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Ligand effect on the iron-catalysed biphasic oxidation of aromatic hydrocarbons by hydrogen peroxide

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Dedicated to Prof. Renato Ugo on the occasion of his 65th birthday

Abstract

The hydroxylation of benzene and toluene with hydrogen peroxide, catalysed by iron complexes with nitrogen ligands in a biphasic reaction medium, was investigated. After testing a series of pyridine and pyrazinecarboxylic acid derivatives, it was found that the ligand markedly affects the catalyst efficiency and the selectivity based on the oxidant. In the case of toluene, the ligand has a tuning effect on the catalyst activity, driving the oxidation preferentially to the ring or to the methyl group. The complex with pyrazine-3-carboxylic acid *N*-oxide was selected as the most efficient catalyst and appears to be a promising tool for the direct synthesis of phenols. The mechanism of the aromatic hydroxylation is also discussed, in comparison with the conventional Fenton's reagent.

Keywords: Arenes; Oxidations; Iron; N–O ligands

1. Introduction

For more than a century [1], the selective oxidation of organic substrates catalysed by transition metals has been an important topic in synthetic, industrial, and biological chemistry. However, the astonishing capability of both heme and non-heme iron enzymes to catalyse a number of fascinating biological oxidations continues to inspire the discovery of new catalytic systems. Not surprisingly, several of them are based on iron compounds, often with nitrogen ligands. These systems include the Gif chemistry [2] and the systems investigated by Tun et al. [3], Sawyer et al. [4,5], Chen and Que [6] and Que and co-workers [7], all providing active catalysts for the oxidation of even poorly reactive alkanes. However, unlike Fenton chemistry [1,8–11], these systems show a poor activity, if any, in the oxidation of aromatic hydrocarbons [12–14]. This is possibly due to the higher bond energy of aromatic C–H bonds (435 kJ mol^{-1} for benzene [15]) compared to aliphatic ones (typically, 380–415 kJ mol^{-1} [15]). Moreover, in spite of the amount of published work, the mechanistic features of these oxidations are still debated, with particular attention to the nature of the active species involved (free radicals or high-valent iron-oxo complexes [16]).

Recently, we reported a new iron-based catalyst (again with a nitrogen ligand, namely 5-carboxy-2-

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methylpyrazine-*N*-oxide) for the biphasic oxidation of benzene to phenol with hydrogen peroxide [17]. Here we describe how subtle modifications in the ligand structure affect the oxidation of both benzene and toluene.

2. Experimental

Pyridine-2-carboxylic acid (**1**), pyrazinecarboxylic acid (**2**) and 2-methylpyrazine-5-carboxylic acid (**3**) were purchased from Fluka Chemie. The *N*-oxide derivatives were synthesised from the corresponding pyrazinecarboxylic acids by oxidation with hydrogen peroxide, in the presence of sodium tungstate as catalyst [18].

*2.1. Synthesis of pyrazine-3-carboxylic acid N-oxide (**4**)*

An aqueous solution of 40% (w/v) hydrogen peroxide (3.3 ml, 30 mmol) and sodium tungstate dihydrate (250 mg, 0.75 mmol) were added to 13 ml of water. The pH was adjusted to 2 with diluted sulfuric acid and pyrazine-3-carboxylic acid (3.7 g, 30 mmol) was added. The solution was stirred at 80 °C for 2 h and left at room temperature for 12 h. The precipitate was then filtered, washed with cool water and dried under reduced pressure giving pyrazine-3-carboxylic acid *N*-oxide (**4**) (3.1 g, 22 mmol). ^{1}H NMR (DMSO-d_6), δ: 8.48 (1H, d), 8.60 (1H, d), 8.61 (1H, d); EIMS (*m*/*z*): 140 (M^+).

*2.2. Synthesis of 2-methylpyrazine-5-carboxylic acid N-oxide (**5**)*

The above described procedure, starting from 2-methylpyrazine-5-carboxylic acid (5.5 g, 40 mmol), afforded 2-methylpyrazine-5-carboxylic acid *N*-oxide (**5**) (4.68 g, 30 mmol). ^{1}H NMR (DMSO-d_6), δ: 2.36 (3H, s), 8.63 (1H, s), 8.70 (1H, s); EIMS (*m*/*z*):154 (M^+).

2.3. Oxidation reactions (general procedure)

A solution of $FeSO_4 \cdot 7H_2O$ (114 mg, 0.41 mmol), trifluoroacetic acid (0.3 ml, 4 mmol) and the selected ligand (1.3 mmol) in water (100 ml) were added in a 500 ml jacketed glass reactor and stirred for 30 min at room temperature. A mixture of acetonitrile (110 ml) and the aromatic substrate (benzene or toluene, 180 mmol) was then added, generating a biphasic system. The temperature was maintained at 37 °C and an aqueous solution of 20% (w/v) hydrogen peroxide (3.1 ml, 18 mmol) was added in 4 h, using a peristaltic pump. The reaction mixture was diluted with acetonitrile (300 ml) and the resulting solution was analysed by HPLC. The product distributions obtained using the ligands **1**–**5** were as follows.

2.3.1. Benzene oxidation

Detected products (phenol/1,4-benzoquinone)—Ligand **1**: 0.351/0.004 mmol. Ligand **2**: 11.372/0.114 mmol. Ligand **3**: 7.834/0.235 mmol. Ligand **4**: 14.364/0.144 mmol. Ligand **5**: 14.573/0.437 mmol.

2.3.2. Toluene oxidation

Detected products (*o*-cresol/*m*-cresol/*p*-cresol/methyl-1,4-benzoquinone/benzyl alcohol/benzaldehyde/benzoic acid)—Ligand **1**: 0.098/0.010/0.132/0.011/0.044/0.349/0.218 mmol. Ligand **2**: 0.621/0.014/0.746/0.150/0.246/1.755/0 mmol. Ligand **3**: 0.510/0.011/0.599/0.080/0.190/1.160/0.210 mmol. Ligand **4**: 1.218/0.035/1.793/0.086/0.225/1.156/0.289 mmol. Ligand **5**: 0.781/0.020/1.103/0.021/0.471/0.867/0.107 mmol.

2.4. Turn over frequency (TOF) determination

The initial turn over frequency (TOF) of the iron was expressed as (mol of product) $\times n$/(mol of Fe $\times h$). The factor *n* takes in account the mole of hydrogen peroxide utilised to produce 1 mol of the given product: its value is 1 (for phenol, cresols and benzyl alcohol), 2 (for benzaldehyde), or 3 (for quinones and benzoic acid).

The TOFs were determined by carrying out the oxidation reactions as described above, but by adding the total amount of hydrogen peroxide at the beginning of the reaction, followed by cooling at an oxidant conversion just below 20% to stop the reaction (the reaction time was tuned depending on the catalyst activity).

3. Results and discussion

As previously reported [17], a series of different iron complexes were tested as catalysts in benzene oxidation with hydrogen peroxide, observing a strong ligand effect on both catalytic activity and selectivity. Bidentate *N*,*N* ligands (phenanthroline derivatives) exerted a detrimental effect on the hydrogen peroxide activation, while bidentate *O*,*O* ligands (catechol derivatives) promoted the hydrogen peroxide decomposition. The best results were obtained using *N*,*O* ligands, particularly 2-methylpyrazine-5-carboxylic acid *N*-oxide.

In the present work we describe in detail the tuning effect of the ligand on benzene and toluene oxidation, focusing the attention on pyridine- and pyrazine-carboxylic acid derivatives.

Unlike the conventional Fenton system, the oxidation reactions were carried out in a biphasic reaction medium generated by water and acetonitrile (volume ratio = 1:1) in the presence of benzene or toluene. With this particular medium, the concentration of benzene in the aqueous phase raised from 0.18% (w/w) (solubility of benzene in water) [19] to 1.11% (measured at 37 °C), and the produced phenol was extracted for the most part (85%) in the organic phase. In this way, the biphasic operation minimises the over-oxidation reactions (formation of catechol, hydroquinone, benzoquinone, tars) by reducing the contact between the phenol and the catalyst, which is soluble in the aqueous phase.

The following ligands were tested: pyridine-2-carboxylic acid (**1**), pyrazinecarboxylic acid (**2**), 2-methylpyrazine-5-carboxylic acid (**3**), pyrazine-3-carboxylic acid *N*-oxide (**4**) 2-methylpyrazine-5-carboxylic acid *N*-oxide (**5**).

The reactions were carried out a 37 °C, using an excess of ligand (iron/ligand molar ratio = 1/3), being the structure of the hydrated iron-pyrazinecarboxylic acid complex reported as $FeL_2(H_2O)_2$ [20].

An acid co-catalyst, although not strictly necessary to activate the iron complexes, was added in order to improve the selectivity based on hydrogen peroxide [17]. The best results were obtained using trifluoroacetic acid in a molar ratio 10:1 with respect to the iron. A similar effect was observed with acetic, methanesulfonic, *p*-toluenesulfonic and sulfuric acids.

The results obtained in the oxidation of benzene are reported in Table 1. With all the ligands, the selectivity to phenol ranged between 97 and 99%. Conversely, by operating in the absence of the ligand, the selectivity to phenol decrease to 62%, for the formation of a relevant amount of biphenyl (10%) and tars (34%). Biphenyl is a typical by-product detected in the Fenton-like reactions, formed by dimerization of hydroxycyclohexadienyl radicals with a yield typically ranging from 8 to 39% [21].

As shown in Table 1, the selectivity based on hydrogen peroxide was higher in the case of the *N*-oxide ligands **4** and **5**.

The initial turn over frequencies were calculated as described in the experimental section, in order to better evaluate the difference in the catalyst efficiencies induced by the ligand. As shown in Fig. 1, the complex with pyridinecarboxylic acid (**1**) (TOF = $1\,h^{-1}$) was remarkably less reactive than those with the pyrazinecarboxylic acid derivatives. The *N*-oxide derivative **4** (TOF = $37\,h^{-1}$) turned out to be the most effective ligand, even more than ligand **5**, previously disclosed [17].

In Table 2 are reported the results obtained in the oxidation of toluene. In this case, a competition occurred between the ring hydroxylation (mainly, to *ortho*- and *para*-cresol) and the benzylic oxidation (to benzylic alcohol, benzaldehyde and benzoic acid).

It is worth noting that the ligand can drive the oxidation preferentially to the ring, as in the case of ligand **4**

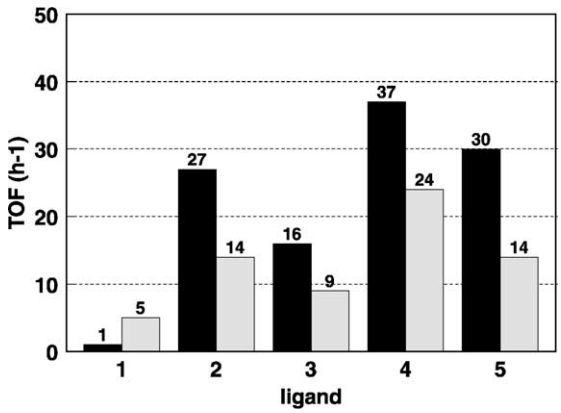
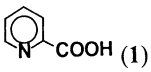
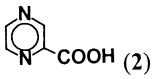
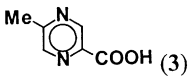
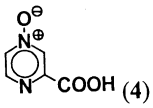
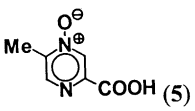


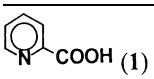
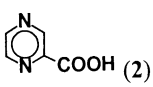
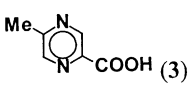
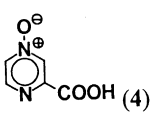
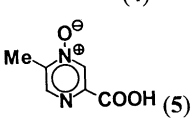
Fig. 1. Catalyst efficiencies. (■) Oxidation of benzene. (□) Oxidation of toluene. Turn over frequency (TOF) of Fe = mol of products (normalised)/(mol of Fe × hour).

Table 1
Oxidation of benzene[a]

Ligand	H_2O_2 conversion (%)	Selectivity on H_2O_2[b] (%)	Selectivity on benzene[c] (%)
None	77	38	62
 (1)	13	15	99
 (2)	81	78	99
 (3)	64	68	97
 (4)	95	84	99
 (5)	92	88	97

[a] Reaction conditions—Fe_2SO_4/ligand/CF_3COOH molar ratio: 1/3/10; H_2O_2/benzene molar ratio: 0.1; temperature: 37 °C; reaction time: 4 h. The reaction medium was water/acetonitrile/benzene 45/45/10 (v/v/v).
[b] Selectivity based on H_2O_2 = (mol of phenol produced × 100)/mol of reacted hydrogen peroxide.
[c] Selectivity based on benzene = (mol of phenol produced × 100)/mol of reacted benzene.

Table 2
Oxidation of toluene[a]

Ligand	H_2O_2 conversion (%)	Selectivity on H_2O_2[b] (%)	Selectivity on ring (%)[c]	Selectivity on methyl (%)[d]
 (1)	12	77	29	71
 (2)	62	50	43	57
 (3)	47	53	43	57
 (4)	53	70	65	35
 (5)	49	51	57	43

[a] Reaction conditions—Fe_2SO_4/ligand/CF_3COOH molar ratio: 1/3/10; H_2O_2/toluene molar ratio: 0.1; temperature: 37 °C; reaction time: 4 h. The reaction medium composition was water/acetonitrile/toluene 44/44/12 (v/v/v).
[b] Selectivity based on H_2O_2 = (mol of products × n × 100)/mol of reacted hydrogen peroxide.
[c] Selectivity based on ring = (mol of ring oxidation products × 100)/mol of reacted toluene.
[d] Selectivity based on methyl = (mol of methyl oxidation products × 100)/mol of reacted toluene.

(ring/methyl = 1.9), or to the methyl group, as in the case of ligand **1** (ring/methyl = 0.4). Radical dimerization products were not detected. Conversely, by operating under the conditions of the Fenton reagent, the product distribution was reported to be: ring hydroxylation (4%), benzylic oxidation (56%), radical dimerization to bibenzyl (30%) [21].

The TOF measured for toluene oxidation are also reported in Fig. 1. Again, the complex with ligand **4** turned out to be the most efficient catalyst. However, with all the ligands, the ring oxidation rates were lower than those measured for benzene. This is not consistent with the higher reactivity expected for toluene in electrophilic aromatic substitutions. This phenomenon could be explained by: (i) the lower solubility of toluene in the aqueous phase, in which the reaction takes place (98.9 mmol/l, with respect to 142.3 mmol/l measured for benzene); (ii) the lower number of reactive C–H bonds, which, in the case of toluene, are reduced from 6 to 3 (*orto* and *para* positions); (iii) the competition with benzylic oxidation.

Although detailed mechanistic information is not currently available, the reaction is likely to start with the oxidation of Fe(II) to Fe(III):

$$L_2Fe^{II} + H_2O_2 \rightarrow L_2Fe^{III}OH + OH^{\bullet}$$

Thus, it is also likely that hydroxyl radicals are present in the reaction mixture, where they probably act as oxidising agents according to the well-established Fenton mechanism. On the other hand, product distribution is definitely different from that observed with typical Fenton reagents. Particularly, in the presence of the ligands, dimeric by-products (biphenyl and bibenzyl) were not observed, whereas they became important in the absence of any added ligand. Moreover, the predominance of the *para* cresol isomer in the toluene oxidation (*o*/*m*/*p* ratio 40/1/59 versus 71/5/24 reported for Fenton oxidation [21]) suggests the intermediacy of a transient species more sterically demanding than the hydroxyl radical. These differences (if not simply due to the different reaction conditions) might be explained by the competition of a second mechanism, possibly triggered by the formation of a Fe(III) hydroperoxo species [6,7,22] which could undergo heterolytic cleavage to afford an electrophilic, high-valent iron-oxo complex, stabilised by the ligand, able to oxidise aromatic hydrocarbons to phenols [23], as shown in Fig. 2.

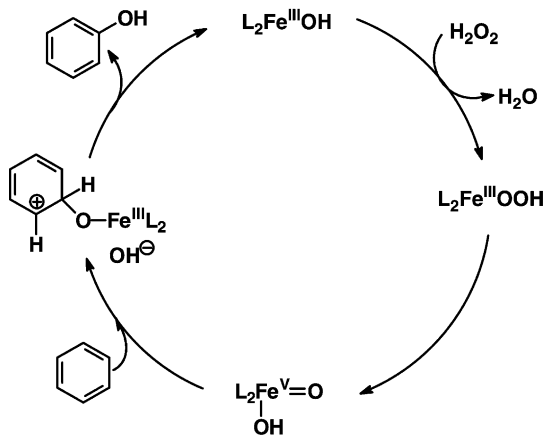


Fig. 2. Hypothesis for the reaction mechanism.

4. Conclusions

The study has proved that the nature of ligand plays a crucial role in the aromatic hydrocarbons hydroxylation catalysed by iron complexes, determining the catalyst efficiency and, in the case of toluene, also the selectivity towards nuclear or benzylic oxidation.

In particular, the complex with pyrazine-3-carboxylic acid *N*-oxide (**4**) was selected as the most effective catalyst for the phenol and cresols synthesis.

The oxidation of a series of substituted aromatic hydrocarbons is currently under investigation, in order to determine the potential of the new catalytic system as a general tool for the direct synthesis of phenols.

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