ortho-Hydroxylation of benzoic acids with hydrogen peroxide at a non-heme iron center†

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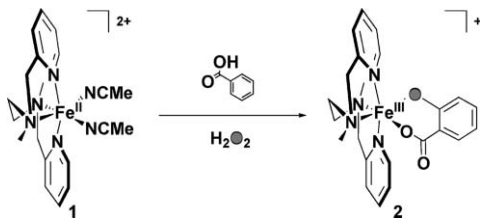
The iron-assisted hydroxylation of benzoic acid to salicylic acid by 1/H_2O_2 has been achieved in good yield under mild conditions (where 1 is [Fe(II)(BPMEN)$(CH_3CN)_2$]$(ClO_4)_2$ and BPMEN = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)ethane-1,2-diamine); the product of this reaction is a novel mononuclear iron(III) complex with a chelating salicylate.

In nature, aromatic hydroxylations are catalyzed by mononuclear non-heme iron centers in pterin-dependent aromatic amino acid hydroxylases,[1,2] and non-heme diiron centers in toluene monooxygenases.[3–5] Synthetically, iron-catalyzed arene hydroxylations have been reported with Fenton's reagent (Fe salt/H_2O_2)[6–8] and related systems that generate either hydroxyl radicals[9–11] or metal-based oxidants.[12–16] However, phenol yields were often poor and the reactions were non-selective, yielding isomers of aromatic hydroxylation compounds as well as products of side chain oxidation. Recently, efficient intramolecular aromatic hydroxylations were reported with mononuclear[17–19] or dinuclear[20–22] iron complexes where the aromatic ring is forced into close proximity of the iron center by covalent binding to the supporting polydentate ligand. The synthetic utility of these interesting systems, however, is limited because of their complicated preparations. Non-covalent substrate binding to the iron center can overcome this shortcoming, as was reported for selective hydroxylation of coordinated phenols with *m*-chloroperbenzoic acid (*m*-CPBA).[23] The desire to use an environmentally clean oxidant, such as H_2O_2, inspired our search for simple biomimetic oxidation reactions of coordinated aromatic substrates.

One of the best examples of a H_2O_2-activating system is [Fe^{II}(BPMEN)$(CH_3CN)_2$]$(ClO_4)_2$ (**1**, Scheme 1, BPMEN = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)ethane-1,2-diamine),[24] an excellent catalyst for alkane hydroxylation[24,25] and olefin epoxidation.[26–28] We report herein a new reaction promoted by complex **1**, the stoichiometric transformation of benzoic and *m*-chlorobenzoic acid into the corresponding salicylic acids upon oxidation by hydrogen peroxide. The reaction proceeds readily with added substrates and yields exclusively *ortho*-hydroxylated products in high yields under mild conditions. Organic products, which are initially coordinated to iron, can be easily isolated, and the ligand BPMEN is recovered after the reactions.

When hydrogen peroxide was added to complex **1** in the presence of benzoic acid, a deep blue color (λ_{max} = 590 nm) developed instantly (Fig. 1). The final spectrum was identical to that of the independently prepared salicylate complex [Fe^{III}(BPMEN)$(OOC(C_6H_4)O)$]$(ClO_4)_3$ (**2**) (Fig. S1†) and the product of reaction was identified *in situ* by ESI-MS, with only one strong peak (>5%) detected at *m*/*z* 462.2, consistent with the formulation {[Fe(BPMEN)$(OOC(C_6H_4)O)$]}$^+$ (Fig. S2†). Similar spectral changes were observed when *m*-ClC_6H_4COOH was used (100% peak at *m*/*z* 496.2 consistent with {[Fe(BPMEN)$(OOC(C_6H_3)(Cl)O)$]}$^+$).

Complex **2** (Scheme 1) was independently synthesized from BPMEN, salicylate and $Fe(ClO_4)_3$ and fully characterized.† The crystal structure of **2** (Fig. 2) shows a six-coordinate Fe(III) center with four coordination sites occupied by the nitrogen atoms of the BPMEN ligand and two sites occupied by oxygens from the salicylate ligand.‡ As previously observed with similar



Scheme 1

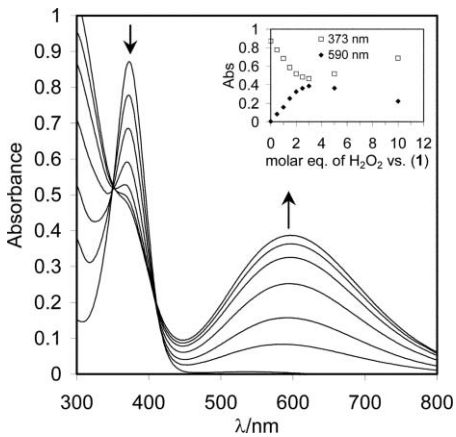


Fig. 1 Spectral change upon addition of different amounts of hydrogen peroxide to **1**/benzoic acid solution in acetonitrile (0 to 3 molar equivalents of H_2O_2 *versus* **1**, with 0.2 mM of **1** and 0.4 mM of benzoic acid). Absorbancies were adjusted for dilution. Inset: the cross sections at 373 nm and 590 nm with 0 to 10 molar equivalents of H_2O_2 *vs.* **1**.

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† Electronic supplementary information (ESI) available: Experimental synthetic procedures and physical measurements, UV-vis spectra, ESI-MS, ^{1}H NMR, EPR. See http://dx.doi.org/10.1039/b508004e

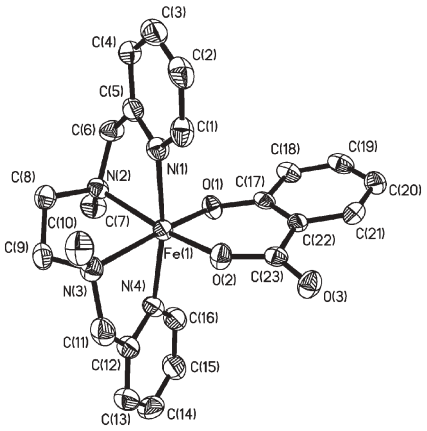


Fig. 2 X-Ray structure of the complex cation in **2**, showing 50% probability thermal ellipsoids. Hydrogen atoms are omitted for clarity.

complexes,[29] BPMEN adopts a *cis*-α conformation, and the observed Fe–N bond length range (from 2.13 to 2.20 Å) is characteristic of high-spin Fe(III) complexes.

When complex **2** was prepared from **1** and PhCOOH, the maximal yield (up to 84% at r.t., 91% at −25 °C, as determined by UV-vis) was obtained with 3 equivalents of H_2O_2 (Fig. 1). Higher amounts of H_2O_2 led to the degradation of the product (Fig. 1, inset), which may be partially responsible for the above-stoichiometric amounts of H_2O_2 required in the synthesis of **2**. In support, the hydroxylation of *m*-ClC_6H_4COOH was found to require only the stoichiometric amount of H_2O_2 (1.5 equivalents, Fig. S3†), consistent with its expected lower susceptibility to subsequent oxidation. Independently prepared complex **2** was stable in the presence of H_2O_2 alone, but degraded upon concomitant addition of 0.2 equivalent of **1**. Therefore, an excess of **1** has to be avoided in the preparation of **2**.

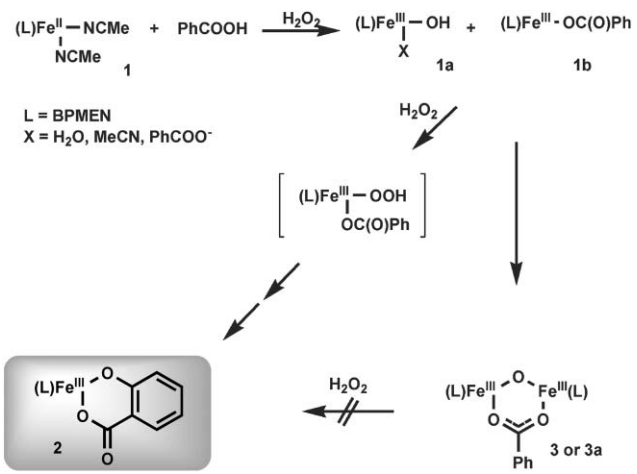
At the end of the reaction of PhCOOH with **1** and H_2O_2, salicylic acid was the only product recovered by extraction with diethyl ether from acidified aqueous solutions with 86% conversion, as determined by ^1H NMR (Fig. S4†). PhCOOH was recovered as the only species in the control experiments that lacked either H_2O_2 or **1**. When *m*-ClC_6H_4COOH was used, the major product of the reaction was 5-chlorosalicylic acid with 83% selectivity (minor product: 3-chlorosalicylic acid) and 80% conversion (Fig. S5†). The high selectivity for *ortho*-hydroxylation suggests the participation of a metal-based oxidant rather than non-discriminatory hydroxyl radicals.[11]

Preliminary stopped-flow experiments revealed two kinetically distinct steps in the formation of **2** from **1**/PhCOOH and H_2O_2 (Fig. S6, S7, Table S1†). The first, rapid step, first-order in both complex **1** and H_2O_2, was accompanied by a drop in absorbance in the near UV region with the disappearance of the band at $\lambda = 373$ nm ($\varepsilon = 4350$ L mol^{-1} cm^{-1}) characteristic of complex **1**. The second, slower step was accompanied by an increase in absorbance in the visible region with the appearance of a band at $\lambda = 590$ nm ($\varepsilon = 2300$ L mol^{-1} cm^{-1}) characteristic of the salicylate complex **2** (Fig. 1 and S6†). This reaction step is also first-order in H_2O_2, but its rate appears to depend on the concentration of **1**, indicating a possible higher order in **1**. Detailed kinetic studies will be reported later.

During the first step of the reaction, a pale-yellow intermediate is formed, characterized by a featureless trace in the visible region with a shoulder at 370 nm in the near-UV region (Fig. S7†). EPR experiments were performed on this intermediate, generated *in situ* by rapidly mixing **1**/PhCOOH and H_2O_2 at −42 °C followed by quenching in liquid nitrogen.† In addition to low-field peaks at $g = 8.00$ (sh) and $g = 4.26$ (broad), corresponding to high spin Fe(III) complexes (such as **2** or **1b**), several signals at higher field with $g_1 = 2.40$, $g_2 = 2.19$ and $g_3 = 1.90$ were observed, indicating the presence of a low-spin Fe(III) species (Fig. S8†). The *g*-value of 2.40 strongly implicates a hydroxo complex $[Fe^{III}(BPMEN)(OH)X]^{2+}$, as shown by Talsi and co-workers[30] in their analysis of the reaction of **1** with H_2O_2. A mononuclear LS intermediate in our system, tentatively formulated as **1a** (Scheme 2), may contain benzoate anion or a solvent molecule as an additional monodentate ligand. If the labile ligand X is PhCOOH, the initial adduct would rearrange, *via* an intramolecular H^+ transfer, into $[Fe^{III}(BPMEN)(OOCPh)]^{2+}$ (**1b**), which may also contain a weakly coordinated solvent molecule.

In order to determine whether a mononuclear Fe(III) complex can indeed act as an intermediate in aromatic hydroxylation, *in situ* one-electron oxidation of **1** with $(NH_4)_2[Ce^{IV}(NO_3)_6]$ was performed. In the presence of PhCOOH, a featureless visible spectrum was obtained (Fig. S9†), and a high-spin Fe(III) complex was detected by EPR (signals at $g = 8.00$ and $g = 4.26$) and ESI-MS (100% peak at $m/z = 509.02$ consistent with $\{[Fe^{III}(BPMEN)(OOCC_6H_5)](NO_3)\}^+$) (Scheme 2, intermediate **1b**). Importantly, when **1** was mixed with an equimolar amount of Ce(IV) and reacted with a mixture of PhCOOH and H_2O_2, high yields (up to 83%) of **2** were obtained (Fig. S9†). Attempts to isolate **1b** as a solid led to the growth of crystallographically characterized green crystals of dinuclear $[Fe^{III}_2(\mu\text{-}O)(\mu\text{-}OOCC_6H_5)(BPMEN)_2](Ce^{III}(NO_3)_6)$ (**3a**),†‡ which does not form salicylate in reaction with H_2O_2. As a control, complex $[Fe^{III}_2(\mu\text{-}O)(\mu\text{-}OOC(C_6H_5))(BPMEN)_2](ClO_4)_3$ (**3**) was independently synthesized from $Fe(ClO_4)_3$, benzoate and BPMEN, and fully characterized.† This material also did not yield hydroxylation products upon reaction with H_2O_2, confirming that dinuclear BPMEN complexes with oxo- and carboxylato-bridges do not activate hydrogen peroxide for aromatic hydroxylation.

Further experiments provided insight into the nature and reactivity of the hydroxylating agent. In parallel experiments with **1** and *m*-CPBA (recrystallized) or *m*-ClC_6H_4COOH/H_2O_2 as



Scheme 2

oxidant, the use of *m*-CPBA led to a slower reaction and a lower yield of chlorosalicylate complex compared to the reaction between **1**/*m*-ClC_6H_4COOH and H_2O_2 (16% yield *vs.* 74%). Therefore the rearrangement of the **1**–*m*-CPBA adduct is much less efficient than the reaction between **1**/*m*-ClC_6H_4COOH and H_2O_2, indicating that the formation of a peroxybenzoate is not essential for the hydroxylation. The importance of H_2O_2, consistent with our preliminary kinetic results (Table S1†), can be explained by the involvement of an iron–hydroperoxo intermediate. This intermediate can either directly attack the coordinated aromatic ring, or undergo subsequent O–O bond cleavage to generate a high-valent iron–oxo oxidant. ^{18}O-labeling experiments showed that the oxygen incorporated in the salicylate product originates from H_2O_2 and that the oxidant responsible for aromatic hydroxylation does not exchange oxygen with water before the C–O bond is formed (Fig. S10–12†). This is consistent with a hydroperoxo intermediate, but does not rule out high-valent iron–oxo species that may undergo slow isotope exchange with water. Lastly, experiments with the deuterated substrate, d_5-PhCOOH, showed no significant H/D kinetic isotope effect on either step of the reaction.† Competition experiments using ESI-MS also showed no preference of **1** in reacting with either protio or deuterio isotopomers (Fig. S13†), so C–H bond breaking on the phenyl ring is not a rate limiting step in this transformation.

Based on combined experimental results, a pathway for aromatic hydroxylation by **1**/H_2O_2 can be proposed (Scheme 2). PhCOOH binds to **1** and/or the product of its subsequent one-electron oxidation. When H_2O_2 is added, both kinetic and EPR studies suggest the formation of a mononuclear Fe(III) complex (most likely, a mixture of low-spin species **1a** and high-spin species **1b**). This intermediate can further react with H_2O_2 to form a short lived mononuclear hydroperoxo species, as previously proposed for BPMEN and related systems.[24,31,32] Such species could then attack the aromatic ring directly or produce high-valent iron–oxo intermediates. The high selectivity observed argues against the participation of hydroxyl radicals.[11] In our hands, ring closed species like **3** or **3a** did not undergo oxidation with H_2O_2. These results, however, do not exclude possible involvement of a dinuclear "open-core" hydroperoxo intermediate, which will be explored in future studies.

In conclusion, mononuclear iron(II) complex **1** efficiently and selectively hydroxylates benzoic acids to their corresponding salicylic acids under mild conditions. The oxygen source is hydrogen peroxide, which generates water as the only by-product of the oxidation reaction.

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Notes and references

‡ X-Ray crystal data for complex **2**, $C_{46}H_{58}C_{12}Fe_2N_8O_{17}$: M = 1177.60, monoclinic, space group $P2_1/c$, a = 15.874(5), b = 11.407(4), c = 29.333(10) Å, β = 101.599(7)°, V = 5203(3) Å^3, T = 193(2) K, Z = 4, μ = 0.739 mm^{-1}, R_{int} = 0.0955 for 12857 independent reflections of the 36665 collected, final R [$I > 2\sigma$] = 0.0838, final R_w [$I > 2\sigma$] = 0.1504. X-Ray crystal data for complex **3a**, $C_{45}H_{58}CeFe_2N_{17}O_{21}$: M = 1424.90, triclinic, space group $P\bar{1}$, a = 11.741(2), b =12.072(2), c = 21.838(4) Å, α = 83.52(3), β = 82.33(3), γ = 74.75(3)°, V = 2949.8(10) Å^3, T = 294 K, Z = 2, μ = 1.332 mm^{-1}, R_{int} = 0.0218 for 8946 independent reflections of the 9218 collected, final R [$I > 2\sigma$] = 0.0385, final R_w [$I > 2\sigma$] = 0.0807. CCDC 174631 and 174632. See http://dx.doi.org/10.1039/b508004e for crystallographic data in CIF or other electronic format.

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