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Direct Comparison of the Reactivity of Model Complexes for Compounds 0, I, and II in Oxygenation, Hydrogen-Abstraction, and Hydride-Transfer Processes

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Abstract: The iron(III) *meso*-tetramesitylporphyrin complex is a good biomimetic to study the catalytic reactions of cytochrome P450. All of the three most discussed reactive intermediates concerning P450 catalysis (namely, Cpd 0, Cpd I, and Cpd II) can be selectively produced, identified, and stabilized for many minutes in solution at low temperature by choosing appropriate reaction conditions. In this way, their reactivity against various substrates was determined by utilizing low-temperature rapid-scan UV/Vis spectroscopy. Since all reactive intermediates are derived from a single model complex, the results of these kinetic measurements provide for the first time a full comparability of the determined rate constants for the three intermediates. The rate constants reveal a significant dependence of the reactivity on the type of reaction (e.g., oxygenation, hydrogen abstraction, or hydride transfer), which closely correlates with the chemical nature of Cpds 0, I, and II. The detailed knowledge of the reactivity of these intermediates provides a valuable tool to evaluate their particular role in biological systems.

Keywords: enzyme models · iron · kinetics · reaction mechanisms · reactivity

Introduction

During the last few decades, chemists and biochemists have contributed significantly to clarify the kinetic, mechanistic, and catalytic properties of the reactive intermediates that occur in the catalytic cycle of cytochrome P450. Although this catalytic cycle is well-known and has been generally accepted for many years,[1] there is still an active discussion in the literature[2,3] on the particular role of the different reactive intermediates and possible side reactions in biological systems. As these systems provide an outstanding redox versatility, they are also very promising tools for important challenges in organic synthesis, since they can catalyze a large number of different reactions (e.g., hydroxylation, epoxidation, and many more) under mild conditions. For a better understanding of biological processes, as well as for the optimization of biomimetic catalysis, a more detailed understanding of these processes is essential. A study of the reactivity of the reactive intermediates turned out to be a valuable instrument to evaluate and interpret the catalytic properties of these systems.

A general problem when using synthetic P450 models is the role of the electron-donating axial ligand, which is not buried in the protein coat as in the case of native enzymes. Therefore, it is not effectively protected against oxidations, which decreases the stability of the complex. Furthermore, the reactivity of such model systems is strongly controlled by the electron-donating ability of this proximal ligand, whereas in biological systems the electron donation from the cysteinate ligand is regulated by hydrogen bonding from the amino acid residues. To rule out these effects, we used $[Fe^{III}(TMP)(OH)]$ (TMP = *meso*-tetramesitylporphyrin, see Scheme 1) as a P450 mimic, which is known to form a stable five-coordinate intermediate in solution.[4]

As pointed out in our recent report,[3] a high-valent iron(IV)–oxo π-cation radical ($[(TMP^{+\bullet})Fe^{IV}{=}O]$, Cpd I) is the most potent oxygen-transfer agent for iron(III)–porphyrin-catalyzed epoxidation and sulfoxidation reactions. Although its oxygenation capability towards selected organic substrates is orders of magnitude higher than that of the acylperoxoiron(III)–porphyrin complex, a Cpd 0 analogue, the latter complex can also act as an oxidant under certain

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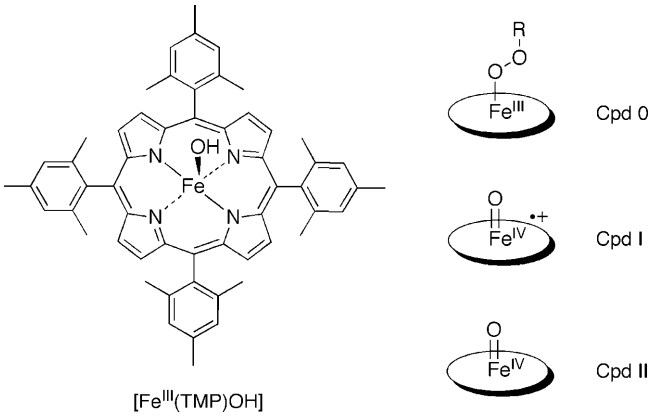
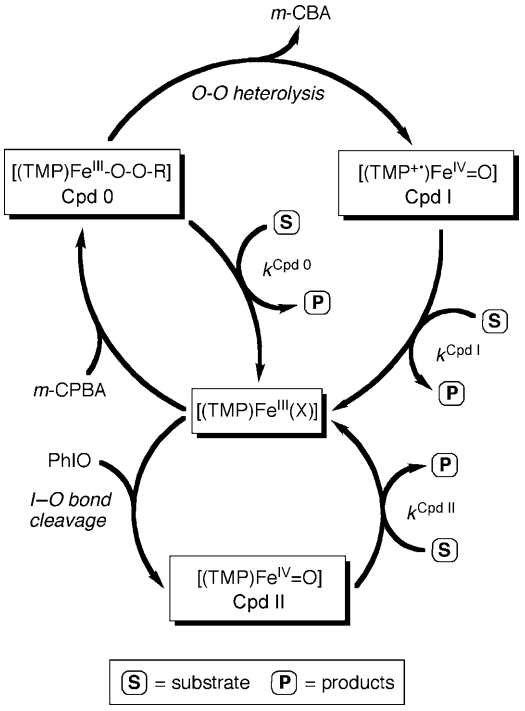


Scheme 1. The [Fe^{III}(TMP)(OH)] porphyrin complex and a schematic presentation of its reactive intermediates.

conditions.[3] In the present study we extended our work to consider a third reactive intermediate, that is, [(TMP)Fe^{IV}=O] (Cpd II), which is also known to be an oxygen-transfer agent in catalytic enzyme reactions. Furthermore, recent progress made in experimental investigations turned our focus towards other reaction types, namely, hydrogen-abstraction and hydride-transfer processes. We now report the first detailed comparison of rate constants for epoxidation, sulfoxidation, C–H and O–H abstraction, as well as hydride-transfer reactions, obtained by direct reaction between models for Cpds 0, I, and II and various organic substrates (see Scheme 2).



Scheme 2. General reaction scheme for the production of Compounds 0, I, and II, and their subsequent reactions with various substrates. Note that the iron(III)–porphyrin complex is denoted as [(TMP)Fe^{III}(X)], in which X = OH or solvent.[3] *m*-CBA = *m*-chlorobenzoic acid.

Results and Discussion

Generation and identification of intermediates: When working with [Fe^{III}(TMP)(OH)] as a cytochrome P450 model complex in acetonitrile at low temperatures, the choice of an appropriate oxidant in combination with carefully selected reaction conditions enabled us to generate and stabilize each particular intermediate (Cpds 0, I, and II) in solution for several minutes. The addition of a subequivalent amount (1:0.7) of *m*-chloroperoxybenzoic acid (*m*-CPBA) to a solution of [Fe^{III}(TMP)(OH)] in acetonitrile leads to the formation of the acylperoxoiron(III)–porphyrin complex as the sole stable product, which can be regarded as a Cpd 0 analogue. The latter is immediately converted to the cation-radical species (Cpd I) when an excess of *m*-CPBA (1:1.7) is used (see Figures 1, 2, and 3). This is due to an acid-cata-

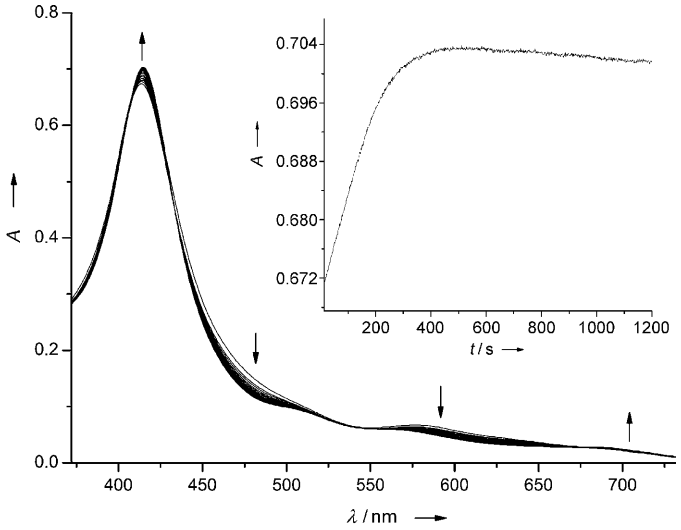


Figure 1. Spectral changes that accompany the formation of Cpd 0 in acetonitrile at −15 °C. Experimental conditions: [Fe^{III}(TMP)(OH)] = 6.5 × 10^{-6} M, [*m*-CPBA] = 3.8 × 10^{-6} M. Inset: Kinetic trace for this reaction recorded at the Soret band.

lyzed heterolytic cleavage of the O–O bond (2e$^-$ oxidation), in which the necessary protons are provided by the excess of *m*-CPBA used, because its acidity can no longer be compensated by hydroxide ligands released from the porphyrin upon the addition of the peroxide. This clarifies why the production of a stable Cpd 0 complex can only be carried out using subequivalent amounts of *m*-CPBA. Earlier studies by Groves and Watanabe have already pointed to the crucial role of acid in the conversion of the acylperoxoiron(III)–porphyrin complex to the cation-radical species.[4] As demonstrated in our previous work, the heterolytic cleavage of the O–O bond is the rate-determining step in the formation of Cpd I.[3] In contrast, even in weakly basic solution an oxoiron(IV)–porphyrin, [(TMP)Fe^{IV}=O] (Cpd II), is formed either by homolytic bond cleavage (1e$^-$ oxidation) due to the lack of protons (see Figure S1 in the Supporting Information) or by a 1e$^-$ reduction of [(TMP$^{+•}$)Fe^{IV}=O] as the

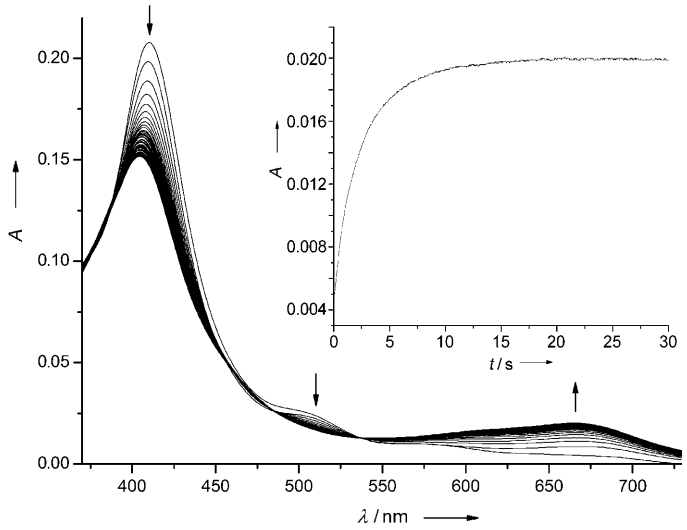


Figure 2. Spectral changes that accompany the formation of Cpd I in acetonitrile at −15 °C. Experimental conditions: $[Fe^{III}(TMP)(OH)] = 2.2 \times 10^{-6}$ M, [*m*-CPBA] $= 4.0 \times 10^{-4}$ M. Inset: Kinetic trace for this reaction recorded at the cation-radical band (660 nm).

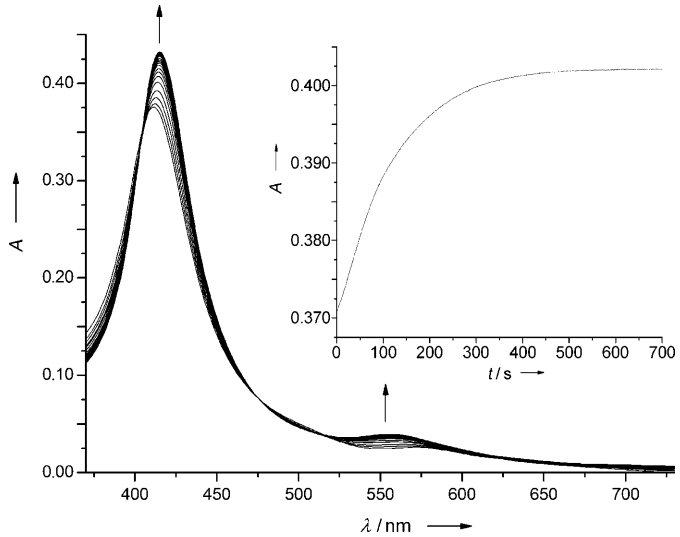


Figure 4. Spectral changes that accompany the formation of Cpd II in acetonitrile at −15 °C. Experimental conditions: $[Fe^{III}(TMP)(OH)] = 3.8 \times 10^{-6}$ M, [PhIO] $= 8.0 \times 0^{-6}$ M. Inset: Kinetic trace for this reaction recorded at the Soret band.

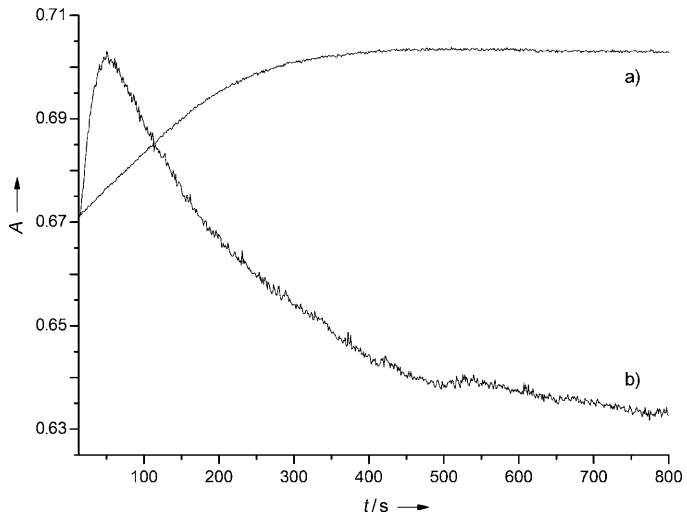


Figure 3. Absorbance changes at the Soret band for a solution of $[Fe^{III}$-(TMP)(OH)] in acetonitrile at −15 °C after the addition of a) a subequivalent amount of *m*-CPBA by which the stable Cpd 0 is formed; b) a small excess of *m*-CPBA by which the initially formed Cpd 0 is converted to Cpd I.

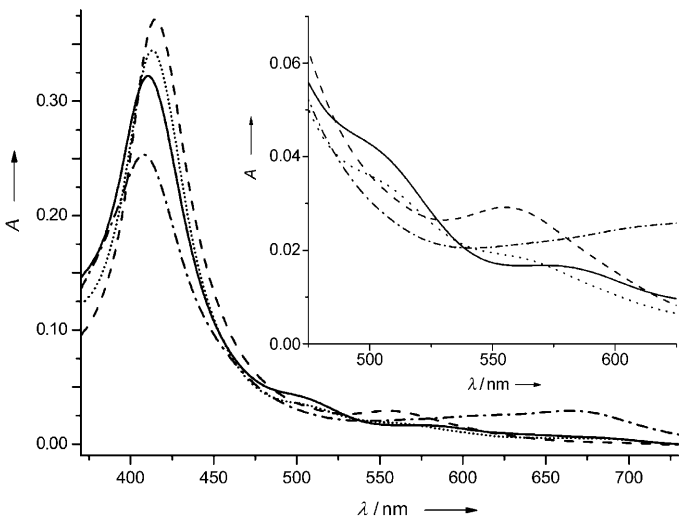


Figure 5. Comparison of the UV/Vis spectra for Cpd 0 (•••••), Cpd I (–•–•), and Cpd II (– – –) produced from $[Fe^{III}(TMP)(OH)]$ (——). Inset: Magnified view of the spectra between 475 and 625 nm.

primary oxidation product.[5] In aprotic solvents like acetonitrile, the choice of a nonacidic oxidizing agent—in our case, a 1:2 excess of PhIO (iodosylbenzene)—results in the formation of Cpd II (see Figures 4 and 5), which was the preferred method in this study. Unlike similar model complexes, $[Fe^{III}$-(TMP)(OH)] is known to form Cpd II as the sole stable product under these conditions.[6]

Cpds 0, I, and II can be unambiguously identified by careful observation of the spectral changes in the resulting time-resolved UV/Vis spectra (see Figures 1 to 5). The formation of Cpd 0 is characterized by a small but significant absorbance increase in the Soret band with a concomitant shift of about 1–2 nm to a longer wavelength, and a substantial absorbance decrease in the range between 440 and 540 nm (see Figure 1). The conversion of Cpd 0 to Cpd I (see Figure 3) is associated with a large absorbance decrease and a shift to a shorter wavelength in the Soret band combined with an absorbance increase between 550 and 700 nm (see Figure 2), which is characteristic for a high-valent oxo-iron(IV)–porphyrin π-cation radical, $[(TMP^{+\bullet})Fe^{IV}{=}O]$.[4]

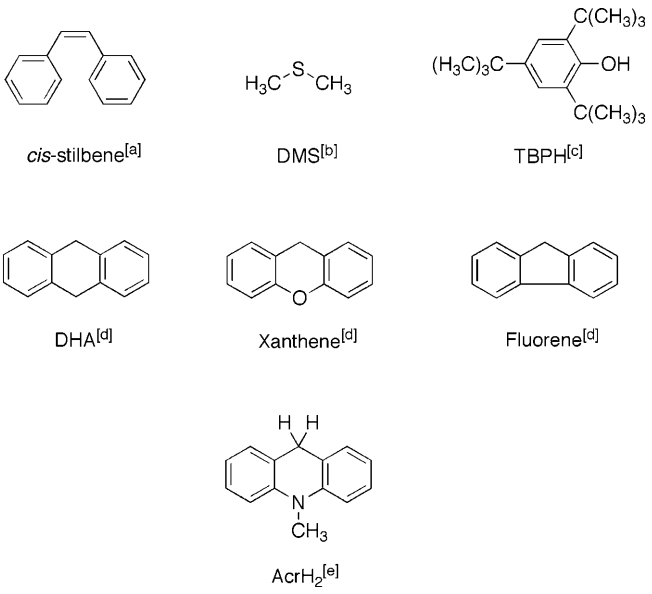
As a matter of fact, the cation-radical band is absent when Cpd II is formed by the addition of PhIO to a $[Fe^{III}$-(TMP)(OH)] solution, which enabled us to rule out a possible disproportionation reaction as proposed by Newcomb

et al.[7] In contrast to the cation radical Cpd I, the plain iron(IV)–oxo species Cpd II shows a small shift to a longer wavelength together with an absorbance increase in the Soret band. Furthermore, a new broad band at 550 nm occurs, which can be utilized to distinguish Cpd II from Cpd 0 spectroscopically (see Figure 5). The ease of selective production and spectroscopic identification of all the different reactive species, along with their remarkable stability for many minutes in acetonitrile at low temperatures, provides an exceptional opportunity to compare their reactivity against various substrates.

Reactions with various substrates: Unless otherwise noted, all epoxidation, sulfoxidation, hydrogen-abstraction, and hydride-transfer reactions by Cpds 0, I, and II were investigated under pseudo-first-order conditions for various excess substrate concentrations in acetonitrile at −15 °C. The particular reactive intermediate was produced in solution as described above, and its formation and stability in solution was continuously monitored by UV/Vis spectroscopy as shown in Figures 1, 2, and 4.

Upon injection of a substrate (see Scheme 3) into the reaction mixture, the decomposition reaction of the generated intermediate could be observed, which was clearly related to the chemical nature and the excess concentration of the selected substrate. To compare the particular reactivity of Cpds 0, I, and II, we examined the reaction of each oxidizing intermediate for various substrates and substrate concentrations. By fitting the kinetic traces to a pseudo-first-order decay function, k_{obs} values for each reaction system were obtained. In all cases the values of k_{obs} plotted against the substrate concentration resulted in a straight line without a significant intercept, from which the corresponding second-order rate constants were calculated (see examples in Figure 6, and Figures S2 and S3 in the Supporting Information).

A closer analysis of the second-order rate constants summarized in Table 1 reveals that the values of $k^{Cpd\,0}$ and $k^{Cpd\,II}$ are of the same order of magnitude for most reaction types. This might be surprising at first, since the reactivity should closely correlate with the electrophilicity of the oxidizing intermediate, which would suggest that Cpd II should be more reactive than Cpd 0 due to the higher oxidation state of the iron center. However, precursor adduct formation between Cpd 0 and the substrate can undergo significant resonance stabilization by the O–O bond structure of the acylperoxoiron(III)–porphyrin, which makes it quite an efficient catalyst.



Scheme 3. Substrates used in this study for [a] epoxidation, [b] sulfoxidation, [c] O–H abstraction, [d] C–H abstraction, and [e] hydride-transfer reactions.

Furthermore, it should be kept in mind that Cpd II can only catalyze $1e^-$-oxidation reactions, whereas Cpd 0 and Cpd I are able to undergo $2e^-$-oxidation processes. This does not play a decisive role in hydrogen-abstraction reactions, but becomes a crucial point in epoxidation and sulfox-

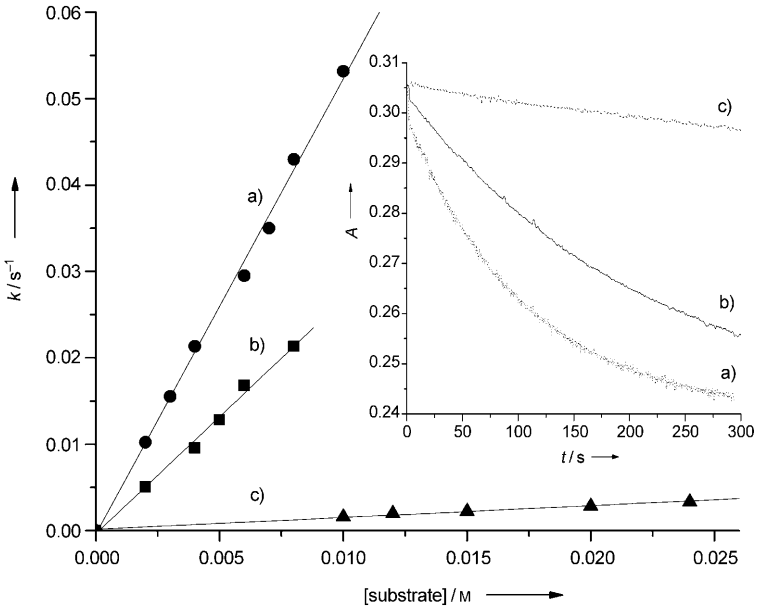


Figure 6. Determination of rate constants for C–H abstraction reactions by means of concentration-dependence measurements for the reaction of Cpd II with a) xanthene, b) DHA, and c) fluorene. Inset: Absorbance–time traces at the Soret band after the addition of 2×10^{-3} M a) xanthene, b) DHA, and c) fluorene to a 3×10^{-6} M solution of Cpd II.

Table 1. Values of the second-order rate constants for the oxidation of selected organic substrates by Cpds 0, I, and II (direct measurements at −15 °C) produced from [Fe^{III}(TMP)(OH)] in MeCN.

Substrate	$k^{Cpd\,0}$ [$M^{-1}s^{-1}$]	$k^{Cpd\,I}$ [$M^{-1}s^{-1}$]	$k^{Cpd\,II}$ [$M^{-1}s^{-1}$]
cis-stilbene[a]	0.142±0.006	66±2	0.063±0.004
DMS[b]	9.7±0.1	(1.7±0.1)×10^4[f]	6.4±0.2
TBPH[c]	(0.50±0.04)×10^3	(7.3±0.8)×10^3	(3.5±0.1)×10^3
DHA[d]	2.2±0.3	(1.1±0.4)×10^2	2.7±0.1
xanthene[d]	4.3±0.3	(4.9±0.4)×10^2	5.3±0.1
fluorene[d]	0.09±0.02	6.1±1.0	0.140±0.002
$AcrH_2$[e]	(5.6±0.3)×10^3	(0.87±0.08)×10^2	(1.50±0.03)×10^4

[a] Epoxidation. [b] Sulfoxidation; [c] O–H abstraction. [d] C–H abstraction. [e] Hydride transfer. [f] At −35 °C.

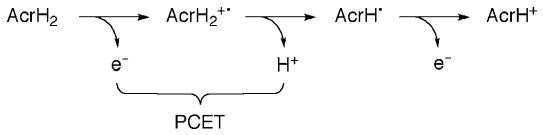
idation reactions, since the latter are $2e^-$-oxidation processes. Thus, for the reaction of Cpd II with *cis*-stilbene or dimethyl sulfide (DMS), a multistep redox process must operate. As a consequence, the epoxidation of *cis*-stilbene with Cpd 0 is more than twice as fast as the reaction with Cpd II. This effect is smaller in sulfoxidation reactions, since sulfides are electronically more versatile reaction partners, which can form more stable intermediate states. In general, the sulfoxidation reaction turned out to be very fast, whereas epoxidation proved to be one of the slowest of all the studied oxygenation reactions. This is actually not surprising since *cis*-stilbene is known to be an inert substrate.[8]

A comparison of the rate constants for the C–H abstraction reactions between Cpds 0, I, and II and the different substrates used for this type of reaction reveals a close correlation between the resulting reactivity order (namely, fluorene < 9,10-dihydroanthracene (DHA) < xanthene; see Table 1) and the corresponding bond dissociation energies of the C–H bond (namely, 80.1, 76.3, and 74.2 kcal mol^{-1} for fluorene, DHA, and xanthene, respectively).[9] This coherence between the strength of the C–H bond and the resulting rate constant is also a strong indication that Cpds 0, I, and II can indeed promote C–H abstractions as postulated above (see Figure 6, as well as Figures S2 and S3 in the Supporting Information). Our results concerning C–H abstraction and hydride-transfer reactions are fully consistent with recent findings by Nam and Fukuzumi et al., who investigated the reactivity of Cpd II for related porphyrin systems.[10]

A special situation can be observed in O–H abstraction reactions, in which second-order rate constants are quite high and rather similar to each other (ca. one order of magnitude difference between Cpds 0, I, and II). This may be due to the fact that hydrogen abstraction in this case is very easy, and the substrate 2,4,6-tri-*tert*-butylphenol (TBPH) is commonly used as a very effective radical scavenger.

The most-discussed and best-analyzed reactive intermediate is surely the high-valent iron(IV)–oxo π-cation radical (Cpd I), due to its outstanding oxidizing capabilities. As expected, it also turned out to be the most effective catalytic species in our experimental studies. In some cases it outperforms Cpd 0 and Cpd II by a few orders of magnitude as far as the rate constants are concerned (see Table 1). The reaction of Cpd I with DMS even had to be studied at −35 °C to enable us to follow the course of the reaction in an appropriate way. That is why in biological systems its generation is controlled by a proton relay from the amino acid residues at the active site. On the one hand, acid catalysis promotes the conversion from Cpd 0 to Cpd I, and on the other hand, it suppresses a possible homolytic cleavage of the O–O bond to form Cpd II. Therefore, this high-valent oxoiron(IV)–porphyrin π-cation radical is commonly accepted as the main reactive intermediate in iron(III)–porphyrin-catalyzed reactions.[1]

A completely different situation was observed for the hydride transfer reaction with 10-methyl-9,10-dihydroacridine ($AcrH_2$) as the nicotinamide adenine dinucleotide (NADH) analogue. As known from recent findings,[10] this kind of reaction can be described as a hydrogen-atom transfer process regarded as proton-coupled electron transfer (PCET) from the NADH analogue to Cpd II, with a subsequent electron transfer from $AcrH^•$ to Cpd II to form $AcrH^+$ as the final product (see Scheme 4).



Scheme 4. General reaction scheme for the sequential 'hydride abstraction' from $AcrH_2$.

In this $e^-/H^+/e^-$ sequence, the proton transfer is the rate-determining step,[11] therefore the reactivity order of Cpds 0, I, and II can be accounted for in terms of the basicity of the formed intermediates. In this case, Cpd II appears to be the most reactive species as a consequence of the mechanism of the hydride-transfer process. In the initial electron-transfer step, Cpd II is reduced to an iron(III)–oxo species, whereas Cpd I is reduced to the iron(IV)-oxo species Cpd II. Since the lower-charged iron center has a higher ability to promote the subsequent proton abstraction from $AcrH_2^{+•}$, the reaction of Cpd II is significantly faster. It is worth noting that in the case of Cpd I the reaction solution is slightly acidified by the excess of *m*-CPBA that also delivers the necessary protons for the heterolytic cleavage of the O–O bond in the conversion of Cpd 0 to Cpd I as stated above.

Due to this effect, even Cpd 0 turned out to be a more effective 'hydride abstraction' agent than Cpd I. Apart from the fact that again a lower-charged iron species is involved in the proton abstraction, Cpd 0 is produced by the addition of a subequivalent amount of *m*-CPBA to prevent the acidification of the solution and thereby the conversion to Cpd I. The latter process implies that also the acylperoxoiron(III)–porphyrin complex (Cpd 0) can act as a base and contribute to the proton abstraction from $AcrH_2^{+•}$.

Conclusion

In conclusion, the exceptional possibility to selectively produce, identify, and stabilize Cpd 0, Cpd I, and Cpd II in solution enabled us to carry out direct kinetic studies on the re-

activity of these intermediates in epoxidation, sulfoxidation, O–H abstraction, C–H abstraction, and hydride-transfer reactions with different substrates at low temperatures. Regardless of the fact that the outstanding reactivity of the cation-radical species Cpd I could be confirmed, Cpd II turned out to be the most efficient catalyst for hydride-transfer reactions. Although the reactivity order in this type of reaction (namely, Cpd II > Cpd 0 > Cpd I) might be surprising at first sight, it can be easily explained as a consequence of the ability of each reactive intermediate to promote the rate-determining proton-abstraction step. Furthermore, a significantly different behavior of Cpd 0 and Cpd II in epoxidation and sulfoxidation reactions could be demonstrated. These findings can also be considered as strong evidence that Cpds 0, I, and II are indeed produced in the way described in this study.

Although much work has been done on special aspects of certain P450 model complex reactions in the past, this experimental study is the first to cover the complete picture from the generation and stabilization of the three most discussed reactive intermediates to the determination of their reactivity towards a broad variety of substrates in many different types of reactions. Since Cpds 0, I, and II were derived from a single model complex and all the reactions were carried out under identical experimental conditions, this work provides a full comparability of the determined rate constants. This delivers valuable insight into the key steps of the catalytic processes in iron(III)–porphyrin chemistry, and lays the foundation for simulations of the complete catalytic cycle of cytochrome P450. Therefore, a challenge for the immediate future will be to find experimental conditions based on the reported rate constants, in which the catalytic cycle can be observed and simulated as done in a recent report from our group.[12]

Experimental Section

Materials: All solutions were prepared in acetonitrile (99.9% AMD CHROMASOLV from Sigma–Aldrich). *m*-CPBA was purchased from Acros Organics and purified before use by recrystallization from hexane. [Fe^{III}(TMP)(OH)] was obtained from [Fe^{III}(TMP)Cl] (Frontier Scientific Porphyrin Product) as described earlier.[13] The resulting [Fe^{III}-(TMP)(OH)] should be washed thoroughly with water to remove small impurities of NaOH, which could disturb the proper generation of Cpd 0, Cpd I, or Cpd II due to the pH sensitivity of these reactions. PhIO (iodosylbenzene) was synthesized according to a literature procedure.[14] DHA, 9*H*-xanthene, *cis*-stilbene (96%), and DMS were purchased from Aldrich. TBPH was obtained form Aldrich and purified by recrystallization from methanol. 9*H*-Fluorene was purchased from Fluka. $AcrH_2$ was synthesized as described earlier.[15]

Low-temperature rapid-scan measurements: Time-resolved UV/Vis spectra were recorded using a quartz glass dip-in detector (Spectralytics, Aalen, Germany) coupled to a TIDAS 16/300–1100 diode array spectrophotometer (J&M, Aalen, Germany). The optical dip-in detector had a light path of 1.0 cm and was connected to the spectrophotometer unit with flexible light guides. A 20 mL double wall reaction vessel was used and temperature was controlled (±0.1 °C) by a combination of cold methanol circulation (Colora WK 14-1 DS, Lorch, Germany) and an 800 W heating unit. Complete spectra were recorded between 372 and 732 nm with the integrated J&M software Kinspec 2.30.

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