

## Evaluation of Octaethyl-7,17-dioxobacteriochlorin as a Ligand for Transition Metals

David Schnable,<sup>§</sup> Nivedita Chaudhri,<sup>§</sup> Ruoshi Li, Matthias Zeller, and Christian Brückner\*Cite This: <https://dx.doi.org/10.1021/acs.inorgchem.9b03231>

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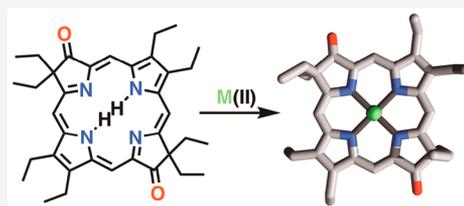
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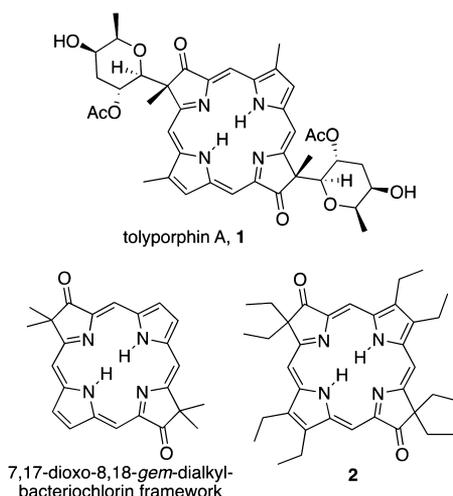
Supporting Information

**ABSTRACT:** The propensity of octaethyl-7,17-dioxobacteriochlorin toward the formation of transition metal complexes was evaluated. A variety of  $M^{II}$  ions ( $M = \text{Co, Ni, Cu, Zn, Pd, Ag, and Cd}$ ) and  $\text{Fe(III)}$  could be inserted using standard methodologies or, more often, using more forcing conditions. The stable products were spectroscopically characterized. The solid-state structures of the  $\text{Ni(II)}$ ,  $\text{Cu(II)}$ ,  $\text{Pd(II)}$ , and  $\text{Ag(II)}$  complexes could also be determined by single crystal X-ray diffractometry, whereby the [7,17-dioxobacteriochlorinato] chromophore was found to be largely planar in all cases. The rate of  $\text{Zn(II)}$  insertion into octaethyl-7,17-dioxobacteriochlorin was less than half that into the corresponding 7-oxochlorin, which itself was about half the rate into the parent octaethylporphyrin. These rate differences reflect the relative decreased basicity of the  $\beta$ -oxo-substituted chromophores and possibly also their decreased conformational flexibility. We compare the basicity of the dioxobacteriochlorin to that of a range of related products of varying reduction state (porphyrin, chlorin, bacteriochlorin), an isomer, and the absence or presence of oxo-functionality, like oxochlorin, chlorin, oxobacteriochlorins, and bacteriochlorin, quantifying the effects of these macrocycle modifications. The work rationalizes earlier reports of the inability of tolyporphyrin A, a natural product possessing a 7,17-dioxobacteriochlorin chromophore, to form metal complexes and provide a more quantitative understanding of the degree of modulation that  $\beta$ -oxo groups have on the coordination properties of porphyrinoids.



## INTRODUCTION

Tolyporphins are a family of tetrapyrroles isolated from the cyanobacterium *Tolypothrix nodosa*.<sup>1–4</sup> They share a unique 7,17-dioxobacteriochlorin chromophore carrying also C-glycoside moieties at their  $\beta$ -positions.<sup>5–8</sup> The most prevalent and well-studied member of this class is tolyporphyrin A (1).



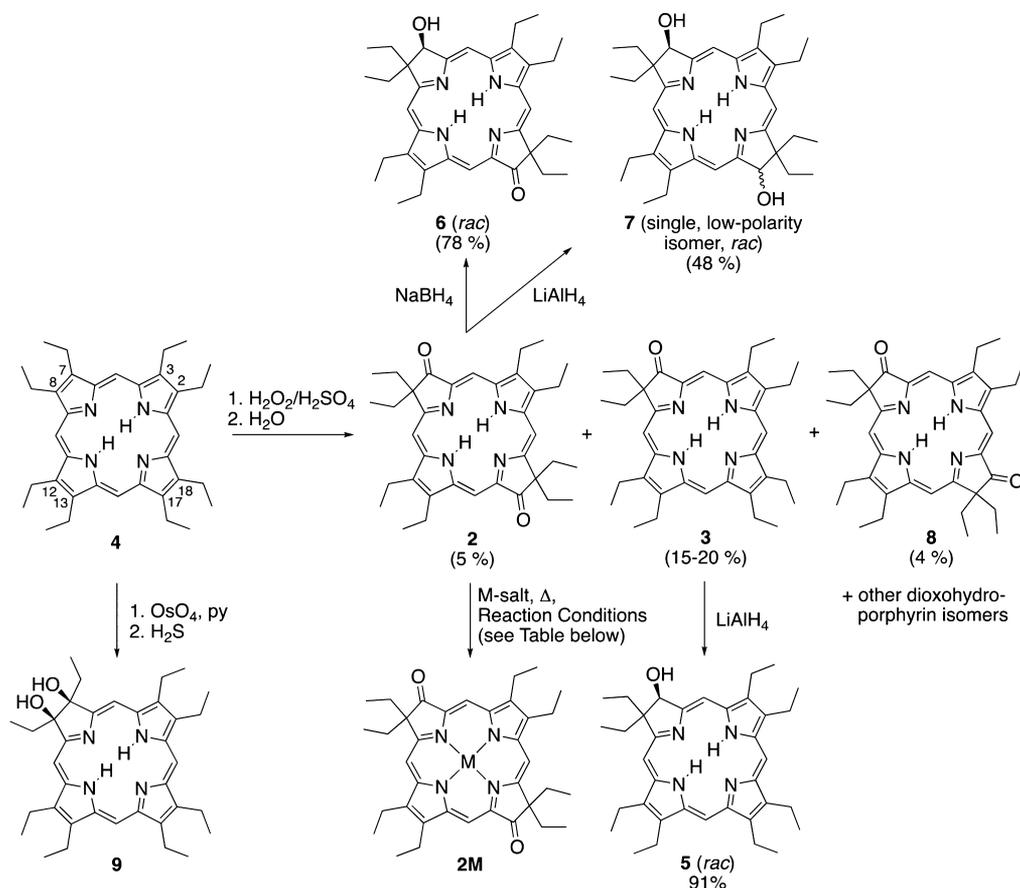
Tolyporphyrin A effectively reverses multidrug resistance (MDR) of cancer cells.<sup>9</sup> MDR describes the phenomenon that cells can become resistant to many chemotherapeutics by an overexpression of a transmembrane P-glycoprotein pump

that detoxifies cells by exporting hundreds of chemically unrelated toxins out of cells, thereby lowering their intracellular concentrations. Finding drugs that reverse this significant limitation of cancer chemotherapies is important.

The tolyporphins, however, also exhibit significant cytotoxicity, limiting their therapeutic potential as MDR reversal drugs. Furthermore, it is also known that tolyporphins are effective photosensitizers; like many tetrapyrrolic pigments, upon irradiation with visible light and in the presence of triplet oxygen ( $^3\text{O}_2$ ) they produce toxic singlet oxygen ( $^1\text{O}_2$ ).<sup>10</sup> Therefore, to more conveniently utilize tolyporphins as potential pharmaceuticals to reverse MDR, at least their phototoxicity must be reduced. Prinsep et al. hypothesized that the insertion of a metal ion into the dioxobacteriochlorin core may reduce its (photo)cytotoxicity,<sup>11</sup> after all, certain metal ions switch off the ability of a photosensitizer to generate singlet oxygen. The authors thus reported the preparation of the  $\text{Ag(II)}$  and  $\text{Cu(II)}$  complexes of tolyporphins.<sup>11</sup> These complexes showed considerably lower cytotoxicity. Alas, they were also less potent in reversing MDR.<sup>11</sup>

In general, tetrapyrrolic macrocycles are excellent metal chelators for a wide range of metal ions.<sup>12</sup> Thus, it was

Received: November 4, 2019

Scheme 1. Synthetic Pathway<sup>a</sup>**Reaction Conditions:**

5 equiv. M source, solvent, temperature, time, base, isolated yield

<b>2Fe:</b> M = Fe(III)Cl	FeCl <sub>3</sub> ·6H <sub>2</sub> O, acetic acid reflux, 40 min, –, 70%
<b>2Co:</b> M = Co(II)	Co(NO <sub>3</sub> ) <sub>2</sub> ·6H <sub>2</sub> O, DMF reflux, 210 min, 10 eq Li <sub>2</sub> CO <sub>3</sub> , 91%
<b>2Ni:</b> M = Ni(II)	Ni(OAc) <sub>2</sub> ·4H <sub>2</sub> O, PhCN reflux, 300 min, –, 84%
<b>2Cu:</b> M = Cu(II)	Cu(OAc) <sub>2</sub> , DMF reflux, 30 min, –, 83%
<b>2Zn:</b> M = Zn(II)	ZnCl <sub>2</sub> ·2H <sub>2</sub> O, DMF or pyridine reflux, 210 min, 10 eq Li <sub>2</sub> CO <sub>3</sub> , 96%
<b>2Pd:</b> M = Pd(II)	PdCl <sub>2</sub> , PhCN reflux, 120 min, –, 71%
<b>2Ag:</b> M = Ag(II)	Ag(OAc), pyridine reflux, 60 min, –, 52%
<b>2Cd:</b> M = Cd(II)	CdCl <sub>2</sub> ·½ H <sub>2</sub> O, DMF reflux, 300 min, 10 eq Li <sub>2</sub> CO <sub>3</sub> , 91%

<sup>a</sup>Synthesis of octaethyl-7,17-dioxobacteriochlorin **2**, together with 7-oxochlorin **3** and 7,18-dioxobacteriochlorin **8** from octaethylporphyrin **4**,<sup>46</sup> formation of the metal complexes **2M**, reduction of 7-oxochlorin **3**<sup>28</sup> and dioxobacteriochlorin **2**, and dihydroxylation of octaethylporphyrin **4**.<sup>51,57</sup> Numbering system used shown in compound **4**.

surprising that Prinsep et al. reported that, besides the Cu(II) and Ag(II) complexes of **1**, no other metal complexes could be prepared. Using stoichiometric excess of the metal salts MgCl<sub>2</sub>·6H<sub>2</sub>O, VO(SO<sub>4</sub>), FeCl<sub>2</sub>·4H<sub>2</sub>O (in air), CoCl<sub>2</sub>·6H<sub>2</sub>O (in air), Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, ZnSO<sub>4</sub>·7H<sub>2</sub>O (the Zn(II) complex was observed under the conditions of ESI+ MS), Na<sub>2</sub>[PdCl<sub>4</sub>] or Pd(NO<sub>3</sub>)<sub>2</sub>, Cd(ClO<sub>4</sub>)<sub>2</sub>, and Pb(NO<sub>3</sub>)<sub>2</sub>, all in MeOH containing NEt<sub>3</sub> at reflux temperature (65–70 °C) over 20–40 min did not form the expected complexes.<sup>11</sup> Regular porphyrins, however, would have been expected to have inserted at least some of the metal ions.<sup>12</sup> The inability to form the metal complexes might have its origins in an intrinsic inhibition of the 7,17-dioxobacteriochlorin framework toward metal insertion, requiring the use of more forcing conditions. Even if this was not stated, we suspect the thermal instability of tolyporphyrin A made this approach impossible.

The assumption that the 7,17-dioxobacteriochlorin is deactivated toward the chelation of metal ions is likely because of two effects. First, bacteriochlorins are much less basic than the corresponding chlorins or porphyrins.<sup>13</sup> Compared to the broadly investigated coordination properties of porphyrins,<sup>12</sup> those of the bacteriochlorins have been studied to a much lesser degree.<sup>14–16</sup> Second, the basicity of the two imine nitrogens in the framework is expected to be further reduced by the presence of the β-oxo-functionalities.

A wide range of β-oxo-porphyrins or β-oxo-hydroporphyrins (excluding here β,β'-dioxo-porphyrins and their secochlorin analogues)<sup>17–19</sup> has become available, either through manipulations of porphyrins or total syntheses.<sup>8,20–23</sup> The strong electronic influences of the β-oxo-auxochrome were described (in oxoporphyrins as well as porpholactones).<sup>23–27</sup> The zinc(II),<sup>28,29</sup> iron(III),<sup>30</sup> nickel(II),<sup>28</sup> copper(II),<sup>28,31</sup>

palladium(II),<sup>29</sup> and platinum(II)<sup>29</sup> complexes of 7-oxochlorin (**3**) were reported. 7,12-Dioxoisobacteriochlorin iron(III) complexes are found as prosthetic groups in nature<sup>32</sup> and were utilized in the study of the metal complexes of 7,12-dioxoisobacteriochlorin model systems aimed at the understanding of the role of the oxo-substituted chromophore.<sup>33–41</sup> Comparably less is known about the coordination properties of the isomeric 7,17-dioxobacteriochlorin system. Nonetheless, in addition to the tolyporphyrin A copper(II) and silver(II) complexes<sup>11</sup> the nickel(II),<sup>24</sup> copper(II),<sup>42,43</sup> palladium(II),<sup>44</sup> and platinum(II)<sup>44</sup> complexes of octaethyl-7,17-dioxobacteriochlorin **2** were formed and characterized. No explicit reference to an assessment of any difficulties to insert the metal ions was made in any of the reports. The group of Lindsey evaluated the conditions for the insertion of metals into a wider range of bacteriochlorins, including  $\beta$ -oxo-derivatives.<sup>16</sup> Other 7,17-dioxobacteriochlorin complexes were formed as a consequence of the synthetic strategy chosen to assemble the macrocycle.<sup>45</sup>

We thus set out to characterize the chelation properties of the 7,17-dioxo-8,18-bis-*gem*-dialkylbacteriochlorin chromophore of the tolyporphyrins in a more systematic fashion. For this purpose, we chose the model compound octaethyl-7,17-dioxobacteriochlorin **2** for its accessibility and predicted thermal stability.<sup>46</sup> We assessed in a qualitative fashion its coordination ability by comparison of the conditions needed to form a range of complexes with other porphyrinic macrocycles. We compared its rate of insertion in comparison to that of the corresponding 7-oxochlorin and porphyrin. We also determined the basicity of the dioxobacteriochlorin chromophore to that of a range of related chromophores of varying reduction state (porphyrin, chlorin, bacteriochlorin) and in the absence or presence of oxo-functionalities. We will present evidence that suggest that the 7,17-dioxobacteriochlorin macrocycle is competent in forming a range of metal complexes but that they require significantly harsher conditions for their formation than the corresponding complexes of the mono-oxochlorin, bacteriochlorin, chlorin, or parent porphyrin. This can be largely attributed to the much-reduced basicity of the 7,17-dioxobacteriochlorin chromophore.

## RESULTS AND DISCUSSION

**Preparation of 7-Oxochlorin and 7,17- and 7,18-Dioxobacteriochlorins.** Octaethyl-7,17-dioxobacteriochlorin **2** and octaethyl-7-oxochlorin **3**, together with all other isomers of the  $\beta$ -diketone series (such as 7,18-dioxobacteriochlorin **8**), were prepared by H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>SO<sub>4</sub> oxidation of multigram quantities of octaethylporphyrin **4**, as described by Inhoffen and Nolte (Scheme 1).<sup>28,46</sup> The reaction itself can be traced back to the work of the groups of Fischer and Johnson.<sup>47,48</sup> Alternate syntheses are available.<sup>49–52</sup>

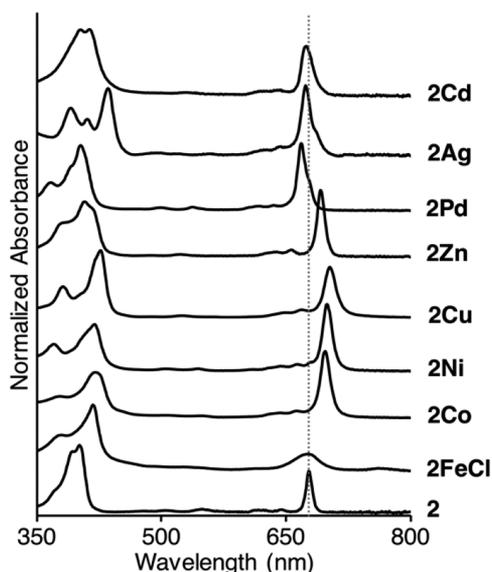
**Reduction Products of Dioxobacteriochlorin **2** and Oxochlorin **3**.** To isolate the electronic effect of the  $\beta$ -oxo group(s) from the effects of the degree of macrocycle reduction (porphyrin, chlorin, bacteriochlorin), we prepared three derivatives by hydride reduction of the carbonyl groups in  $\beta$ -oxohydroxy porphyrins **2** and **3** (Scheme 1): known  $\beta$ -hydroxyoctaethylchlorin **5**,<sup>28,51,53,54</sup> and novel monoreduced products  $\beta$ -hydroxyoxobacteriochlorin **6** and bis-reduced  $\beta$ -dihydroxybacteriochlorin **7**, respectively. Only the low polarity isomer of the two possible stereoisomers of **7** was utilized. The spectroscopic properties of the alcohols **6** and **7** are equivalent to those of related derivatives<sup>55,56</sup> and support their connectivity (see SI for details). Hydroxychlorin **5** shows a

typical chlorin UV–vis spectrum,  $\beta$ -hydroxyoxobacteriochlorin **6** possesses a red-shifted chlorin-type spectrum, whereas  $\beta$ -dihydroxybacteriochlorin **7** exhibits a typical bacteriochlorin spectrum (see SI). Lastly, we included another regular chlorin in this investigation, known *vic*-dihydroxychlorin **9**, prepared by OsO<sub>4</sub>-mediated dihydroxylation of porphyrin **4**.<sup>51,57</sup>

**Metal Insertions.** The insertion of metal ions into porphyrinic compounds is typically accomplished by heating a solution of the porphyrin and a metal salt in a (coordinating) solvent.<sup>12</sup> The reaction may require the presence of an additional base (or basic solvent). Alternative mechanochemical methods have emerged for some metal ions.<sup>58,59</sup> Generally, the rate-limiting steps of the metal insertion are determined by the considerable kinetic barrier of the planar and relatively rigid porphyrin to distort from planarity to present the imine-type nitrogen atoms to the metal ions in solution, the basicity of the ligand nitrogen atoms, and the intrinsic kinetic lability of the metal ion to be inserted.<sup>60</sup> The sum of these factors determines the solvent/reaction temperature needed for the metal insertion reaction to be successful.<sup>12</sup>

The results of the metal insertion reactions to generate the Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Pd(II), Ag(II), and Cd(II) complexes **2M** are presented in Scheme 1. The conditions were derived from a screen of a range of organic and mineral bases. The often modest yields are the result of the small-scale reaction and their workup, including crystallizations; only under the harshest conditions was some minor degree of ligand decomposition observed. Remarkably, the reaction conditions to affect efficient metal insertion are in most cases harsher than the standard reaction conditions<sup>12</sup> for the insertion of the respective metal ion into regular porphyrins. For instance, the insertion of zinc into porphyrins under standard conditions (Zn(II) source in CHCl<sub>3</sub>/MeOH at ~65 °C; no need for an extraneous base)<sup>12</sup> failed to yield **2Zn**. Instead, hot pyridine (115 °C) or DMF (153 °C) in the presence of lithium carbonate was required. Likewise, expedient nickel insertion required PhCN (at 191 °C) instead of hot pyridine or DMF. Others, like the insertion of Ag(II) by disproportionation of an Ag(I) source, take place in the customary solvent pyridine, albeit the yield of the reaction is relatively low after 60 min and we found it necessary to degas the solution to prevent a further reduction of yield by way of decomposition of the ligand. Otherwise we note the thermal stability of the dioxobacteriochlorin ligand, even at extended times at elevated temperatures under oxic conditions. Other metals were tested but failed to form complexes with **2** under all conventional, thermal conditions tested, including V(IV) (as vanadyl, VO<sup>2+</sup>), Cr(II), Sn(II), and Au(III). However, some of those (kinetically inert) metals are also not readily inserted into porphyrins.<sup>12</sup>

**UV–vis Spectroscopic Properties of the Metal Complexes.** The normalized UV–vis absorption spectra of free base **2** and its metal complexes **2M** are shown in Figure 1 (and tabulated in Table S1). Upon insertion of the metal ions into free base **2**, the UV–vis absorption spectra of **2M** amplify the split of the Soret bands already present in the free base. The prominent single Q-band (and  $\lambda_{\text{max}}$  band) of the free base is retained and, depending on the particular metal ion, at essentially the same position (for **2Fe**), slightly hypsochromically (for the 4d element complexes **2Cd**, **2Ag**, and **2Pd**), or bathochromically (for the 3d element complexes **2Co**, **2Cu**, **2Zn**, and **2Ni**) shifted. The other less prominent Q-bands of the free base become even less so upon metalation.

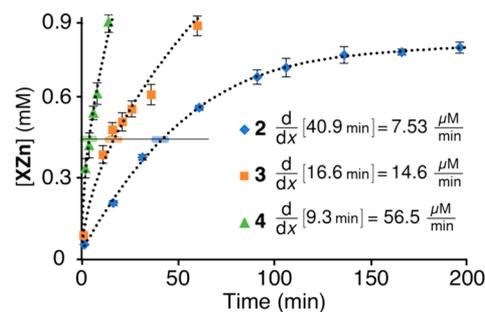


**Figure 1.** Stacked normalized UV-vis spectra ( $\text{CH}_2\text{Cl}_2$ ) of free-base **2** and its metal complexes **2M** indicated. A vertical dotted line at 677 nm ( $\lambda_{\text{max}}$  of **2**) serves as a reference line. See Supporting Information for full-scale spectra.

**Crystallographic Analysis.** XRD-quality single crystals could be grown for the Cu(II), Ni(II), Ag(II), and Pd(II) complexes of octaethyl-7,17-dioxobacteriochlorin **2** (Figure 2; for details, see SI). All of the structures were found to be almost perfectly planar, possessing  $\Delta_{24}$  RMS value of significantly less than 0.1 Å with the largest deviation observed, as expected,<sup>19</sup> for the complex with the smallest ion, **2Ni**. A survey of crystal structures of **4M** deposited at the CCDC reveals that the complexes of **2** tend toward more planar conformations, that is, exhibiting smaller  $\Delta_{24}$  values when compared to most complexes of **4** with the same metal ion. The  $\Delta_{24}$  values for some **4Ni** complexes are larger (0.46<sup>61</sup> or 0.30<sup>62</sup>) than that for **2Ni** (0.075), though more planar polymorphs are also known (0.03).<sup>63</sup> Overall, this may suggest a larger stiffness of the 7,17-dioxobacteriochlorin chromophore and may contribute to the markedly increased difficulty of inserting metals into it. Others have argued on the basis of

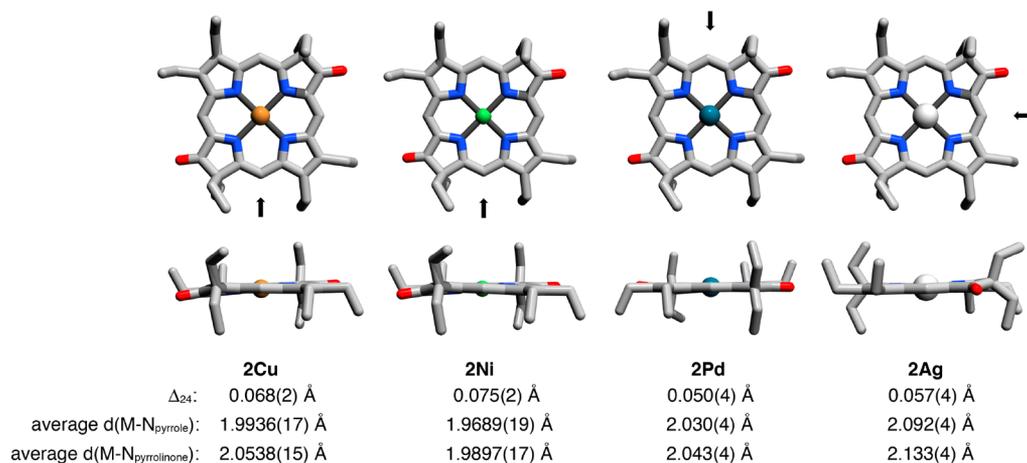
electrochemical experiments that the oxo-groups increase the flexibility of the macrocycle.<sup>24</sup> For all four complexes, the displacement of the metal from the  $\text{N}_4$  plane is found to be less than 0.01 Å. This necessitates increased in-plane “stretching” of the macrocycle to accommodate larger metal ions within the ring. This is observed by the generally increasing diagonal  $\text{N}_1\text{—N}_3$  distances as the size of the metal ion increases (e.g., from 4.107(2) to 4.263(4) Å for **2Cu** and **2Ag**, respectively).

**Relative Metal Insertion Rates.** To provide a more quantitative measure of the generally perceived slower metal ion insertion rates for dioxobacteriochlorin **2**, we directly compared its zinc(II) insertion rate with that for oxochlorin **3** (forming **3Zn**)<sup>28,29</sup> and the parent octaethylporphyrin **4** (forming **4Zn**)<sup>64</sup> using identical metal ion insertion conditions (Figure 3). Evidently, the multistep metathesis reactions are

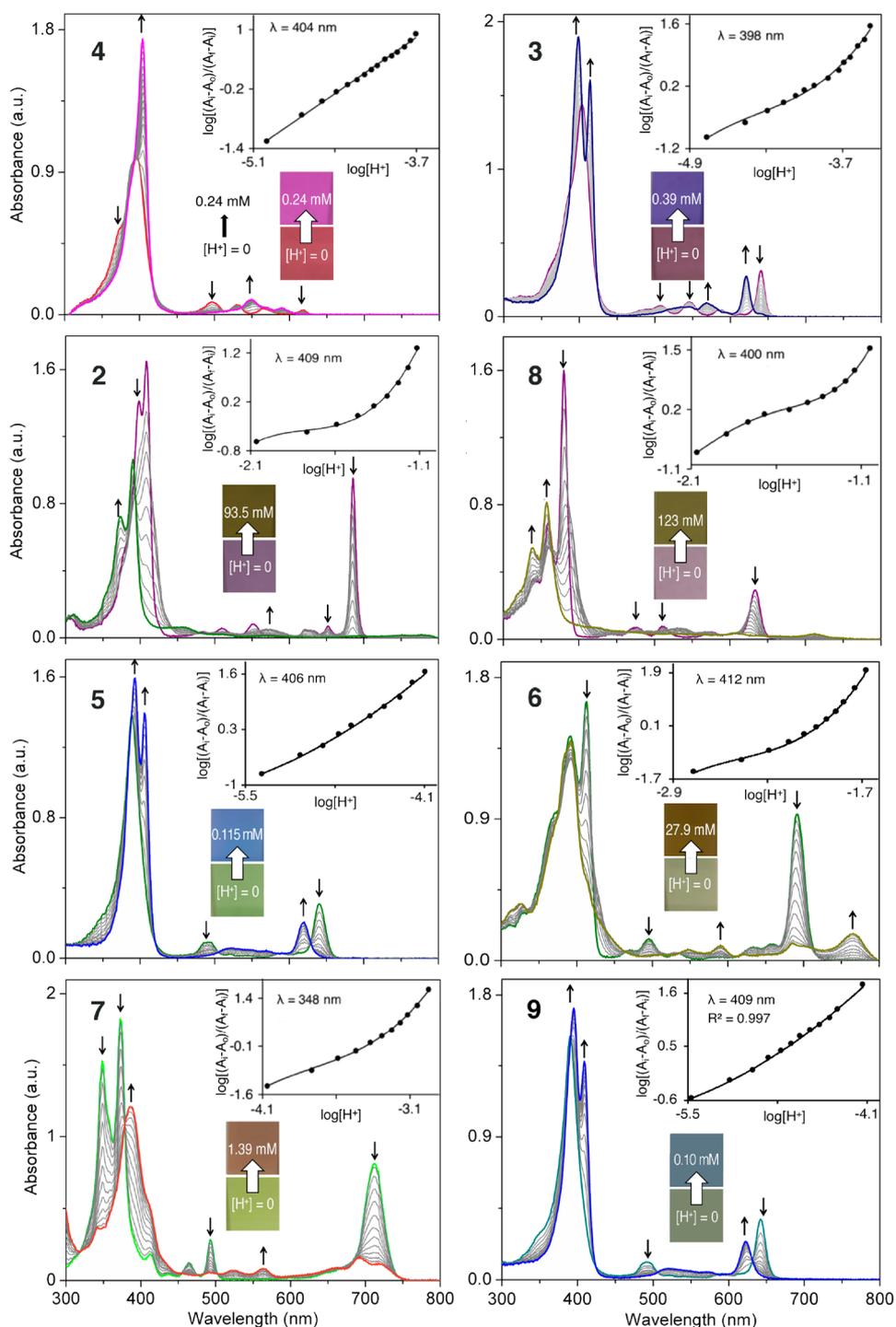


**Figure 3.** Relative rates of zinc insertion into porphyrin **4**, oxochlorin **3**, and dioxobacteriochlorin **2** under identical reaction conditions (starting concentrations:  $[\text{X}] = 8.8 \times 10^{-4}$  M,  $[\text{Zn}(\text{OAc})_2] = 4.4 \times 10^{-3}$  M (5.00 equiv); combined in 10.0 mL DMF with 15.0 mg  $\text{Li}_2\text{CO}_3$ , 154 °C). The lines of best fit are higher order polynomial functions. The horizontal markers at 0.45 M, the 50% conversion point, indicate the points at which the slope was determined; error bars indicate standard error.

complex as we could not fit the reaction kinetics to simple rate laws.<sup>60</sup> Thus, for the purpose of this comparison the slope of the best-fit function at the point where the product concentration  $[\text{XZn}]$  reaches the half-conversion point (0.445 mM) was determined. In this manner, the relative rates are measured to be 7.53, 14.6, and 56.5  $\mu\text{M}/\text{min}$  for **2**, **3**, and **4**, respectively. Thus, relative to the rate of the fastest



**Figure 2.** Stick representation of the X-ray single-crystal structures of the metal complexes **2M** indicated. The arrow in the top view indicates the direction of the side view below.  $\Delta_{24}$  = RMSD of all macrocycle C and N atoms from the mean plane defined by them. For experimental details, see SI.



**Figure 4.** UV-vis titration of octaethylporphyrin **4** ( $7.18 \times 10^{-6}$  M), 7-oxochlorin **3** ( $1.82 \times 10^{-5}$  M), 7,17-dioxochlorin **2** ( $2.12 \times 10^{-5}$  M), its isomer 7,18-dioxochlorin **8** ( $1.41 \times 10^{-5}$  M), 7-hydroxychlorin **5** ( $1.52 \times 10^{-5}$  M), 7-hydroxy-17-oxobacteriochlorin **6** ( $4.23 \times 10^{-5}$  M), 7,17-dihydroxybacteriochlorin **7** ( $5.88 \times 10^{-5}$  M), and 7,8-dihydroxychlorin **9** ( $1.83 \times 10^{-5}$  M) (all in  $\text{CH}_2\text{Cl}_2$ ) with TFA in the  $[\text{TFA}]$  range indicated. Insets show a best fit Hill plot. Color fields show the color of the porphyrinoids before and after the addition of TFA. For further details, see SI.

ligand porphyrin **4** (set to 1), oxochlorin **3** is about four times slower and dioxobacteriochlorin **2** is about another factor of 2 slower (for a total of 7.5-fold relative to the rate for **4**).

**UV-vis Titrations.** To quantitatively determine the differences in basicity of the oxohydroporphyrins versus porphyrins and the corresponding hydroporphyrins, we performed UV-vis titrations with trifluoroacetic acid (TFA) and base (tetrabutylammonium hydroxide, TBAOH). Next to the three species porphyrin **4**, oxochlorin **3**, and dioxobacterio-

chlorin **2**, we also included hydroxychlorin **5**, hydroxyoxobacteriochlorin **6**, dihydroxybacteriochlorin **7**, and 2,3-dihydroxychlorin **9**.<sup>51,57</sup> This allows us to distinguish between the effects of the oxo-functionalities and the intrinsic change of basicity of the various reduction states of the chromophore (plus the alcohol functionality).<sup>13,65</sup> Lastly, we also included 7,18-dioxobacteriochlorin **8**,<sup>46</sup> an isomer of the 7,17-dioxobacteriochlorin **2**, as a test for the influence of the relative positions of the two  $\beta$ -oxo-functionalities.

All compounds showed strong halochromic responses upon addition of TFA (Figure 4). Across the series, the colors of the compounds (free base as well as protonated) and, correspondingly, their general UV–vis spectra, vary widely. Generalized, however, the changes follow the established patterns for many porphyrinoids: Upon protonation, the free base Soret bands give way to new, often hypsochromically shifted bands, and the number of Q-bands is reduced, simplifying the overall appearance of the spectra; the new  $\lambda_{\max}$  band is frequently red-shifted.

The titration curves of some porphyrinoids (like porphyrin 4 or chlorin 5) show clear isobestic points and the corresponding Hill plots are linear and show positive cooperativity, indicating one-step protonation (by two protons), as observed for regular porphyrins and chlorins (with the first protonation constant lower than the second).<sup>66–68</sup> Select chlorins are also known that can be monoprotated.<sup>65,69</sup> On the other hand, all  $\beta$ -oxo-functionalized derivatives show no isobestic points and convoluted Hill plots, indicative of complex protonation behavior involving multiple binding sites; for diketone isomer 2, the complex, multistage protonation behavior was noted previously.<sup>44</sup> Whether diprotonation is always achieved also remains unclear.<sup>65</sup> Likewise, the IR spectra of oxochlorin 3 and dioxobacteriochlorin 2 in the presence of TFA were inconclusive as to whether oxo-protonation is taking place. Thus, no  $pK_b$  values were derived. Nonetheless, we took the absolute [TFA] concentrations at half the end point value of the titration of the porphyrinoids with acid ( $[\text{TFA}]_{1/2}$  value) as a suitable metric to compare their relative basicities.

The  $[\text{TFA}]_{1/2}$  value ranks the porphyrinoids investigated in the order of decreasing amount of [TFA] needed for half-protonation, that is, increasing order of basicity: dioxobacteriochlorin 2 ( $4.27 \times 10^{-2}$  M) < dioxobacteriochlorin 8 ( $3.42 \times 10^{-2}$  M) < hydroxyoxobacteriochlorin 6 ( $1.02 \times 10^{-2}$  M) < dihydroxybacteriochlorin 7 ( $4.27 \times 10^{-4}$  M) < oxochlorin 3 ( $1.02 \times 10^{-4}$  M) < octaethylporphyrin 4 ( $6.14 \times 10^{-5}$  M) < hydroxychlorin 5 ( $2.14 \times 10^{-5}$  M) < dihydroxychlorin 9 ( $1.36 \times 10^{-5}$  M) (Figure 5). Thus, increase of the number of  $\beta$ -oxo groups drastically decreases the basicity of the chromophore

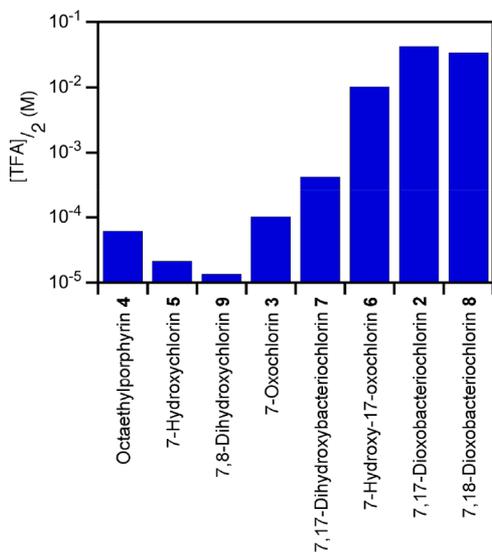


Figure 5. Bar graph of the  $[\text{TFA}]_{1/2}$  values determined for the compounds indicated (cf. to Figure 4).

over 3 orders of magnitude (comparing basicity of 4 to that of 3 and 2/8). Inversely, stepwise reduction of the  $\beta$ -oxo functionalities in the bacteriochlorin (2 to 6 to 7) and chlorin series (3 to 5) increases the basicity significantly, whereby the removal of one of two oxo-groups has less of an effect than the removal of the second. The basicities of the dioxobacteriochlorin regioisomers 2 and 8 vary slightly from each other, reflecting their electronic differences, a circumstance also observed and rationalized in the *meso*-aryldilactone regioisomers.<sup>27,70–72</sup> Bacteriochlorins are, as expected,<sup>13</sup> less basic than the porphyrins and chlorins but we find against expectations the  $\beta$ -hydroxychlorins 5 and 9 to be slightly more basic than the corresponding porphyrin 4. We attribute this to the effects of the electron-rich benzylic alcohol functionalities.

None of the compounds described above showed any major halochromic response upon addition of base (TBAOH in  $\text{CH}_2\text{Cl}_2$ ), even at large stoichiometric excess (see SI). At most, minor changes (like in 9) may be attributable to an onset of the deprotonation of an alcohol moiety. Thus, the NH functionalities of the dioxobacteriochlorins neither possess a particularly strong acidity (as corroles, for example, exhibit),<sup>73</sup> nor are the  $\beta$ -oxo functionalities accessible to nucleophilic attack under the conditions tested (as the  $\beta$ -oxo functions of some *meso*-pentafluorophenyl-substituted porpholactones are).<sup>74–77</sup>

## CONCLUSIONS

In conclusion, the metal ions Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Ag(II), and Pd(II) can be inserted into octaethyl-7,17-dioxobacteriochlorin 2 to form the corresponding complexes 2M. The single crystal X-ray structures of 2Cu, 2Ni, 2Pd, and 2Ag prove the complexes to be essentially planar. Arguably, they are slightly more planar than the corresponding oxochlorin or porphyrin complexes, suggestive of a larger conformational rigidity of the dioxobacteriochlorin chromophore. The zinc(II) insertion kinetics for dioxobacteriochlorin isomer 2 is  $\sim 4$ -fold slower than the corresponding reaction for oxochlorin 3, and  $\sim 7.5$ -fold slower compared to the rate observed for octaethylporphyrin 4. The slow kinetics necessitate the use of more forceful reaction conditions than traditionally employed for the metal insertion to be completed within a few hours of reaction time. The basicity of the inner nitrogen atoms, ranked in the order of dioxobacteriochlorins < hydroxyoxobacteriochlorin  $\ll$  dihydroxybacteriochlorin < oxochlorin < porphyrin < hydroxychlorin  $\sim$  dihydroxychlorin, spanning a range 3 orders of magnitude, may be primarily responsible for the slow reaction kinetics of the metal insertion reaction, while the inferred increased rigidity of the dioxobacteriochlorin framework may add to this. Our findings rationalize why Prinsep et al. could not form a number of metal complexes of tolyporphyrin A 1 under the relatively mild conditions tested.

On the other hand, the retardation of the metal insertion rate by the  $\beta$ -oxo-functionalities in, for example, 7,17-dioxobacteriochlorin 2, are somewhat contradicting findings by Lindsey and co-workers that found that electron-withdrawing substituents helped in the metal insertion into bacteriochlorins,<sup>16</sup> albeit the effects of  $\beta$ -oxo-functionalities were not tested. This suggests that  $\beta$ -oxo-functionalities may have more profound electronic and conformational effects on the macrocycle than many other substituents, and their large effect on the macrocycle electronic structure supports this.

Multiple examples of  $\beta$ -oxo- and  $\beta$ -dioxohydroporphyrins have become known in recent years and the unique auxochromic effects of the  $\beta$ -oxo-functionality have become to be understood.<sup>8,20–23,26</sup> Some of the free base compounds, or their metal complexes, were described to possess useful optical or electrochemical properties.<sup>24,28,44,78,79</sup> This study lays the basis for the further investigation of the metal complexes of other  $\beta$ -oxoporphyrinoids for which, by extension, we assume the same retarded metal insertion kinetics to be operational.

## EXPERIMENTAL SECTION

**Instruments.** <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded using Bruker AVANCE III 400 and 500 MHz spectrometers from solutions in CDCl<sub>3</sub>. UV/vis spectra were obtained using Varian Cary 50 or 100 Bio spectrometers in the solvents indicated. IR spectra were recorded from neat material on a Bruker Alpha FTIR spectrometer using an attenuated total reflection (ATR) diamond crystal. Low- and high-resolution SI spectra were recorded from CH<sub>3</sub>CN solutions (~10<sup>-6</sup> M) using AB Sciex API 2000 Triple Quadrupole and AB Sciex QStar Elite Quadrupole-TOF MS instruments, respectively.

**Materials.** 7-Oxochlorin **3**, 7,17-dioxobacteriochlorin **2**, and 7,18-dioxobacteriochlorin **8** were prepared by H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>SO<sub>4</sub> oxidation of octaethylporphyrin **4**, as described in the literature.<sup>46</sup> Known hydroxychlorin **5** was, in a variation to literature procedures,<sup>13,53</sup> prepared by LiAlH<sub>4</sub> reduction of 7-oxochlorin **3** (a procedure and complete data are included for comparison). Chlorin diol **9** was also prepared as described.<sup>51,57</sup> All other materials were analytical grade from commercial sources and were used as received. Silica gel 60 aluminum-backed 250  $\mu$ m analytical TLC plates, silica gel 60 glass-backed 250  $\mu$ m analytical TLC plates, 500  $\mu$ m or 1 mm silica gel 60 on glass 20  $\times$  20 cm preparative TLC plates, Brockmann I (50–200  $\mu$ m) basic alumina, and flash column silica gel (premium grade, 60  $\text{Å}$ , 40–75  $\mu$ m) were provided by Sorbent Technologies, Atlanta, GA.

**[Octaethyl-7,17-dioxobacteriochlorinato]zinc(II) (2Zn).** Free base dioxobacteriochlorin **2** (11.6 mg, 2.0  $\times$  10<sup>-5</sup> mol), ZnCl<sub>2</sub>·H<sub>2</sub>O (12.2 mg, 8.9  $\times$  10<sup>-5</sup> mol, 4.5 equiv), and 18 mg Li<sub>2</sub>CO<sub>3</sub> were dissolved in DMF (10 mL) and heated to reflux for 3.5 h. The solution was cooled to rt and then slowly diluted with DI water (~75 mL). The precipitate formed was isolated by microfiltration. Recrystallization by solvent exchange from CH<sub>2</sub>Cl<sub>2</sub>/hexanes provided green microcrystals in 96% yield (12.4 mg, 2.0  $\times$  10<sup>-5</sup> mol): MW = 628.3 g/mol; R<sub>f</sub> = 0.10 (silica-25% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  9.54 (s, 1H), 8.88 (s, 1H), 3.87–3.80 (m, 8H), 2.69–2.65 (q, <sup>3</sup>J = 7.4 Hz, 8H), 1.79–1.74 (m, 6H), 0.42 (t, <sup>3</sup>J = 7.4 Hz, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  209.5, 158.2, 148.5, 147.1, 143.0, 142.2, 141.4, 95.1, 94.9, 60.2, 31.7, 19.53, 19.34, 18.39, 18.23, 8.4 ppm. UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 382 (4.69), 407 (4.88), 691 (4.97) nm. HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF): *m/z* calc'd for C<sub>36</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub>Zn, 628.2750 (for M<sup>+</sup>); found, 628.2789.

**[Octaethyl-7,17-dioxobacteriochlorinato]copper(II) (2Cu).** Free base dioxobacteriochlorin **2** (9.7 mg, 1.71  $\times$  10<sup>-5</sup> mol) and Cu(OAc)<sub>2</sub> (16.2 mg, 9.2  $\times$  10<sup>-5</sup> mol, 5.4 equiv) were dissolved in DMF (10 mL) and heated to reflux for 30 min. The solution was cooled to room temperature and then diluted with DI water (~75 mL) followed by microfiltration. Recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexanes provided the product as green crystals in 83% yield (8.8 mg, 1.4  $\times$  10<sup>-5</sup> mol): MW = 627.3 g/mol; R<sub>f</sub> = 0.37 (silica-25% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 385 (4.65), 428 (5.01), 705 (4.87) nm. HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF): *m/z* calc'd for C<sub>36</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub>Cu, 627.2755 (for M<sup>+</sup>); found, 627.2805.

**[Octaethyl-7,17-dioxobacteriochlorinato]nickel(II) (2Ni).** Free base dioxobacteriochlorin **2** (10.4 mg, 1.8  $\times$  10<sup>-5</sup> mol) and Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O (22.0 mg, 8.8  $\times$  10<sup>-5</sup> mol, 4.8 equiv) were dissolved in benzonitrile (10 mL) and heated to reflux for 5 h. The solution was cooled to rt, diluted with CH<sub>2</sub>Cl<sub>2</sub>, and twice washed with equal volume of DI water. The organic fraction was isolated and dried over Na<sub>2</sub>SO<sub>4</sub>, then reduced by rotary evaporation, followed by drying

under a stream of dry N<sub>2</sub> overnight. The crude material was purified by column chromatography (silica-25% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). Recrystallization by precipitation from DMF/water provided the nickel complex **2Ni** in 84% yield (9.6 mg, 1.5  $\times$  10<sup>-5</sup> mol): MW = 622.3 g/mol; R<sub>f</sub> = 0.45 (silica-25% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 370 (3.51), 419 (3.75), 699 (3.92) nm. HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF): *m/z* calc'd for C<sub>36</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub>Ni, 622.2812 (for M<sup>+</sup>); found, 622.2805.

**[Octaethyl-7,17-dioxobacteriochlorinato]cobalt(II) (2Co).** Free base dioxobacteriochlorin **2** (10.1 mg, 1.8  $\times$  10<sup>-5</sup> mol), Co(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (31.2 mg, 1.1  $\times$  10<sup>-4</sup> mol, 6.0 equiv) and 15.7 mg Li<sub>2</sub>CO<sub>3</sub> were combined in DMF (10 mL) and heated to reflux for 3.5 h. The solution was cooled to rt and then slowly diluted with DI water (~75 mL). The precipitate formed was isolated using microfiltration. Recrystallization by solvent exchange from CH<sub>2</sub>Cl<sub>2</sub>/hexanes provided **2Co** as green crystals in 91% yield (10.1 mg, 1.6  $\times$  10<sup>-5</sup> mol): MW = 623.3 g/mol; R<sub>f</sub> = 0.38 (silica-25% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 378 (4.37), 420 (4.70), 697 (4.86) nm. HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF): *m/z* calc'd for C<sub>36</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub>Co, 623.2796 (for M<sup>+</sup>); found, 623.2761.

**[Octaethyl-7,17-dioxobacteriochlorinato]iron(III) Chloride (2FeCl).** **2FeCl** was prepared by combining free base dioxobacteriochlorin **2** (9.6 mg, 1.7  $\times$  10<sup>-5</sup> mol) and FeCl<sub>3</sub>·6H<sub>2</sub>O (29.0 mg, 9.9  $\times$  10<sup>-4</sup> mol, 5.8 equiv) in acetic acid (10 mL) and heated to reflux for 40 min. The solution was chilled in an ice bath, poured onto crushed ice (~15 g), mixed with brine (10 mL), and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (~30 mL). The organic layer was isolated, washed with 0.5 M aq HCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, then reduced to dryness using rotary evaporation. Recrystallization by solvent exchange from CH<sub>2</sub>Cl<sub>2</sub>/hexanes provided green crystals of **2FeCl** in 70% yield (7.7 mg, 1.2  $\times$  10<sup>-5</sup> mol): MW = 655.3 g/mol; R<sub>f</sub> = 0.05 (silica-0.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 377 (3.36), 411 (3.51), 675 (3.16) nm. HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF): *m/z* calc'd for C<sub>36</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub>Fe, 620.2814 (for M<sup>+</sup>); found, 620.2834.

**[Octaethyl-7,17-dioxobacteriochlorinato]cadmium(II) (2Cd).** **2Cd** was prepared by combining free base dioxobacteriochlorin **2** (9.8 mg, 1.7  $\times$  10<sup>-5</sup> mol), CdCl<sub>2</sub>·H<sub>2</sub>O (20.3 mg, 8.9  $\times$  10<sup>-5</sup> mol, 5.1 equiv), and Li<sub>2</sub>CO<sub>3</sub> (15.6 mg) in DMF (10 mL) and heating to reflux for 5 h. The solution was then cooled to rt and then slowly diluted with DI water (~75 mL). The precipitate formed was isolated using microfiltration. Recrystallization by solvent exchange from CH<sub>2</sub>Cl<sub>2</sub>/hexanes provided **2Cd** as green crystals in 91% yield (10.7 mg, 1.6  $\times$  10<sup>-5</sup> mol). MW = 676.2 g/mol; R<sub>f</sub> = 0.20 (silica-25% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 402 (3.50), 413 (3.50), 672 (3.35) nm. HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF): *m/z* calc'd for C<sub>36</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub>Cd, 678.2498 (for M<sup>+</sup>); found, 678.2538.

**[Octaethyl-7,17-dioxobacteriochlorinato]silver(II) (2Ag).** Free base dioxobacteriochlorin **2** (10.6 mg, 1.9  $\times$  10<sup>-5</sup> mol) and Ag(OAc) (6.4 mg, 3.8  $\times$  10<sup>-5</sup> mol, 2.0 equiv) were dissolved in deoxygenated pyridine (8 mL) and heated under N<sub>2</sub> to reflux for 1 h. The solution was then cooled to rt, diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed twice with equal volumes of DI water. The organic fraction was isolated and reduced to dryness by rotary evaporation. The crude material was purified by column chromatography (silica-50% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). Recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexanes provided **2Ag** in 52% yield (6.5 mg, 9.6  $\times$  10<sup>-6</sup> mol): MW = 672.6 g/mol; R<sub>f</sub> = 0.50 (silica-25% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 391 (4.27), 411 (4.15), 435 (4.42), 673 (4.42) nm. HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF): *m/z* calc'd for C<sub>36</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub>Ag, 671.2515 (for M<sup>+</sup>); found, 671.2560.

**[Octaethyl-7,17-dioxobacteriochlorinato]palladium(II) (2Pd).** **2Pd** was prepared from free base 7,17-dioxobacteriochlorin **2** (10.4 mg, 1.8  $\times$  10<sup>-5</sup> mol) and PdCl<sub>2</sub>·6H<sub>2</sub>O (17.4 mg, 1.8  $\times$  10<sup>-5</sup> mol, 5.4 equiv) in benzonitrile (10 mL) heated to reflux for 1 h. The solution was cooled to rt, diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed twice with equal volumes of DI water, then the organic fraction was isolated, dried over Na<sub>2</sub>SO<sub>4</sub>, and reduced by rotary evaporation, followed by drying under a stream of dry N<sub>2</sub> overnight. The crude material was purified by column chromatography (silica-25% hexanes/CH<sub>2</sub>Cl<sub>2</sub>). Recrystallization by precipitation from DMF/water provided **2Pd** in

71% yield (8.7 mg,  $1.3 \times 10^{-5}$  mol). MW = 670.3 g/mol;  $R_f$  = 0.67 (silica-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>):  $\delta$  9.65 (s, 2H), 8.94 (s, 2H), 3.87–3.79 (m, 8H), 2.72 (qd,  $J$  = 13.4, 7.3 Hz, 8H), 1.80 (dt,  $J$  = 15.3, 7.6 Hz, 12H), 0.47 (t,  $J$  = 7.4 Hz, 12H). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ): 366 (3.79), 402 (4.15), 668 (4.16) nm. HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF):  $m/z$  calc'd for C<sub>36</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub>Pd, 670.2499 (for M<sup>+</sup>); found, 670.2517.

**Octaethyl-7-hydroxychlorin (5).** 7-Oxochlorin 4 (50 mg,  $9.07 \times 10^{-5}$  mol) was dissolved in dry THF (2 mL). To this, a suspension of LiAlH<sub>4</sub> (10 mg,  $2.7 \times 10^{-4}$  mol, 3 equiv) in THF (1.5 mL) was added at 0 °C under N<sub>2</sub> and stirred for 5 min. The reaction mixture was quenched by slurrying with Glauber's salt (Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O, about 1.5 g) and the resulting mixture was filtered through a pad of Celite, and the pad was washed with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were reduced by rotatory evaporation. The crude solid was dissolved in a minimum amount of CH<sub>2</sub>Cl<sub>2</sub> and purified by column chromatography (silica, 100% CH<sub>2</sub>Cl<sub>2</sub>, followed by 2% acetone in CH<sub>2</sub>Cl<sub>2</sub>) to provide the product in 91% yield (46 mg,  $8.32 \times 10^{-5}$  mol). Data for the known compound are included for comparison. MW = 552.8 g/mol;  $R_f$  = 0.19 (silica-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  9.78 (d,  $J$  = 3.3 Hz, 2H), 9.20 (s, 1H), 8.79 (s, 1H), 6.53 (s, 1H), 4.07–3.87 (m, 12H), 2.71 (s, 1H), 2.61–2.51 (m, 3H), 2.35–2.25 (m, 1H), 1.89–1.79 (m, 18H), 0.97 (t,  $J$  = 7.2 Hz, 3H), 0.74 (t,  $J$  = 7.2 Hz, 3H), 2.55 (s, 2H). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ): 390 (5.02), 493 (3.85), 521 (3.25), 588 (3.31), 611 (3.26), 642 (4.38). HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF):  $m/z$  calc'd for C<sub>36</sub>H<sub>48</sub>N<sub>4</sub>O, 553.3901 (for MH<sup>+</sup>); found, 553.3936.

**Octaethyl-7-hydroxy-17-oxobacteriochlorin (6).** A solution of octaethyl-7,17-dioxobacteriochlorin 2 (50 mg,  $8.82 \times 10^{-5}$  mol) in THF (3 mL) was stirred under N<sub>2</sub> on an ice bath. NaBH<sub>4</sub> (17 mg,  $4.4 \times 10^{-5}$  mol, 5 equiv) was added (at 0 °C) and the reaction mixture was stirred for 24 h at ambient temperature. Then CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added and the mixture was washed with a sat'd aq solution of NH<sub>4</sub>Cl. The organic layer was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and filtered. The filtrate was reduced to dryness using rotatory evaporation. The residue was purified by silica-gel column chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>) to yield 6 in 78% (39 mg,  $6.86 \times 10^{-5}$  mol) yield. MW = 568.8 g/mol;  $R_f$  = 0.33 (silica-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): 9.60 (s, 1H), 9.05 (s, 1H), 8.82 (s, 1H), 8.67 (s, 1H), 6.40 (s, 1H), 3.95–3.84 (m, 8H), 2.64 (q,  $J$  = 7.3 Hz, 5H), 2.57–2.44 (m, 3H), 2.26 (dt,  $J$  = 14.8, 7.4 Hz, 1H), 1.81–1.73 (m, 12H), 1.00 (t, 7.4 Hz, 3H), 0.82 (t, 7.4 Hz, 3H), 0.39 (dt,  $J$  = 11.4, 7.4 Hz, 6H), –2.10 (s, 1H), –2.22 (s, 1H). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ): 392 (4.84), 414 (4.91), 497 (3.83), 532 (3.10), 632 (3.59), 660 (3.70), 693 (4.65). HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF):  $m/z$  calc'd for C<sub>36</sub>H<sub>48</sub>N<sub>4</sub>O<sub>2</sub>, 568.3777 (for M<sup>+</sup>); found, 568.3747.

**7,17-Dihydroxybacteriochlorin (7).** Prepared in 48% yield (24 mg,  $4.2 \times 10^{-5}$  mol) from octaethyl-7,17-dioxobacteriochlorin 2 (50 mg,  $8.82 \times 10^{-5}$  mol) and LiAlH<sub>4</sub> (17 mg,  $4.4 \times 10^{-5}$  mol, 5 equiv) as described for the preparation of 7-hydroxychlorin 5. MW = 570.8 g/mol;  $R_f$  = 0.29 (silica-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (400 MHz; DMSO-*d*<sub>6</sub>): 9.00 (s, 2H), 8.62 (s, 2H), 6.41 (d,  $J$  = 5.7 Hz, 2H), 6.27 (d,  $J$  = 5.5 Hz, 2H), 3.87–3.76 (m, 8H), 2.44–2.38 (m, 6H), 2.09 (dt,  $J$  = 16.5, 6.3 Hz, 2H), 1.73–1.65 (m, 12H), 0.90 (t,  $J$  = 6.1 Hz, 6H), 0.54 (t,  $J$  = 6.0 Hz, 6H), –2.54 (s, 2H). UV–vis (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ): 350 (4.72), 375 (4.79), 464 (3.56), 496 (3.96), 713 (4.42). HR-MS (ESI+, 100% CH<sub>3</sub>CN, TOF):  $m/z$  calc'd for C<sub>36</sub>H<sub>50</sub>N<sub>4</sub>O<sub>2</sub>, 570.3934 (for M<sup>+</sup>); found, 570.3893.

**Crystallography.** Crystals were grown of 2Ni, 2Cu, 2Pd, and 2Ag by slow vapor diffusion of hexanes into a concentrated solution of the species dissolved in CH<sub>2</sub>Cl<sub>2</sub>. Single crystal data for 2Pd were collected on a Bruker Quest diffractometer with a fixed  $\chi$ -angle, a sealed tube fine focus X-ray tube, single crystal curved graphite incident beam monochromator, a Photon100 CMOS area detector and an Oxford Cryosystems low temperature device. Examination and data collection were performed with Mo K $\alpha$  radiation ( $\lambda$  = 0.71073 Å) at 150 K. Single crystal data for 2Ag, 2Ni, and 2Cu were collected on a Bruker Quest diffractometer with  $\kappa$ -geometry, an I- $\mu$ S microsource X-ray tube, laterally graded multilayer (Goebel) mirror single crystal for monochromatization, a Photon2 CMOS area detector and an Oxford

Cryosystems low-temperature device. Examination and data collection were performed with Cu K $\alpha$  radiation ( $\lambda$  = 1.54178 Å) at 150 K. Data were collected, reflections were indexed and processed, and the files were scaled and corrected for absorption using APEX3 and SADABS or TWINABS. The space groups were assigned and the structures were solved by direct methods using XPREP within the SHELXTL suite of programs and refined by full matrix least-squares against  $F^2$  with all reflections using ShelXL2016 using the graphical interface ShelXle; for details, including on the software, see [Supporting Information](#).

All four structures are isomorphic with close to identical molecular conformations, unit cell shapes, and symmetry and packing interactions. The structures are pseudo-B centered with a pseudo-translation along the *a*-*c* diagonal. Exact translational symmetry is broken by a slight modulation of the two *gem*-C(Et)<sub>2</sub> units, preventing an exact fit of a larger volume C-centered monoclinic structure. The *b* and *c* axes in the four structures are close in length, and the order of the two axes is swapped between the structures, thus resulting in different standard settings for the four isomorphic structures. Each of the two structures have the same standard setting: 2Ag and 2Cu, and 2Pd and 2Ni. The latter two were also found to be twinned by identical twin operations based on the emulated monoclinic symmetry (see [Supporting Information](#) for details on twinning).

If not specified otherwise, H atoms attached to carbon atoms were positioned geometrically and constrained to ride on their parent atoms with carbon hydrogen bond distances of 0.95 Å for aromatic C–H, and 0.99 and 0.98 Å for aliphatic CH<sub>2</sub> and CH<sub>3</sub> moieties, respectively. Methyl H atoms were allowed to rotate but not to tip to best fit the experimental electron density.  $U_{\text{iso}}(\text{H})$  values were set to a multiple of  $U_{\text{eq}}(\text{C})$  with 1.5 for CH<sub>3</sub>, and 1.2 for CH<sub>2</sub> units, respectively.

Complete crystallographic data in CIF format have been deposited with the Cambridge Crystallographic Data Centre. CCDC 1955054–1955057 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](http://www.ccdc.cam.ac.uk/data_request/cif).

**Kinetic Comparison.** A series of parallel reactions were conducted for porphyrin 4, oxochlorin 3, and dioxobacteriochlorin 2 to compare their relative metal-insertion reaction rates: 8.86  $\times 10^{-6}$  mol of 2 (5.0 mg), 3 (4.9 mg), and 4 (4.7 mg), as well as 5.0 equiv. Zn(OAc)<sub>2</sub>·2H<sub>2</sub>O (4.41  $\times 10^{-5}$  mol, 9.7 mg) and Li<sub>2</sub>CO<sub>3</sub> (15.0 mg) were combined in 25 mL three-necked round-bottom flasks equipped with a reflux condenser and stir bar. These three flasks were then all secured in the same oil bath. DMF (10 mL) was added simultaneously to all and the mixtures were set stirring and heated to reflux. Once refluxing, aliquots of  $\sim 10$   $\mu$ L were periodically withdrawn and added to a small vial preloaded with 1.0 mL of HPLC-grade CH<sub>2</sub>Cl<sub>2</sub>. The frequency of withdrawal was chosen such that 10 samples were interspersed throughout the total reaction time. The vials were then capped, inverted to mix, and placed on dry ice until all of the samples were collected.

Once the reaction was complete, the samples were diluted to 3.0 mL with CH<sub>2</sub>Cl<sub>2</sub> and a UV–vis spectrum of this solution was recorded. Then, each solution was spiked three times successively with a small (4–10  $\mu$ L) recorded volume of conc. solutions ( $\sim 0.8$  mM) of pure starting material, collecting a full UV–vis spectrum between each. Using the same solution, the same procedure was carried out using a concentrated solution of pure product, for a total of seven collected spectra per sample.

Data analysis consisted of constructing two successive-standard-addition plots, one for the starting material and one for the product. Single wavelengths were selected, one corresponding to either species. The generated plots were checked to ensure a linear response ( $r^2$  value of greater than 0.998). In this plot, the *x*-intercept is taken to be the absolute value of the concentration of the analyte in the original solution. In this manner, the concentration of both materials was determined in the sample. This value was tracked back through the dilution procedure in order to determine the concentration of each in the reaction mixture at the time of withdrawal.

**UV–visible Titrations.** These were performed using a Varian Cary 100 spectrometer with a thermostated cell holder (held at 25 °C) in standard 1 cm (3 mL) cuvettes. Additions of the TFA stock solutions were pipetted to the concentrations indicated.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.inorgchem.9b03231>.

A reproduction of the spectroscopic data and details to the titrations and crystallographic measurements (PDF)

## Accession Codes

CCDC 1955054–1955057 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION

### Corresponding Author

Christian Brückner – Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060, United States; [orcid.org/0000-0002-1560-7345](https://orcid.org/0000-0002-1560-7345); Email: [c.bruckner@uconn.edu](mailto:c.bruckner@uconn.edu)

### Authors

David Schnable – Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060, United States; [orcid.org/0000-0002-8650-997X](https://orcid.org/0000-0002-8650-997X)

Nivedita Chaudhri – Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060, United States; [orcid.org/0000-0001-9604-606X](https://orcid.org/0000-0001-9604-606X)

Ruoshi Li – Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060, United States

Matthias Zeller – Department of Chemistry, Purdue University, West Lafayette, Indiana 47907-2084, United States; [orcid.org/0000-0002-3305-852X](https://orcid.org/0000-0002-3305-852X)

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acs.inorgchem.9b03231>

### Author Contributions

<sup>§</sup>D.S. and N.C. contributed equally.

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. M.Z. performed the X-ray diffraction analyses.

### Funding

Funding for this work was provided by the U.S. National Science Foundation (NSF) through Grants CHE-1465133 and CHE-1800631 (to C.B.) and CHE-1359081 (summer research fellowship to D.S.) and CHE-1625543 (X-ray diffractometers).

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank David Dolphin, University of British Columbia, and Chi-Kwong (Chris) Chang, Michigan State University, for donation of the octaethylporphyrin used in this study.

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