Bio-inspired arene *cis*-dihydroxylation by a non-haem iron catalyst modeling the action of naphthalene dioxygenase

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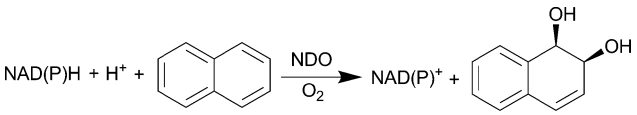
Reported in this paper is the first example of a biomimeticiron complex, $([Fe^{II}(TPA)(NCMe)_2]^{2+}$ (TPA = tris(2-pyridylmethyl)-amine), that catalyses the *cis*-dihydroxylation of an aromatic double bond, mimicking the action of the non-haem iron enzyme naphthalene dioxygenase and shedding light on its possible mechanism of action.

Nature has evolved a pathway to degrade arenes by soil bacteria.[1] The bio-degradation of aromatic compounds is initiated by the *cis*-dihydroxylation of an arene double bond by Rieske dioxygenases,[2] which belong to a family of non-haem enzymes with mononuclear iron active sites that share a common 2-His-1-carboxylate facial triad motif.[3] The best characterized of these Rieske dioxygenases is naphthalene 1,2-dioxygenase (NDO),[4] which catalyses the conversion of naphthalene to *cis*-(1*R*,2*S*)-1,2-dihydro-1,2-naphthalenediol (Scheme 1).[5] An important goal in our biomimetic efforts has been to identify or design iron catalysts that mimic the functions of Rieske dioxygenases in order to gain better insight into the mechanisms of these unique transformations and discover new synthetic reactions that may be useful in synthetic organic and/or environmental applications.[6] In the past few years, we and others have been successful in finding non-haem iron catalysts that catalyse the *cis*-dihydroxylation of olefins.[7–12] However, the *cis*-dihydroxylation of aromatic double bonds by such catalysts has thus far not been reported. Here we report for the first time a non-haem iron complex that catalyses the *cis*-dihydroxylation of naphthalene and thus serves as a functional model for naphthalene 1,2-dioxygenase.

$[Fe^{II}(TPA)(NCMe)_2](OTf)_2$ (**1**, TPA = tris(2-pyridylmethyl)-amine) is a complex that has been shown to catalyse olefin epoxidation and *cis*-dihydroxylation with H_2O_2 as oxidant.[7] When naphthalene was used instead of an olefin under nearly identical reaction conditions (1 mM catalyst and 0.5 M naphthalene in CH_3CN at 25 °C under air with 10 mM H_2O_2 syringe-pumped into the reaction mixture at a rate of 2 equivalents min^{-1} followed by 20 min additional stirring), **1** was found to catalyse the oxidation of naphthalene. Four oxidation products from these reactions were identified (after treatment of the reaction mixture with acetic anhydride and imidazole to acetylate the alcohol functions[7]) by gas chromatography (GC) and gas chromatography mass spectrometry (GC/MS), namely *cis*-1,2-dihydro-1,2-naphthalenediol, 1-naphthol, 2-naphthol and 1,4-naphthoquinone. The diol product represents the major product of naphthalene oxidation and is identical to that produced in the NDO-catalysed reaction.[5] The correspondence to the enzyme-produced product was demonstrated by the appearance of a peak that gave rise to an ion with a mass corresponding to *cis*-1,2-dihydro-1,2-diacetoxynaphthalene in GC/MS analysis and co-migrated in the GC and GC/MS analysis with the acetylated derivative of a commercially available authentic sample. Diol yields as determined by gas chromatography corresponded to around three turnovers (30% conversion of the 10 equivalents of H_2O_2 used as oxidant). As a control experiment, $[Fe^{II}(OTf)_2(NCMe)_2]$ was also tested as a catalyst for this reaction, but the result was negative. These results represent the first example of iron-catalysed arene *cis*-dihydroxylation, thereby mimicking NDO in its ability to use H_2O_2 as the oxidant in a peroxide shunt pathway.[13]

The other three products of naphthalene oxidation were obtained in much lower yields, namely 5% for 1-naphthol, 2% for 2-naphthol and 3% for 1,4-naphthoquinone. (These values were reduced relative to the observed yields of 1-naphthol and 2-naphthol by GC to account for the thermal decomposition of *cis*-1,2-dihydro-1,2-diacetoxynaphthalene to the two naphthols in the course of GC analysis. Control experiments showed that 5% of the observed *cis*-1,2-dihydro-1,2-diacetoxy-naphthalene was converted into naphthols.) Based on the prevailing mechanistic notion that arene hydroxylation involves the initial attack of a metal–oxo species on the arene C=C double bond,[14] the two naphthol products may be considered as corresponding to the epoxide products obtained in the **1**-catalysed oxidations of olefins.[7] From this perspective, the diol : naphthol ratio of 4 : 1 can be compared to diol/epoxide ratios of 1.2 : 1 for cyclooctene and 5 : 1 for 1-octene. Thus, naphthalene is comparable to 1-octene in having a much stronger preference to undergo *cis*-dihydroxylation than monooxygenation. However the overall percentage conversion of oxidant into naphthalene oxidation products is about a factor of two lower than corresponding values for olefin oxidation,[7] perhaps reflecting the greater oxidative stability of naphthalene.

The effect of adding more equivalents of H_2O_2 was investigated to determine whether the lower oxidant conversion observed for naphthalene reflects catalyst decomposition or



Scheme 1 Naphthalene oxidation by naphthalene 1,2-dioxygenase (NDO).

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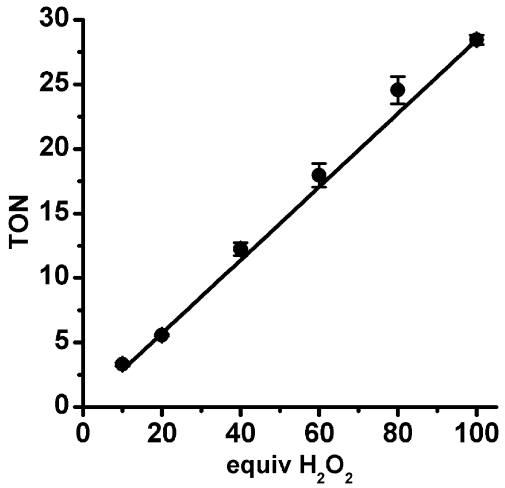


Fig. 1 Yield of naphthalene *cis*-dihydroxylation in CH_3CN using **1** as catalyst as a function of H_2O_2 equivalents added (relative to catalyst). A solution of H_2O_2 oxidant was delivered by syringe pump at a rate of 2 equiv. min^{-1} at room temperature under air to a vigorously stirred CH_3CN solution containing 1 mM catalyst and 500 equiv. naphthalene. The solution was stirred an additional 20 min after syringe pump addition and products were determined by GC analysis.

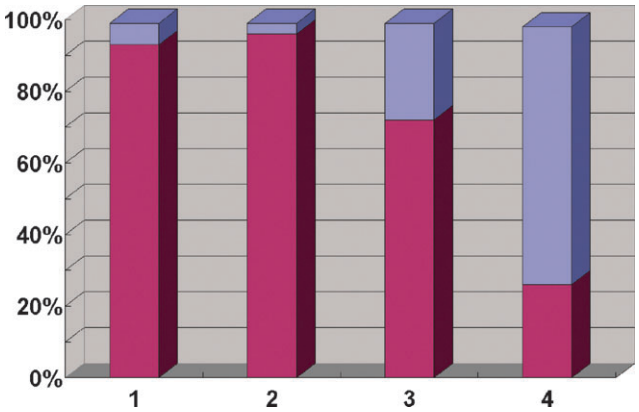


Fig. 2 Isotope labeling results from **1**-catalysed oxidations of naphthalene in CH_3CN. Entries 1 and 2 show the labeling patterns for the *cis*-diol product, while entries 3 and 4 show the labeling patterns for the naphthol products (□ unlabeled product, ■ singly labeled product.). For entries 1 and 3, 10 equiv. $H_2{}^{18}O_2$ (2% aqueous solution) relative to catalyst was used as oxidant; for entries 2 and 4, 10 equiv. H_2O_2 (0.5 M in CH_3CN from 35% aqueous solution) diluted with 1000 equiv. $H_2{}^{18}O$ was used as oxidant. See Table 1 for numerical values.

a lower efficiency in oxidizing naphthalene relative to olefins. The reactions were carried out under the same conditions with the additional equivalents of H_2O_2 being added into the reaction system at the same constant injection rate of 2 equiv. min^{-1}. Fig. 1 shows that the catalyst remains comparably active even after addition of 100 equiv. H_2O_2. There is a linear relationship between the amount of H_2O_2 added and the amount of diol produced and a 30% conversion of H_2O_2 to product is maintained.[15] This demonstrates that **1** is a robust catalyst for *cis*-dihydroxylation of naphthalene.

^{18}O labeling studies have proven very useful in our earlier studies of iron-catalysed olefin oxidation for determining the sources of the oxygen atoms incorporated into products.[7] Thus analogous studies were carried out for naphthalene oxidation, focusing on diol and naphthol products. When 10 equiv. 2% $H_2{}^{18}O_2$ (100 equiv. H_2O per $H_2{}^{18}O_2$) was used as oxidant, more than 90% of the diol product was singly labeled (Fig. 2 and Table 1: entry 1). The complementary experiment carried out with 10 equiv. H_2O_2 and 1000 equiv. $H_2{}^{18}O$ (relative to catalyst) also afforded more than 90% of the singly labeled diol product (Fig. 2 and Table 1: entry 2). These results show that the *cis*-diol product of naphthalene oxidation derives one O atom from H_2O_2 and the other from H_2O, following the labeling pattern found in cyclooctene *cis*-dihydroxylation by **1**, and strongly suggest that the water-assisted mechanism previously proposed for the **1**-catalysed *cis*-dihydroxylation of olefins[7] applies to naphthalene *cis*-dihydroxylation as well (Scheme 2). The water-assisted mechanism involves initial formation of a low-spin Fe^{III}–OOH species to which water can bind. The coordinated water is proposed to facilitate the heterolytic cleavage of the O–O bond to form the *cis*-HO–Fe^{V}=O oxidant that adds across the substrate double bond to form *cis*-diol and give rise to the signature labeling pattern observed.

In our experiments, 1-naphthol and 2-naphthol could be resolved on the GC column used for quantification but could not be resolved on the GC-MS column used for determining the ^{18}O label incorporation. Thus the reported label incorporation for naphthols represents a composite value. ^{18}O-labeling studies of the naphthol products with 2% $H_2{}^{18}O_2$ showed that 72% of the naphthols incorporated the ^{18}O label while 27% was unlabeled (Fig. 2 and Table 1: entry 3). The complementary experiment with 1000 equiv. added $H_2{}^{18}O$ confirmed this pattern (Fig. 2 and Table 1: entry 4). (When corrected for the contribution from the thermal decomposition of the labeled diol product, the value for percentage incorporation from H_2O decreases to 21%.) For comparison, 90% of the epoxide oxygen derived from H_2O_2 in the **1**-catalysed epoxidation of cyclooctene. These results support the mechanism proposed in Scheme 2. The observed incorporation of water into the epoxide or the naphthol products cannot be rationalized by invoking the Fe^{III}–OOH intermediate as oxidant and requires oxo–hydroxo tautomerism of the putative HO–Fe^{V}=O oxidant and transfer of the oxo atom to the substrate.

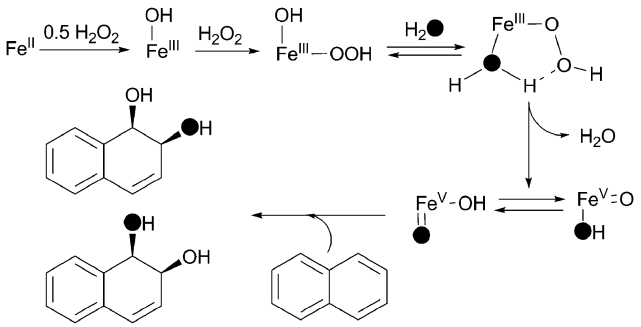
It is interesting to note that $H_2{}^{18}O$ incorporation into the naphthol products under the same conditions is twofold higher than for cyclooctene oxide in the epoxidation of cyclooctene by **1**[7] but somewhat lower than the 27% value reported for cyclohexanol in the hydroxylation of cyclohexane by the same catalyst.[16] We interpret these results as reflecting the different activation barriers associated with the attack of the putative HO–Fe^{V}=O oxidant on the various substrates. The more difficult the substrate is to oxidize, the greater the extent of oxo–hydroxo tautomerism before substrate attack, so more label from water would be introduced into the oxidized product for the substrates with the higher activation barriers. Thus the observed progression for percentage label incorporation, cyclooctene < naphthalene < cyclohexane, is in accord with this notion.

In summary, we report the first example of a synthetic non-haem iron complex capable of catalysing the *cis*-dihydroxylation of naphthalene.[17] This transformation can be carried out

Table 1 Isotope labeling results (%) for naphthalene oxidation catalysed by **1**

Entry	Unlabeled	Singly labeled	Doubly labeled
1 (*cis*-diol from $H_2{}^{18}O_2/H_2{}^{16}O$)[a]	6	93	<1
2 (*cis*-diol from $H_2{}^{16}O_2/H_2{}^{18}O$)[b]	3	96	0
3 (naphthols from $H_2{}^{18}O_2/H_2{}^{16}O$)[a]	27	72	—
4 (naphthols from $H_2{}^{16}O_2/H_2{}^{18}O$)[b]	72	26	—

[a] 10 equiv. $H_2{}^{18}O_2$ (2% aqueous solution) relative to catalyst was used as oxidant. [b] 10 equiv. H_2O_2 (0.5 M in CH_3CN from 35% aqueous solution) diluted with 1000 equiv. $H_2{}^{18}O$ was used as oxidant.



Scheme 2 Proposed mechanism for the *cis*-dihydroxylation of naphthalene catalysed by **1**.

under ambient conditions with H_2O_2 as oxidant and thus models the action of naphthalene dioxygenase, *via* the peroxide shunt pathway.[13] ^{18}O labeling experiments strongly implicate a HO–Fe^V=O oxidant that is formed *via* a water-assisted mechanism originally proposed for the **1**-catalysed hydroxylation of alkanes[16] and *cis*-dihydroxylation of olefins.[7] By extension, this work suggests that the crystallographically characterized side-on peroxo intermediate of NDO[4] could convert to a similar high-valent HO–Fe^V=O oxidant that is responsible for the biological *cis*-dihydroxylation of naphthalene.

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