin [6, 7], as well as a fortuitously observed mesoarylporphyrin oxidation product [8, 9], supported this. Also, multiple porphyrinoids containing non-pyrrolic building blocks had already been prepared by total synthesis [2, 3]. We surmised that systematic perturbations of the porphyrinic macrocycle could be used as tools to teach us something about the nature of the parent pigments of life. Perhaps some compounds would even possess unique physical (optical) or chemical properties of utility in medical or technical applications.

Over time, these hypotheses could be verified and we made many unexpected discoveries along the way. In fact, this seemingly simple reaction sequence became to define a major portion of our independent research program [10].

2. THE SCOPE OF THE BREAKING AND MENDING OF PORPHYRINS

The scope of what we later dubbed the ‘breaking and mending of porphyrins’ approach toward the synthesis of PMPs proved most...
versatile. For example, PMPs with cleaved $\beta,\beta'$-bonds, such as 4 (also a key intermediate in the generation of a host of PMPs) [1], 5 [11], 6 [11], or 7 [12], became accessible (Scheme 2). The pyrrole moiety could be contracted by one $\beta$-carbon atom (8) [13], one $\beta$-carbon could be replaced by oxygen (9, 10, 11, 12) [14-17] or nitrogen atoms (13, 14) [18, 19], or the pyrrole moiety could be expanded by carbon (15) [20], nitrogen (16) [21], oxygen (17) [1, 22-24], or sulfur (18) [20, 25] atoms to form 6-membered heterocycle-based PMPs. Many reactions were discovered that further interconverted or derivatized PMPs (see, e.g. 6 $\rightarrow$ 14) [14, 15, 25, 26]. The structural variety of the PMPs could be extended by the conversion of a second pyrrolic building block, as done in bacteriochlorin analogues 19 [26], 20 [16], and 21 [24]. The subject of this report are meso-arylporphyrin-based PMPs, but more recently we also found $\beta$-octaalkylporphyrins to be amenable to conversion to a number of PMPs [27-29].

3. RED-SHIFTS, NON-PLANARITY, AND CHIRALITY

The pyrrole-modifications resulted in a broad modulation of the physical and chemical spectra of the parent porphyrin/chlorin. Some PMPs, e.g., 9, 13, 14, and even 16 are planar and possess most regular porphyrin-like optical spectra under neutral conditions, but when protonated or treated with base, respectively, they revealed their non-standard behavior [14, 18-19]. PMPs like the azeteochlorin 8, chlorophin 5, oxazolochlorins 10 and 11, or oxazolobacteriochlorins 20 are chlorin- or bacteriochlorin-like, respectively.

Others, like the morpholinochlorins 17 (or their metal complexes), possess (metallo)chlorin-like optical spectra [1, 30], but they are non-planar, exhibiting stable conformations of helimeric chirality [22, 23], and they are electrochemically principally different from regular chlorins [31]. These PMPs also allow distortions...
modes not possible in regular porphyrins [24]. The panchromatic UV-vis spectra of the π-extended, non-planar indaphyrins 7 and 19, for example, do not resemble those of porphyrins or any other hydroporphyrins [12, 26]. Thus, PMPs helped to illuminate principle aspects of porphyrin conformation, conformational flexibility, structure-optical properties relationships, aromaticity, and other fundamental questions of broad interest.

4. ‘PORPHYRIN IS THE MOST STABLE PMP’

As the structural variety of the PMPs made along the ‘breaking and mending’ of porphyrins route increased, we made a number of curious observations where a PMP incorporating a 7-membered (or larger) ring was expected, but only a PMP with a 5-membered ring was formed (Scheme 3) [19, 32, 33].

Thus, fragmentation reactions took place that established more porphyrin-like structures composed of four 5-membered rings. Evidently, the achievement of the most stable architectures that are free of major distortions or bond strains drove the unusual fragmentation chemistry. While this constitutes a limitation of the ‘breaking and mending’ approach, we developed a work-around solution. For example, under certain circumstances, the inversion of the breaking and mending steps yields ‘super-sized’ PMPs incorporating larger than 6-membered heterocycles, such as 24, even though many related compounds still fragment spontaneously to generate the porphyrin-like porpholactam 13 [33].

5. FINDING PROBLEMS TO MATCH THE SOLUTIONS

Some PMPs contain functionalities on the periphery of their chromophore that sense the presence of specific chemical species and respond with an optical signal. For instance, porpholactones 9 (as the Pt(II) complex of the pentafluorophenyl derivative) emerged as an excellent sensor to indicate the presence of nucleophiles, like cyanide and hydroxide (in the range between ~pH 9 and 13) [34, 35]. Healthy concrete maintains a high pH that is lowered upon a range of ageing processes, but only much limited methods to track this process were available. In collaboration with civil engineers, we developed porpholactones into a ratiometric optical dye for the temporally and spatially resolved imaging of the ageing of concrete [36]. Curiously, the same porpholactone platinum complex was also shown – albeit not by us – to be a component in pressure-sensitive paints that can optically map the airflow around objects, whereby the mechanism of action is not directly involving the lactone functionality [37].

Oxochlorins, such as 10 and 11, are singlet-oxygen generating photosensitizers and possess light absorption in the NIR range. These properties recommend their use as photosensitizers for PDT [14-16]. Moreover, the hemiacetal functionality on 11 allows for rapid bond formation and breaking/exchanging with a variety of alcohols [14]. In part, we attribute the in vivo efficacy of 11 as a PDT drug to its ability to mediate its solubility and bioavailability by dynamic association with different (polymeric) alcohols [38].

Other PMPs (such as 21) exhibited the conformational flexibility and conformation-dependent optical properties that suggest their use as mechanochromic dyes [24], others were shown to be better lanthanide sensitizers than the corresponding porphyrins [39], or they were tested as photoacoustic contrast agents [40]. While some of the applications for the PMPs that emerged are within the traditional realms of porphyrinoids (PDT photosensitizers, optical imaging, light harvesting), their utility in these applications is often because of the structural and chemical properties unique to PMPs. In addition, some of the less traditional applications, such as their use in dyes for infrastructure health monitoring or other chemosensing

Scheme 3. Examples of reactions designed to generate a PMP incorporating a 7-membered heterocycle but where the desired products collapses into a more porphyrin-like structure.
applications [17], were made possible specifically by the extra functionality introduced into the PMPs.

6. LOOKING AHEAD

Aside from the general search for the broadening of the known PMP classes, the inclusion of examples of isobacteriochlorin-type PMPs, i.e., PMPs in which two adjacent pyrrolic moieties were modified, is desirable from a fundamental point of view. The corresponding isobacteriochlorin tetrabis(12) are available [41]. Curiously, examples of the latter compound class was observed in one of the earliest reports on porpholactones [9], but detailed studies or rational syntheses have yet to be presented. Likewise, the generation and understanding of tris-substituted systems are attractive. We are actively engaged in filling these gaps.

What began as purely curiosity-driven investigations blossomed into its own burgeoning sub-field within synthetic porphyrin chemistry. The end of the possibilities of the ‘breaking and mending strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight. In fact, the general interest into the strategy’ to generate novel porphyrinoids and the discovery of their useful properties is not in sight.


