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## Acid-catalyzed disproportionation of oxoiron(IV) porphyrins to give oxoiron(IV) porphyrin radical cations

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### Abstract

Disproportionation of oxoiron(IV) porphyrin (Compound II) to oxoiron(IV) porphyrin radical cation (Compound I) was studied in three P450 model systems with different electronic structures. Direct conversion of Compound II to Compound I has been observed for 5,10,15,20-*tetrakis*(2,6-dichlorophenyl)porphyrin (TDCPP) in acid-catalyzed reactions in a mixed solvent of acetonitrile and water (1:1, v/v) containing excess *m*-CPBA oxidant, with a second-order rate constant of  $(1.3 \pm 0.2) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ . The acid-catalyzed disproportionation heavily depends on the electron demand of the substituted aryl groups on the porphyrin macrocycle. The disproportionation equilibrium constants show drastic change for the three porphyrin systems.

### Keywords

oxoiron; disproportionation; Compound I; Compound II; P450 model

High-valent oxoiron porphyrin intermediates play important roles in the mechanisms of hemoproteins such as the peroxidases and cytochrome P450 enzymes [1, 2]. Much effort has been devoted to the enigmatic spectral and kinetic characteristics of highly oxidized states [3–7]. Since the first report in 1981 [8], oxoiron(IV) porphyrin radical cations, models for Compounds I in enzymes including cytochrome P450, have been generated and characterized for several different porphyrin systems [7, 9–11]. Another important oxoiron(IV) species, referred to as Compound II in heme enzymes, involves a single-electron oxidation from ferric porphyrin. In principle, Compound II species could be formed by the homolytic O–O bond cleavage in an acylperoxo-iron(III) complex [12]. Increasing interest has been directed at the study of Compound II analogues, especially regarding their reactivity towards organic substrates and the protonation of ferryl-oxo bonds [11, 13–17]. For example, oxoiron(IV) complexes were also able to effect two-electron oxidations [17, 18], which suggests that they might serve as one of the active intermediates in oxygen transfer process by cytochrome P450.

Electronic effects were found to be important factors in controlling the reactivity of high-valent oxoiron species. For example, it was demonstrated that the axial ligands on iron

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significantly affected the reactivity of Compound I analogues in oxygenation reactions [19–21]. For a series of oxoiron(IV) tetraarylporphyrin radical cations prepared by Fujii [22], the effects of the aryl ring *meso* substituents on electronic structures and reactivities revealed that the reactivity of the oxygen atom of Compound I depends on the redox potential of the porphyrin macrocycles. With the same axial ligand and similar sterics of aryl ring *meso* substituents, the reactivities of Compound I models with electron-deficient porphyrins were greater than the reactivities of those with electron-rich porphyrin rings [23–25]

In a study of oxidations by oxoiron(IV) porphyrins, our group proposed a disproportionation step in the reaction mechanism where the oxoiron(IV) species disproportionates to give an iron(III) species and a more reactive oxoiron(IV) porphyrin radical cation that is the true oxidant [26]. This conclusion was based on inverted reactivity patterns in regard to the electron demand of the porphyrin ring. Supporting evidence for a disproportionation step included dual-parameter Hammett analyses and the observation of suppressed reactivity with the addition of excess iron(III) species. Herein we report direct spectroscopic observation of conversion of oxoiron(IV) species to the corresponding iron(IV)-oxo porphyrin radical cation in a mixed solution of acetonitrile and water (1:1, v/v). The results support the conclusion that oxoiron(IV) species react by initial disproportionation to give oxoiron(IV) porphyrin radical cations that are true oxidants.

Three porphyrin systems, 5,10,15,20-*tetrakis*(2,6-dichlorophenyl)porphyrin (TDCPP), 5,10,15,20-*tetrakis*(2,6-difluorophenyl)porphyrin (TDFPP) and 5,10,15,20-*tetrakis*(pentafluorophenyl)porphyrin (TPFPP), were studied in this work (Scheme 1). The commercially available free porphyrin ligands with chloride counterions were converted to the iron(III) hydroxide complexes (porphyrin)Fe<sup>III</sup>(OH) (**1**), which were then oxidized to oxoiron(IV) porphyrin species (**2**) according to literature methods [15]. Two equivalents of the terminal oxidant *m*-chloroperoxybenzoic acid (*m*-CPBA) were found to be necessary for the complete formation of **2** in acetonitrile solution for all three porphyrin systems as determined by UV-visible spectroscopy [15, 26].

Attempts to prepare (TDCPP)<sup>+</sup> Fe<sup>IV</sup>(O)(X) (**3a**) at room temperature by adding an excess of *m*-CPBA (2–100 equivalents) to ferric species **1a** were not successful in either CH<sub>2</sub>Cl<sub>2</sub> or CH<sub>3</sub>CN solutions. Addition of two equivalents of *m*-CPBA to the CH<sub>2</sub>Cl<sub>2</sub> solution of **1a** led to axial ligand exchange and formation of a high-spin (TDCPP)Fe<sup>III</sup>(*m*-CPBA) (417, 509, 573 nm) [27]. In acetonitrile, addition of the same amount *m*-CPBA to **1a** generated red species (TDCPP)Fe<sup>IV</sup>(O) (**2a**), which slowly decayed to a mixture of **1a** and (TDCPP)Fe<sup>III</sup>(*m*-CBA) (414, 505, 577 nm). A large excess of *m*-CPBA (100 equivalents) could prolong the life-time of **2a** because of the regeneration of **2a** from ferric porphyrin, but no oxoiron(IV) porphyrin radical cation species was observed.

It was known that water can substantially stabilize oxoiron(IV) porphyrin radical cation species [19]. When a mixed solvent of acetonitrile and water (1:1, v/v) was used, the UV-visible spectra of **1a** and **2a** were the same as those in pure acetonitrile solution as expected for the OH ligation of ferric porphyrin **1a** and the neutral character of oxoiron(IV) porphyrin species **2a**. Addition of 100 equivalents *m*-CPBA to either **1a** or **2a** resulted in formation of a new green species that showed a weak Soret band at 390 nm and a broad Q-band at 550–750 nm (Figure 1) in addition to partial porphyrin degradation. The UV-visible spectrum of the green species was characteristic for oxoiron(IV) porphyrin radical cation and very similar to the reported Compound I spectra of several (TDCPP)<sup>+</sup> Fe<sup>IV</sup>(O)(X) (**3a**) species generated by oxidizing ferric porphyrins containing weak axial ligands at low temperature [9, 22, 28]. When excess amounts of organic reductants such as styrene or diphenylmethane were added to above solutions of **3a**, the UV-visible spectrum returned to that of ferric

porphyrin **1a**, which was recovered in high yield (>95%). The overall reaction sequence is consistent for the behavior expected for oxoiron(IV) porphyrin radical cation species.

Conversion from (TDCPP)Fe<sup>IV</sup>(O) (**2a**) to (TDCPP)<sup>+</sup>Fe<sup>IV</sup>(O)(X) (**3a**) was shown not to be due to direct reaction of **2a** with excess *m*-CPBA. A solution of **2a** prepared in acetonitrile using six equivalents of *m*-CPBA was stable, but addition of excess acid *m*-chlorobenzoic acid (*m*-CBA) resulted in complete conversion of **2a** to **3a** with a second-order rate constant of  $(1.3 \pm 0.2) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$  (inset of Figure 1). This result demonstrated that acid could catalyze the disproportionation reaction of the Compound II model **2a** to the Compound I model **3a** in the presence of six equivalents of *m*-CPBA. With smaller amounts of oxidant, such as two equivalents of *m*-CPBA used in the preparation of **2a** before addition of *m*-CBA, incomplete transformation to **3a** was observed. Apparently, slow disproportionation occurs in the absence of acid catalysis, and the oxidant is degraded by reaction with solvent.

Similar experiments were conducted with the other two porphyrin systems **2b** and **2c** generated with six equivalents of *m*-CPBA. Addition of *m*-CBA (up to 5 mM) to the corresponding CH<sub>3</sub>CN/H<sub>2</sub>O (1:1, v/v) solution of oxoiron(IV) porphyrin species **2b** and **2c** ( $2 \times 10^{-5} \text{ M}$ ) at ambient temperature was studied. As shown by the UV-visible spectrum in Figure 2, (TDFPP)Fe<sup>IV</sup>(O) (**2b**) was not fully converted to the corresponding oxoiron(IV) porphyrin radical cation (TDFPP)<sup>+</sup>Fe<sup>IV</sup>(O) (**3b**). In addition to the absorbance at 551 nm from **2b** [15], a characteristic Q-band at 550–750 nm for Compound I analogue **3b** [19] was observed together with broad Soret band. The UV-visible spectrum of most electron-deficient system, TPFPP (**3b**) did not reveal any detectable amount of conversion of **2c** to **3c** upon the addition of excess *m*-CBA.

The diverse results for the three oxoiron(IV) porphyrin species **2** upon the addition of *m*-CBA can be explained by the different disproportionation equilibrium constants  $K_{\text{dis}}$  for the three porphyrin systems [29]. By considering the cationic feature of the oxoiron(IV) porphyrin radical cations, one can expect that the order of apparent  $K_{\text{dis}}$  values is TDCPP > TDFPP > TPFPP. That is, the strongest electron-withdrawing pentafluorophenyl groups at *meso* positions disfavor conversion of neutral (**2c**) to a mixture of cationic species (**3c**) and ferric species [29–31]. On the contrary, the TDCPP system has the least electron-withdrawing aryl groups on the porphyrin ring for the systems we studied, and **2a** undergoes an acid-catalyzed disproportionation reaction to form **3a** readily, and **3a** is stabilized by water in the polar environment. The observation that (TDCPP)Fe<sup>IV</sup>(O) (**2a**) oxidizes organic substrates faster than **2b** and **2c** can be explained by a significantly large  $K_{\text{dis}}$  value for **2b** resulting in a relatively high concentration of true oxidant **3a** [29]. Using previously reported data of suppressing the oxidation reaction by adding excess **1a** [26], the equilibrium constant for the disproportionation reaction in TDCPP system is determined to be at the level of ca.  $6 \times 10^8 \text{ M}^{-1}$ . [32]

Previous research found that porphyrin-iron(IV)-oxo species (**2**) were more stable in alkaline solutions than in neutral or acidic solutions [11, 33, 34], which might be attributed to slow formation of reactive oxoiron(IV) porphyrin radical cations in the absence of acid catalysts for the disproportionation reactions. The disproportionation mechanism also explains the decreased life-time of **2** in NMR experiments versus UV-visible spectral studies [26]; at higher concentrations of **2** used in NMR experiments, the rate of the disproportionation reaction would be increased such that the lifetime of **2** decreased significantly from several hours in the UV-visible spectral studies to a few minutes in NMR studies.

In summary, direct conversion of oxoiron(IV) porphyrin species (**2**) to oxoiron(IV) porphyrin radical cations (**3**) has been observed in acid-catalyzed reactions in a mixed solvent of acetonitrile and water (1:1, v/v) containing excess *m*-CPBA oxidant. Depending

on the electron demand of the substituted aryl groups on the porphyrin macrocycle and the corresponding effects on the disproportionation equilibrium constants, the acid-catalyzed reaction results in different observations for the three porphyrin systems studied here ranging from complete conversion to the Compound I model for **2a** to undetectable amounts of the Compound I species for **2c**.

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32.  $K_{eq} = v_{obs}[1]/k_3[\text{benzyl alcohol}][\text{H}^+][2]^2$ , where  $v_{obs}[1] \sim 10^{-8} \text{ M}^2 \text{ s}^{-1}$  and  $v_{obs}$  is the observed reaction rate,  $k_3$  is the second-order rate constant for oxidation by **3** ( $17.5 \text{ M}^{-1} \text{ s}^{-1}$  from tetramesitylporphyrin was used for the estimation),  $[\text{benzyl alcohol}] = 0.1 \text{ M}$ ,  $[\text{H}^+] = 10^{-7} \text{ M}$  in a mixed solvent of acetonitrile and water (1:1, v/v) containing no excess m-CPBA, and  $[2] = 10^{-5} \text{ M}$ .
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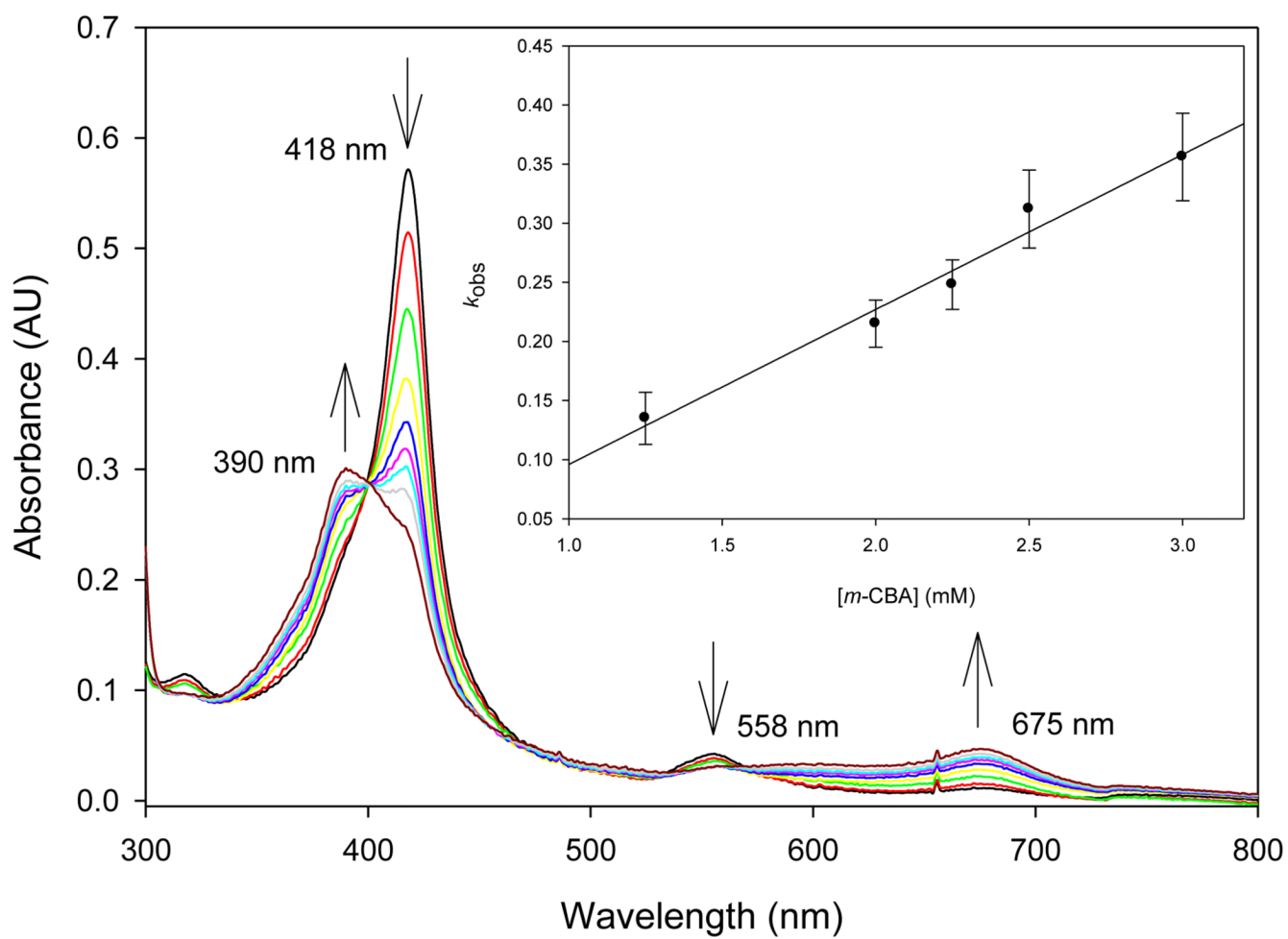
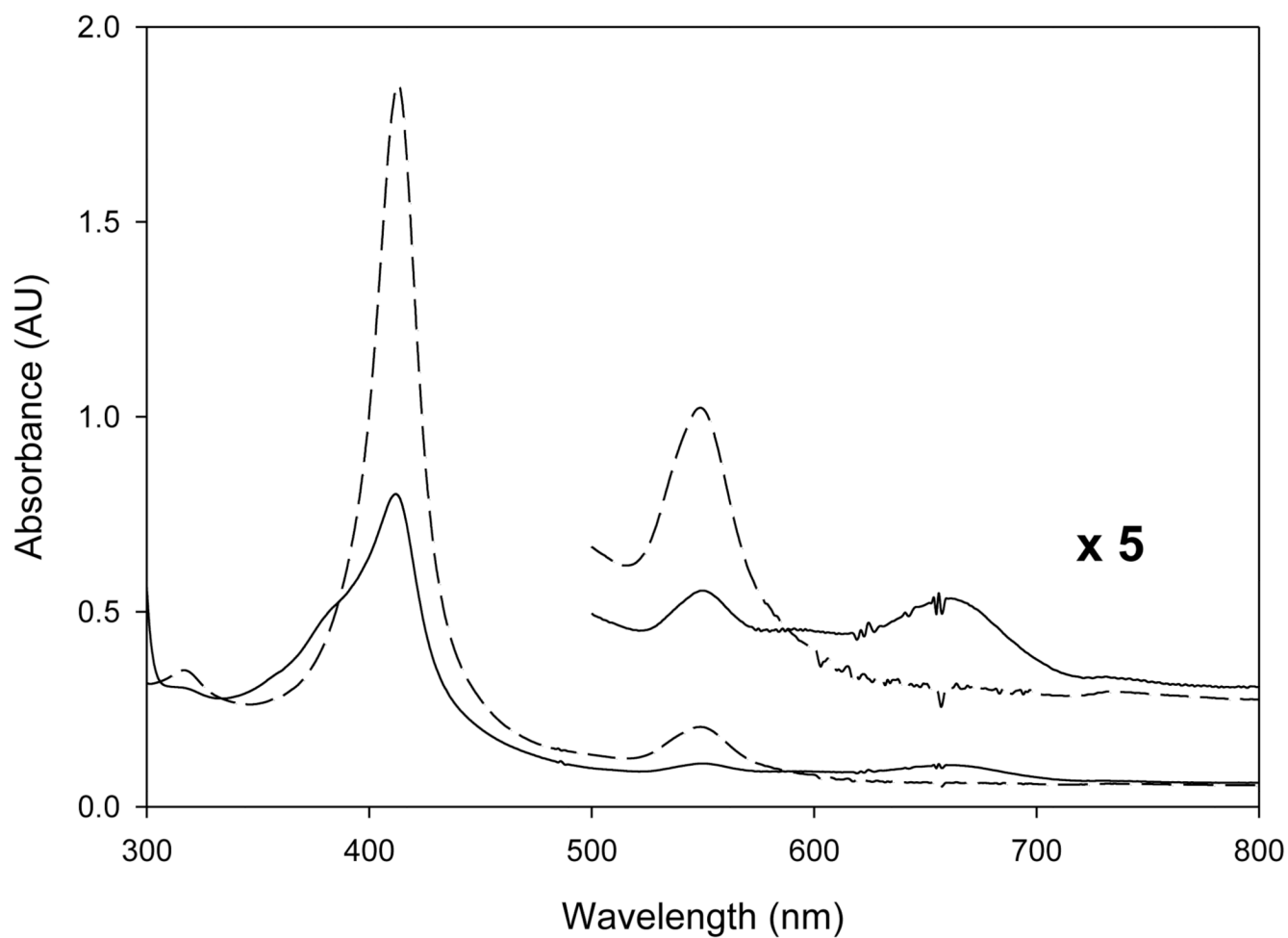
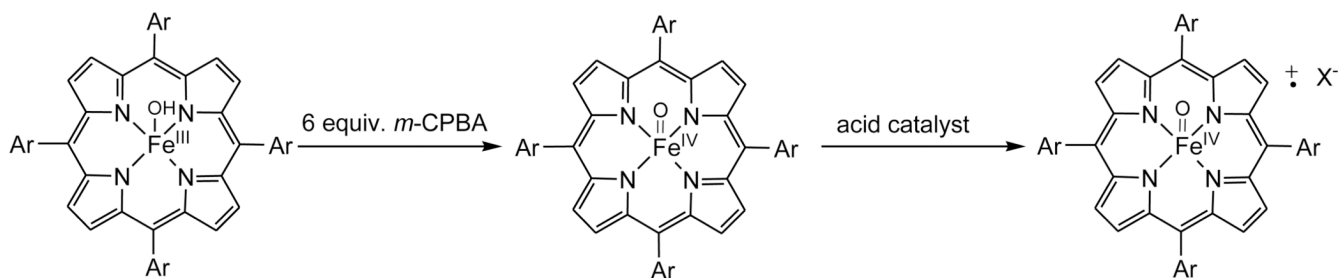


Figure 1.



**Figure 2.** UV-visible spectra of (TDFPP)Fe<sup>IV</sup>(O) (**2b**) before (dashed line) and after (solid line) the addition of excessive amount of *m*-CBA in CH<sub>3</sub>CN/H<sub>2</sub>O (1:1, v/v) solution.



**1a, 2a, 3a:** Ar = 2,6-dichlorophenyl

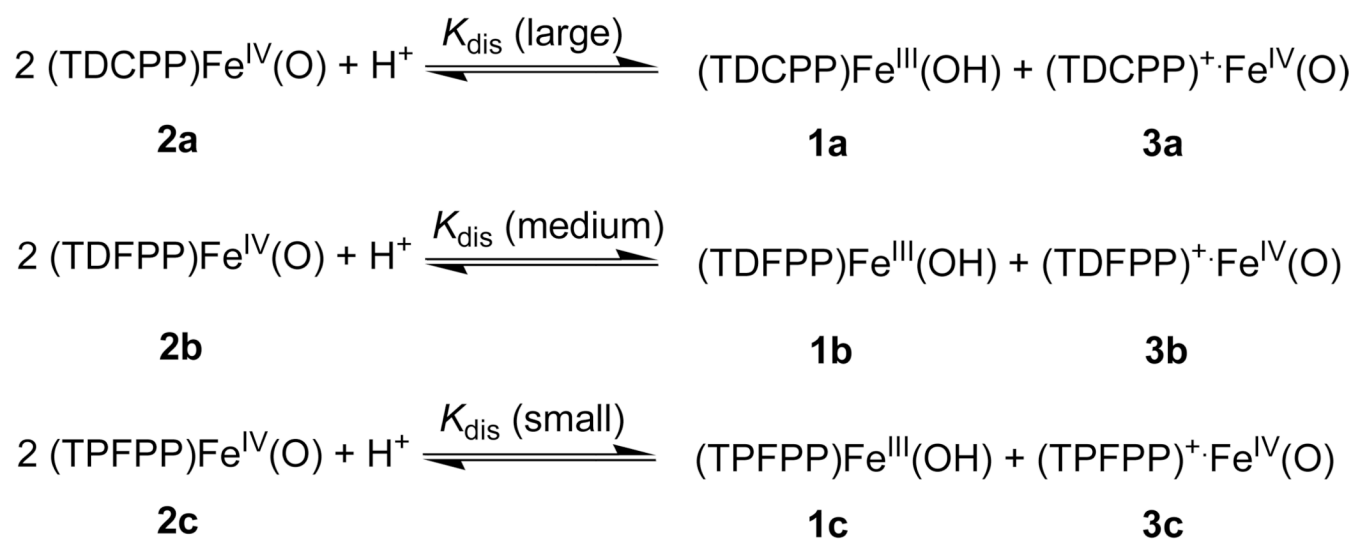
**1b, 2b, 3b:** Ar = 2,6-difluorophenyl

**1c, 2c, 3c:** Ar = pentafluorophenyl

**Scheme 1.**

A reaction scheme for the oxidation of (porphyrin)Fe<sup>III</sup>(OH) (**1**) and acid-catalyzed conversion of oxoiron(IV) porphyrin species (**2**) to oxoiron(IV) porphyrin radical cations (**3**).



**Scheme 2.**

Different disproportionation equilibrium constants  $K_{\text{dis}}$  in three porphyrin systems.