Self-hydroxylation of perbenzoic acids at a nonheme iron(II) center†

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Treatment of mononuclear nonheme iron(II) complexes bearing two *cis*-labile sites with perbenzoic acids results in the self-hydroxylation of the aromatic ring to form the corresponding iron(III)–salicylate complexes through an intramolecular oxo-transfer process.

Oxygen-activating enzymes with mononuclear nonheme iron active sites participate in many metabolically important oxidative transformations.[1,2] Among these are aromatic amino acid hydroxylases such as phenylalanine, tyrosine, and tryptophan hydroxylases that catalyze the aromatic hydroxylation of the namesake amino acids, concomitant with the two-electron oxidation of the requisite organic cofactor tetrahydropterin to its quinonoid dihydropterin form.[1,3] A mechanism is proposed in which oxoiron(IV) intermediates are involved as active oxidants in the hydroxylation of aromatic rings,[1,3,4] although such oxoiron(IV) species have not yet been experimentally observed in the catalytic cycles of the enzymes.

The hydroxylation of aromatic compounds by biomimetic nonheme iron complexes has also been reported.[5,6] Notably, Que and co-workers have shown that mononuclear nonheme iron(II) complexes in combination with alkyl hydroperoxides are capable of oxygenating a pendant aromatic ring on the ligand.[5] The authors provided strong mechanistic evidence that metal-centered electrophilic oxidants, presumably mononuclear nonheme oxoiron(IV) intermediates, are involved in the arene hydroxylations, but direct evidence for such intermediates in the catalytic cycle has yet to be reported.

Very recently, a number of synthetic mononuclear nonheme oxoiron(IV) complexes bearing tetradentate N4 and pentadentate N5 ligands have been isolated and characterized with various spectroscopic techniques including X-ray crystallography.[7,8] Such nonheme oxoiron(IV) complexes can effect a variety of oxygenation reactions including olefin epoxidation and alkane hydroxylation.[7,8] Since nonheme oxoiron(IV) intermediates have been proposed to participate in arene hydroxylations under catalytic conditions,[5,6] we have investigated aromatic hydroxylations with the well-characterized nonheme oxoiron(IV) complexes. In the present study, we report that perbenzoic acids are converted to the corresponding salicylates when reacted with mononuclear nonheme iron complexes. Interestingly, the aromatic hydroxylation does not occur in the reaction of nonheme oxoiron(IV) complexes with benzoate but does so only with additional perbenzoic acid.

The reaction of $[Fe^{II}(TPA)(NCCH_3)_2]^{2+}$ (**1**) (TPA = tris(2-pyridylmethyl)amine) with 3 equiv. of *m*-chloroperbenzoic acid (*m*-CPBA) in CH_3CN at −40 °C produced a green species with an absorption maximum wavelength λ_{max} at 720 nm (Fig. 1a, dotted bold line) and a prominent mass peak at a mass-to-charge ratio (*m*/*z*) of 461 (data not shown), results indicating the generation of $[(TPA)Fe^{IV}{=}O]^{2+}$ (**2**).[7h] The conversion of **1** to **2** took less than 5 min under these conditions. Subsequently, the green intermediate converted slowly to a new purple species (**3**) with a λ_{max} at 560 nm (Fig. 1a, solid bold line), and the conversion was completed over a period of ∼5 h at −40 °C. Titration experiments showed that the maximum formation‡ of **3** required ∼3 equiv. of *m*-CPBA (Fig. 1a, inset). This intermediate was stable at least for several days at −40 °C in CH_3CN solution but slowly decayed to an

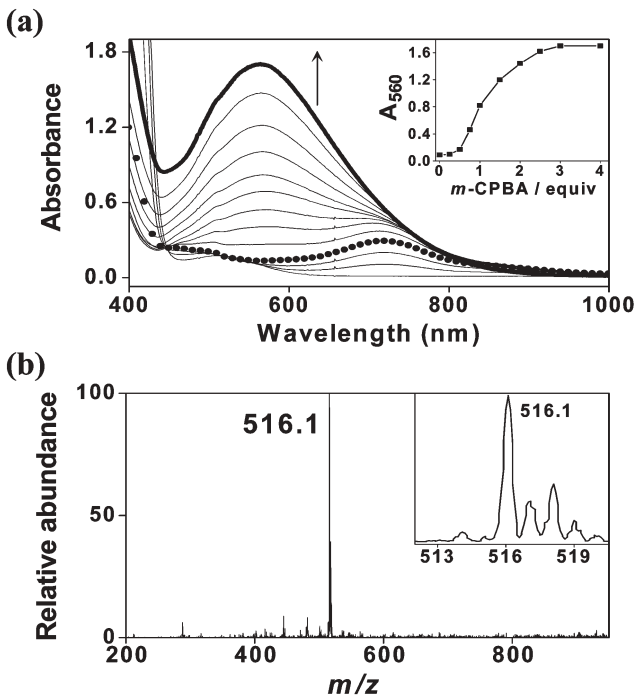

Fig. 1 (a) UV-vis spectral changes of **1** to **2** (dotted bold line) and then to **3** (solid bold line) upon addition of 3 equiv. of *m*-CPBA to a solution of **1** (1 mM) in CH_3CN at −40 °C. Inset shows the absorbance changes at 560 nm upon addition of *m*-CPBA incrementally at −20 °C. (b) Electrospray ionization mass spectrum of **3**. Inset shows observed isotope distribution pattern for an ion at *m*/*z* of 516.1.

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orange species upon warming to room temperature, showing a typical absorption spectrum of a μ-oxo-bridged dinuclear iron TPA complex (data not shown).[9]

The purple species **3** was further characterized with various spectroscopic techniques and identified to be mainly [Fe^{III}(TPA)(5-Cl-salicylate)](ClO_4), which was synthesized independently by reacting **1** with 5-chlorosalicylic acid in air (Electronic supplementary information,† Experimental Conditions). First, the electrospray ionization mass spectrum (ESI MS) of **3** exhibits a prominent peak at *m*/*z* 516.1 (Fig. 1b), whose mass and isotope distribution pattern are identical to those of the synthesized complex (Fig. S1-b†). These results indicate that **3** contains a chlorosalicylate ligand that must derive from the oxidation of the phenyl ring of *m*-chlorobenzoate (*m*-CBA) in the reaction of **1** and *m*-CPBA. The EPR spectra of **3** and the authentic compound show a strong signal at $g = 4.3$, typical of a high-spin ($S = 5/2$) Fe^{III} species (Fig. S1-c† for the authentic compound).[10] In order to determine the site(s) of oxygenation on *m*-CBA, **3** was treated with acid, and the extracted free ligand was analyzed with ^{1}H NMR (Fig. S2-a†). By comparing the ^{1}H NMR spectrum of the extract with those of authentic 5- and 3-chlorosalicylic acids, we found that the oxygenation of *m*-CBA occurred mainly at the position *para* to the chloro substituent, yielding 5-chlorosalicylate as a major product with a small amount of 3-chlorosalicylate (Fig. S2†). The crystal structure of the independently synthesized [Fe^{III}(TPA)(5-Cl-salicylate)](ClO_4) complex shows that the salicylate ligand coordinates to iron in a bidentate fashion (Fig. 2).‡ On the basis of the spectral comparisons of **3** and the authentic compound, the purple species, **3**, formed in the reaction of **1** and *m*-CPBA, is assigned as [Fe^{III}(TPA)(5- or 3-Cl-salicylate)]$^+$ that is formed in about 80% yield.§ It is worth noting that the conversion of *m*-CPBA to chlorosalicylate was also observed in the reaction of [Fe(BPMEN)]$^{2+}$ (BPMEN = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)-1,2-diaminoethane) (Fig. S3 for UV-vis and ESI mass spectra†) but not in the reactions of [Fe(N4Py)]$^{2+}$ (N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine) and [Fe(TMC)]$^{2+}$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane). These results demonstrate that the aromatic ring oxidation occurs only in nonheme iron complexes having two *cis*-labile sites such as [Fe(TPA)]$^{2+}$ and [Fe(BPMEN)]$^{2+}$.[11]

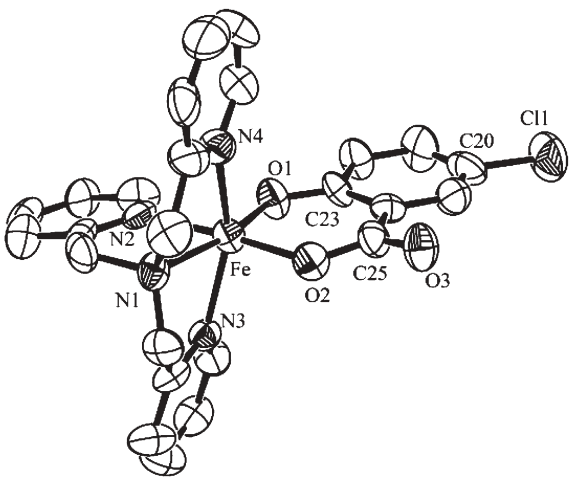


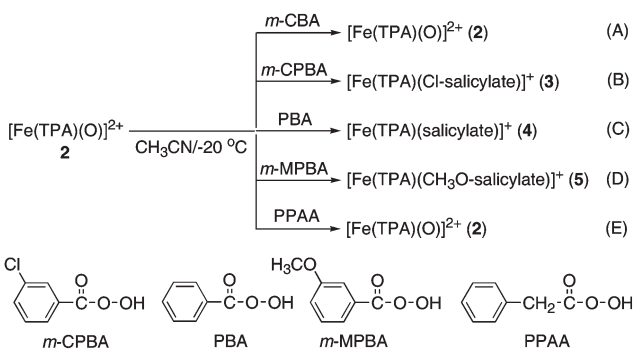
Fig. 2 ORTEP representation of [Fe^{III}(TPA)(5-Cl-salicylate)]$^+$ showing 50% thermal ellipsoids. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Fe–O1 1.845(7), Fe–O2 1.914(7), Fe–N1 2.216(9), Fe–N2 2.129(9), Fe–N3 2.137(8), Fe–N4 2.156(10), C23–O1 1.342(11), C25–O2 1.316(11), C25–O3 1.200(12), C20–Cl1 1.767(13); O1–Fe–O2 93.8(3), O1–Fe–N1 168.4(3), O1–Fe–N2 88.5(3), O1–Fe–N3 106.3(3), O1–Fe–N4 100.8(4).

We then focused our efforts on characterizing the nature of the species responsible for the aromatic hydroxylation. The observations that **2** was formed initially and then converted to **3** in the reaction of **1** and *m*-CPBA (see Fig. 1a) led us to consider whether **2** is an active oxidant that hydroxylates the aromatic ring of *m*-CBA to the corresponding Cl-salicylate. We therefore first generated **2** by reacting **1** with CH_3CO_3H in CH_3CN at −40 °C (Experimental Conditions†)[7h] and then added *m*-CBA to the solution of **2**. Different from the *m*-CPBA reaction, the formation of **3** was not observed in this reaction (Scheme 1, reaction A). Thus **2** *cannot* be the active oxidant that hydroxylates the aromatic ring of *m*-CBA.

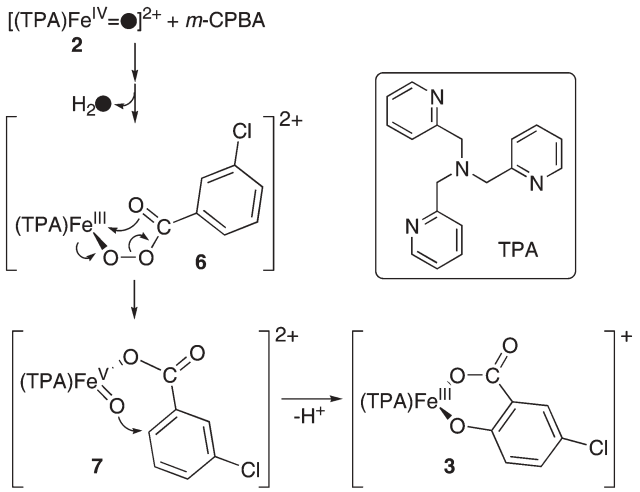
Interestingly, when *m*-CPBA instead of *m*-CBA was added to the solution of **2**, we have observed the formation of **3** (Scheme 1, reaction B) (Fig. S4 for UV-vis and ESI mass spectra†). Furthermore, when perbenzoic acid (PBA) instead of *m*-CPBA was added to the solution of **2**, a purple species formulated as [Fe(TPA)(salicylate)]$^+$ (**4**) by ESI MS (Fig. S5-a†) was formed as the major product in this reaction (Scheme 1, reaction C). Similarly, the formation of [Fe(TPA)(CH_3O-salicylate)]$^+$ (**5**) was observed when *m*-methoxyperbenzoic acid (*m*-MPBA) was added to the solution of **2** (Scheme 1, reaction D) (Fig. S5-b for ESI MS†). However, in contrast to the perbenzoic acids, the reaction of phenylperacetic acid (PPAA) with either **1** or **2** did not produce the purple species (Scheme 1, reaction E). The latter result indicates that the additional methylene group in PPAA gives rise to a situation not favourable for ring hydroxylation.

^{18}O labeling experiments show that the oxygen incorporated into **3** derives neither from the oxo group of **2** nor from molecular oxygen (Fig. S6 for ESI MS of **2** and **3** and detailed experimental procedures†).[7a,12] These results leave the perbenzoic acid as the only possible source of the oxygen atom in the salicylate product formed.[13] Thus a species generated from the reaction of **2** and perbenzoic acids must be the oxidant which hydroxylates the aromatic ring of benzoates to the corresponding salicylates.

In Scheme 2, we propose a plausible mechanism for the self-hydroxylation of perbenzoic acids by mononuclear nonheme iron(II) complexes to form the corresponding iron(III)-salicylate complexes. This mechanism takes into account the following



Scheme 1 Reactions showing the aromatic ring oxidation of benzoates to the corresponding salicylates.



Scheme 2 A proposed mechanism for the formation of **3** through a proposed oxoiron(V) intermediate in the reaction of **2** and perbenzoic acid. The structure of TPA ligand is shown in a box.

observations: (1) that the initially formed oxoiron(IV) complex is not the reactive species for the aromatic hydroxylation but is involved in activating perbenzoic acids in a subsequent step, (2) that salicylates are formed only with nonheme iron complexes having two *cis*-labile sites (*e.g.*, $[Fe(TPA)]^{2+}$ and $[Fe(BPMEN)]^{2+}$), (3) that the aromatic ring oxidation occurs only with perbenzoic acids, which can form a six-membered-ring transition state (see the proposed intermediate **7** in Scheme 2), and (4) that the oxygen incorporated into the salicylate products derives not from the oxo group of the oxoiron(IV) intermediate but from the perbenzoic acids. The mechanism depicted in Scheme 2 proposes an oxoiron(V) species **7**,[14] which is generated from the reaction of the initially formed oxoiron(IV) intermediate with peracid, as the oxidant that intramolecularly attacks the aromatic ring. At this stage of our investigation, it is not clear how this oxidizing species is formed, although a (κ^2-acylperoxo)iron(III) species (**6**) would be a reasonable precursor.¶ It is also not clear why the initially formed $(TPA)Fe^{IV}$=O species does not carry out this hydroxylation, since such oxoiron(IV) species have previously been shown to be capable of alkane hydroxylation[7f] and olefin epoxidation[7h] and implicated in the intramolecular hydroxylation of the arene ring of Fe^{II}(6-PhTPA) by ^{t}BuOOH.[5a] Future studies will focus on attempts to elucidate the exact nature of the hydroxylating intermediate and, if the hydroxylating intermediate is indeed the oxoiron(V) species, the formation of an oxoiron(V) intermediate in the reaction of an oxoiron(IV) complex and perbenzoic acid.

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Notes and references

‡ Crystal data of $[Fe^{III}(TPA)(5\text{-Cl-salicylate})]^+$: C_{25} H_{21} Cl_2 Fe N_4 O_7: M = 616.21, *orthorhombic*, space group *F*dd2 (No.43), a = 27.042(13) Å, b = 48.74(2) Å, and c = 8.026(3) Å, V = 10579(8) Å^3, T = 233(2) K, Z = 16, μ = 0.825 mm^{-1}, R_{int} = 0.1767 for 5678 independent reflections of the 15501 collected, final R [$I > 2\sigma$] = 0.0901, final R_w [$I > 2\sigma$] = 0.1547. CCDC 281062. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b511302d

§ The yield of **3** formed in the reaction of **1** and *m*-CPBA was calculated on the basis of the molar extinction coefficient (ε 2100 M^{-1}cm^{-1}) of the independently synthesized $[Fe^{III}(TPA)(5\text{-Cl-salicylate})](ClO_4)$ complex.

¶ An EPR spectrum of the solution taken during the reaction shows signals at g_1 = 2.6, g_2 = 2.4, and g_3 = 1.9, indicating the presence of a low-spin Fe(III) species.

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