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Mechanistic insights into the biomimetic catalytic hydroxylation of arenes by a molecular Fe(NHC) complex

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ABSTRACT

The mechanism of the hydroxylation of benzene by an iron(II) bis(NHC) complex, $[Fe^{II}(NCCN)(CH_3CN)_2](PF_6)_2$ (**1**; NCCN = bis(*o*-imidazol-2-ylidenepyridine)methane), in the presence of hydrogen peroxide was investigated. The invariance of the catalytic system towards the presence of radical scavengers and an inverse intermolecular kinetic isotope effect (KIE) allow to rule out a hydrogen abstraction pathway. Additionally, using 1,3,5-$[D_3]$benzene as substrate, NIH-shift products were detected, resembling the reactivity of naturally occurring enzymes and some molecular biomimetic iron complexes. Supported by density functional theory calculations, the aromatic hydroxylation reaction is proposed to proceed via an iron-arene σ-complex as intermediate species.

1. Introduction

The selective oxygenation of arenes is an important reaction class in synthetic organic chemistry as phenols and other hydroxylated arene derivatives are central building blocks for the synthesis of pharmaceuticals, polymers, agrochemicals and a range of biologically active natural compounds [1–3]. Moreover, it is a key step in numerous biological processes, such as the synthesis of aromatic amino acids and the metabolism of xenobiotics [4]. Highly selective, iron-containing enzymes, such as cytochromes P450 or aromatic amino acid hydroxylases, are employed by nature to mediate such reactions [5], which are particularly challenging due to two main reasons: Firstly, in course of the reaction a C—H bond needs to be broken and aromatic compounds possess a relatively high bond strength compared to, for example, aliphatic analogues ($BDE_{C\text{-}H}$ = 112.9 kcal mol^{-1} for benzene and $BDE_{C\text{-}H}$ = 99.5 kcal mol^{-1} for cyclohexane [6]). Secondly, the phenolic products are usually more reactive than the non-activated substrates, often resulting in overoxidation and reduced selectivity [7].

In order to allow the rational design of new catalysts many efforts were made to elucidate the machanism of aromatic oxygenation reactions catalyzed by both, naturally occurring enzymes and bioinspired iron complexes [8,9]. A common feature of many of these systems is the formation of a ferric peroxo intermediate upon reaction with the respective oxidant. However, such ferric peroxo compounds turned out to be sluggish oxidants in many cases and by homolytic or heterolytic cleavage of the O—O bond, they are further transformed into high-valent iron-oxo species [10,11]. The latter have been shown to be the active oxidizing species in several cases. In context of the hydroxylation of arenes three alternative reaction pathways have been proposed based on the presence of such iron(IV)- or iron(V)-oxo species (Scheme 1) [12–14]. The first reaction pathway involves the abstraction of a hydrogen atom followed by the transfer of the hydroxyl group to the arene radical (path a). Alternatively, either a tetrahedral iron-arene σ-complex intermediate may be generated (path b) or the aromatic oxidation proceeds via an arene oxide species (path c).

Our group has reported an iron(II) complex bearing a tetradentate bis(*o*-imidazol-2-ylidenepyridine)methane ligand (NCCN) to be active in a broad range of catalytic applications, such as epoxidation of olefins, oxygenation of aliphatic and aromatic substrates as well as aldehyde olefination [15–19]. With hydrogen peroxide as the oxidant the migration of substituents (so-called “NIH shift”) was observed during the oxidation of various alkylbenzenes suggesting the presence of a high-valent iron-oxo species as oxidant

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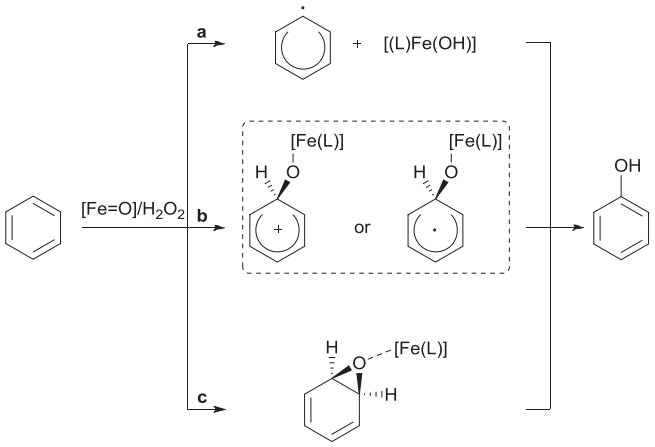


Scheme 1. Alternative mechanistic pathways for the iron catalyzed hydroxylation of benzene [12–14].

[20]. The present work therefore sets out to closer investigate the mechanistic details of the hydroxylation of arenes by [Fe^{II}(NCCN)$(CH_3CN)_2$]$(PF_6)_2$ (**1**, Fig. 1) including the nature of the oxidizing species and the pathway by which the reaction proceeds employing catalytic probe reactions as well as computational methods.

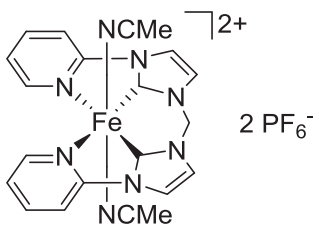
2. Results and discussion

2.1. Catalytic oxidation of benzene

In order to elucidate the mechanism of the catalytic hydroxylation of arene substrates by complex **1** with hydrogen peroxide, benzene (**B**) was chosen as a model substrate. It is converted exclusively to phenol (**P**) and 1,4-benzoquinone (**BQ**, Scheme 2).

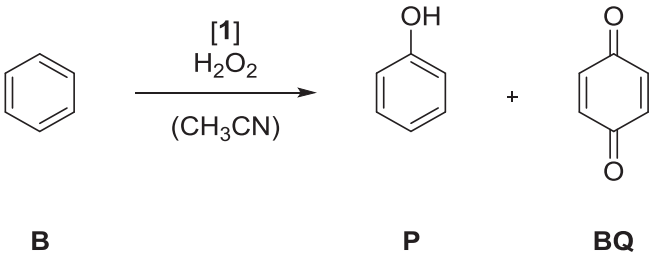
Kinetic experiments were performed at 20 °C and 0 °C using 1.0 equivalent of hydrogen peroxide (50 wt% in H_2O) relative to the benzene amount (Fig. S1 in the SI). Expectedly, they reveal that the reaction is significantly faster at 20 °C. The overall conversion of benzene amounts to 7.1% at 20 °C and 6.9% at 0 °C and is thus equal within the error range at both temperatures. Regarding the selectivity for the two products, the formation of phenol is favored over the formation of 1,4-benzoquinone at 20 °C, while at 0 °C the ratio is almost inverted. At this temperature a decrease of the phenol concentration can be noted after 10 min as it is further converted to 1,4-benzoquinone.

Well-established catalytic probe reactions were used to investigate the underlying reaction mechanism of the aromatic hydroxylation of benzene by **1**. Table 1 shows that the addition 0.5 equivalents of 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT), which may act as a trap for free radicals in solution [21], to the catalytic reaction does not significantly affect the reaction outcome as



[Fe^{II}(NCCN)$(CH_3CN)_2$]$(PF_6)_2$ (**1**)

Fig. 1. Iron(II) complex of a tetradentate bis(pyridyl-*N*-heterocyclic carbene) (NCCN) ligand [19].



Scheme 2. Catalytic oxidation of benzene (**B**) to phenol (**P**) and 1,4-benzoquinone (**BQ**) in acetonitrile solution by **1**/H_2O_2.

Table 1
Catalytic oxidation of benzene to phenol and 1,4-benzoquinone by complex **1** and hydrogen peroxide. Reaction conditions: benzene (2.0 mmol), **1** (0.02 mmol, 1 mol%), BHT (1.0 mmol, 0.5 equiv.), H_2O_2 (50 wt% in H_2O, 2.0 mmol, 1.0 equiv.), CH_3CN (4.0 mL), 60 min.

	20 °C	20 °C + BHT
Conversion (Benzene)/%	7.1	6.9
Yield (Phenol)/%	5.0	4.8
Yield (1,4-Benzoquinone)/%	2.2	2.1

the benzene conversion as well as the product selectivity remain nearly constant. This result suggests that the catalytic oxidation of benzene to phenol and 1,4-benzoquinone by **1**/H_2O_2 does not proceed via a Fenton-type reaction initiated by hydrogen peroxide and catalyst decomposition products nor an initial hydrogen abstraction by a high-valent iron-oxo species (Scheme 1, path a). These findings correspond well to the previously reported observation that no radical recombination products such as biphenyl are observed [17].

At 20 °C an inverse intermolecular kinetic isotope effect (KIE) of $[k_H/k_D]_{inter} = 0.81 \pm 0.07$ for the competitive oxidation of C_6H_6 and C_6D_6 was determined, which is in accordance with the previously reported value of 0.9 detected at 25 °C [17]. The inverse KIE indicates a hybridization change from sp^2 to sp^3 at a deuterium substituted carbon atom to be involved in the rate determining step, which is consistent with an electrophilic addition of an iron-oxo species to the benzene ring yielding either an iron-arene σ-complex or an epoxide intermediate (Scheme 1, path b or c) [12,14,22–25]. However, the only reaction products observed by GC-FID/MS are phenol and 1,4-benzoquinone, but no benzene oxide was detected in any of the catalytic reactions. Moreover, considering the intermolecular KIE, a hydrogen abstraction pathway (Scheme 1, path a) can be excluded for the oxidation of benzene with **1**/H_2O_2 as C-H/D bond breakage is expected to induce a high, normal kinetic isotope effect (KIE > 1) [24,25].

In addition to kinetic isotope effects, migration and rearrangement reactions may help to elucidate the reaction mechanism. For aromatic hydroxylation reactions catalyzed by iron containing enzymes as well as iron heme and non-heme complexes the so-called "NIH-shift" has been reported frequently and comprises the intramolecular migration of a substituent of the aromatic ring (e.g. H, D, CH_3, Cl) [13,14,22,25–31]. 1,3,5-[D_3]benzene (**[D_3]B**) has been established as a powerful test substrate to detect NIH shift reactions based on the analysis of the degree of deuteration of the 1,4-benzoquinone product (Scheme 3) [32,33]. If no NIH shift occurs, only the formation of **[D_2]BQ** is expected, in case of a deuterium migration also **[D_1]BQ** and **[D_3]BQ** may be formed. The 1,4-benzoquinone compositions resulting from the oxidation of **[D_3]B** with **1**/H_2O_2 at different temperatures were determined by GC–MS and are summarized in Table 2.

The results displayed in Table 2 strongly suggest an NIH shift as at both temperatures only 49% of **[D_2]BQ** are formed. The other 51%