



Direct synthesis of phenols by iron-catalyzed biphasic oxidation of aromatic hydrocarbons with hydrogen peroxide

Daniele Bianchi^{a,*}, Marcello Bertoli^a, Roberto Tassinari^a,
Marco Ricci^a, Rodolfo Vignola^b

^a *Polimeri Europa S.p.A.-Istituto G. Donegani, Centro Ricerche Novara, Via Fauser 4, Novara I-28100, Italy*

^b *EniTecnologie, Via Ramarini 32, I-00016 Monterotondo, Italy*

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Abstract

The hydroxylation of a series of aromatic hydrocarbons with hydrogen peroxide, catalyzed by iron complexes with pyrazine-3-carboxylic acid *N*-oxide, was investigated, operating in a biphasic reaction medium.

The new catalyst showed a high selectivity to the corresponding phenols, minimizing the over-oxidation reactions to polyoxygenated derivatives and tars which, along with dimers formation, are the major limitations of the classical Fenton's reagent for a practical synthetic application.

In the case of alkylbenzenes, the competitive side chain oxidation at the benzylic positions also occurred. Electron rich substrates, such as anisole, were oxidized with very poor selectivity.

The reactions were carried out in a biphasic system that allows a convenient recovery and recycling of the catalyst by phase separation techniques. The catalyst showed a complete retention of activity after six consecutive reaction cycles.

The new catalyst appears as a promising tool for the direct synthesis of phenols, in alternative to the conventional multi-step methods.

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1. Introduction

The selective oxidation of organic substrates catalyzed by transition metals is an important topic in synthetic, industrial, and biological chemistry [1].

Simple hydrocarbons are among the most difficult substrates to oxidize. However, nature has evolved

both heme and non-heme iron enzymes which carry out this task under mild conditions. Thus, the search for new catalytic systems, often based on iron complexes with nitrogen ligands, has been the subject of extensive studies, with the final aim to mimic or emulate the catalytic properties of natural enzymes. These systems include the Gif chemistry [2] and the systems investigated by Tung et al. [3] and Chen and Que [4], all providing active catalysts for the oxidation of even poorly reactive alkanes. However, unlike Fenton chemistry [1a,5], these systems show a very poor reactivity, if any, in the oxidation of aromatic

* Corresponding author. Fax: +39-0321-447425.

E-mail address: daniele.bianchi@polimerieuropa.com (D. Bianchi).

hydrocarbons [6]. With these substrates, furthermore, even the Fenton reagent shows only a moderate selectivity to monohydroxylated products, since further oxidation occurs, making the system more useful for degradation purposes (e.g. soil or water remediation) [7] than for synthetic applications.

Recently we reported that iron complexes with pyrazinecarboxylic acid derivatives are efficient catalysts for the direct hydroxylation of benzene with hydrogen peroxide [8a]. Successively, the complex with pyrazine-3-carboxylic acid *N*-oxide has been selected as the best catalyst [8b] which, compared with the classical Fenton reagent, allows higher selectivities to phenol. This difference, if not simply due to the different reaction conditions, might be the result of the intermediacy of electrophilic, high-valent iron-oxo species [8b].

Here we report the application of the new catalytic system to the oxidation of a series of aromatic hydrocarbons to the corresponding phenols. Such a direct hydroxylation is a valuable alternative to the multi-step methods, currently used for the industrial synthesis of substituted phenols, including the catalytic alkylation of phenol [9] or the alkaline hydrolysis of chloroderivatives [10].

2. Experimental

Pyrazine-3-carboxylic acid *N*-oxide was synthesized according to a published procedure [8b,11], by oxidation of pyrazine-3-carboxylic acid with hydrogen peroxide, catalyzed by sodium tungstate. All other chemicals were purchased from Fluka.

2.1. Oxidation reactions (general procedure)

A solution of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (114 mg, 0.41 mmol), trifluoroacetic acid (0.3 ml, 4 mmol) and pyrazine-3-carboxylic acid *N*-oxide (182 mg, 1.3 mmol) in water (100 ml) was 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 (180 mmol) was then added, generating a biphasic system. The temperature was regulated 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 analyzed by HPLC. The products were separated and purified by silica-gel chromatography.

The product distributions obtained using different aromatic substrates were as given further.

- *Oxidation of benzene*: detected products are phenol (14.4 mmol), 1,4-benzoquinone (0.14 mmol).
- *Oxidation of toluene*: detected products were *ortho*-cresol (1.3 mmol), *meta*-cresol (0.04 mmol), *para*-cresol (1.8 mmol), benzyl alcohol (0.24 mmol), benzaldehyde (1.2 mmol), benzoic acid (0.30 mmol).
- *Oxidation of ethylbenzene*: detected products were *ortho*-ethylphenol (0.47 mmol), *meta*-ethylphenol (0.02 mmol), *para*-ethylphenol (0.52 mmol), 1-phenylethanol (0.99 mmol), acetophenone (2.8 mmol).
- *Oxidation of tert-butylbenzene*: detected products were *para*-*tert*-butylphenol (6.2 mmol), tars (47 mg, corresponding to 0.30 mmol of dioxygenated monomer).
- *Oxidation of anisole*: detected products were tars (327 mg, corresponding to 2.4 mmol of dioxygenated monomer).
- *Oxidation of chlorobenzene*: detected products were *ortho*-chlorophenol (3.1 mmol), *meta*-chlorophenol (1.1 mmol), *para*-chlorophenol (3.5 mmol), chloro-1,4-benzoquinone (0.25 mmol), tars (34 mg, corresponding to 0.24 mmol of dioxygenated monomer).
- *Oxidation of nitrobenzene*: detected products were *ortho*-nitrophenol (1.5 mmol), *meta*-nitrophenol (2.0 mmol), *para*-nitrophenol (2.2 mmol), 4-nitrocatechol (0.89 mmol), tars (59 mg, corresponding to 0.39 mmol of dioxygenated monomer).
- *Turnover frequency (TOF) determination*: the initial turnover frequency of the iron, only referred to ring oxidation, was expressed as (moles of ring oxidation products) $\times n$ / (moles of Fe \times hour). The factor *n* takes into account the moles of hydrogen peroxide utilized to produce a mole of the given product: its value is 1 (for phenols), 2 (for hydroquinone or catechol derivatives), or 3 (for quinones).

The TOF were determined carrying out the oxidation reactions as described above, but adding total amount of hydrogen peroxide at the beginning of the reaction and stopping it (by quick cooling) at an oxidant conversion lower than 20%.

3. Results and discussion

The complex of iron with pyrazine-3-carboxylic acid *N*-oxide is an effective catalyst for the direct hydroxylation of benzene and toluene with hydrogen peroxide [8b]. In order to evaluate its potential as a general tool for the direct synthesis of phenols, in the present paper we report the results obtained in the oxidation of a series of mono-substituted aromatic hydrocarbons, namely: toluene, ethylbenzene, *tert*-butylbenzene, anisole, chlorobenzene and nitrobenzene.

Unlike the conventional iron based Fenton system, the new catalyst is best used in a biphasic reaction medium generated by water and acetonitrile (volume ratio = 1:1) in the presence of the aromatic substrate. With this particular medium, the concentration of the hydrophobic hydrocarbon in the aqueous phase is enhanced, and the produced phenols are extracted for the most part in the organic phase. In this way, the biphasic operation minimizes the over-oxidation reactions (with formation of dihydroxylated products, quinones and tars) by reducing the contact between the produced phenols and the catalyst, which is soluble in the aqueous phase.


The reactions were carried out at 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 Fe(pyrazinecarboxylate)₂·(H₂O)₂ [12]. An acid co-catalyst (trifluoroacetic acid) was added in order to increase the selectivity based on hydrogen peroxide [8].

The values of selectivity and the products distribution obtained for the series of substrates are reported in Tables 1 and 2, respectively. In most cases, satisfactory to good yields to phenols were obtained.

In the case of toluene and ethylbenzene, however, a competition reaction occurred between the ring hydroxylation (mainly, to *ortho*- and *para*-positions) and the benzylic oxidation (see Table 2). The side chain oxidation was predominant in the case of ethylbenzene (the selectivity to phenol was reduced to 21%) due to the higher reactivity of the secondary benzylic position. No evidence for the oxidation of the terminal methyl group was obtained.

Conversely, *tert*-butylbenzene yielded *para-tert*-butylphenol as virtually the sole product (selectivity = 97%), confirming the low reactivity of the methyl

Table 1
Oxidation of aromatic hydrocarbons^a

Substrate 	Conversion of H ₂ O ₂ (%)	Selectivity on H ₂ O ₂ ^b (%)	Selectivity to phenols ^c (%)
R = H	92	84	99
R = Me	53	71	65
R = Et	44	96	21
R = <i>t</i> Bu	55	75	97
R = OMe	59	n.d.	0
R = Cl	84	61	93
R = NO ₂	94	56	81

^a Reaction conditions: Fe₂SO₄/ligand/CF₃COOH molar ratio, 1/3/10; H₂O₂/substrate molar ratio, 0.1; temperature, 37 °C; reaction time, 4 h. The reaction medium composition was water/acetonitrile 50/50 (v/v) containing 0.9 M aromatic substrate.

^b Moles of products × *n* × 100/moles of reacted hydrogen peroxide.

^c Moles of phenols produced × 100/moles of reacted substrate.


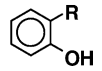
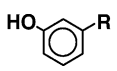
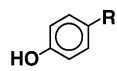
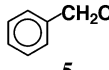
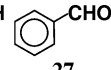
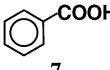
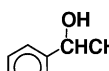
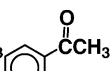
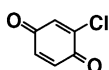
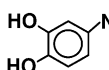
group (if not in benzylic position), and indicating a strong orienting effect exerted by the bulky *tert*-butyl moiety.

It is worth to note that, even for substrates more activated than benzene towards electrophilic attacks, such as alkylbenzenes, the formation of over-oxidation products and tars was negligible. A dramatic change in the reactivity was, however, observed in the case of the very electron rich anisole, which yielded a complex mixture of high molecular weight products, mainly oligomers of polyoxygenated aromatic rings, as confirmed by the mass-spectrometry analysis. The absence of the methyl substitution on most of the detected fragments, suggests the occurrence of oxidative demethylation secondary reactions [13].

The presence of over-oxidation products was detected, although to a minor extent, also in the case of substrates bearing electron-withdrawing groups such as chlorobenzene and nitrobenzene (see Table 2). Surprisingly, the strongly deactivated nitrobenzene showed a selectivity to the corresponding nitrophenols (81%) lower than that obtained in the case of the oxidation of benzene to phenol (99%). This may be a consequence of the higher hydrophilic nature of the nitroderivatives, which are less efficiently extracted from the aqueous phase of the biphasic system and, consequently, are more exposed to consecutive oxidation to nitrocatechol and tars (Table 2).

As reported in Table 1, the presence of a deactivating substitution determines also a decrease of the

Table 2
 Products distribution^a

Substrate 	Products (molar ratio, %)				
				Others	Tars
R = Me	25	–	36	 5  27  7	–
R = Et	10	0.5	10.5	 20  59	–
R = <i>t</i> Bu	–	–	97		3
R = OMe	–	–	–		100
R = Cl ^b	37	13	43	 4	3
R = NO ₂ ^c	21	28	32	 13	6

^a The reaction were carried out as described in Table 1.

^b The isomer distribution measured at low conversion of the chlorobenzene, in order to minimize the consecutive oxidation processes: *ortho/meta/para*, 41/15/44.

^c The isomer distribution measured at low conversion of the nitrobenzene, in order to minimize the consecutive oxidation processes: *ortho/meta/para*, 19/50/31.

selectivity based on hydrogen peroxide (see Table 1), which is partially decomposed through the competitive pathway: $2\text{H}_2\text{O}_2 \rightarrow \text{O}_2 + \text{H}_2\text{O}$.

The isomer distribution obtained for alkylbenzenes and chlorobenzene, essentially with *ortho/para*-orientation, is consistent with that usually observed in aromatic electrophilic substitutions. Conversely, in the case of nitrobenzene the *meta*-orientation was 50%, suggesting an intermediate character of the oxidizing species, between a strong electrophile (*meta*-orientation >90%) [14] and a mild electrophile, such as the hydroxyl radical (*meta*-orientation = 37%) [15]. Furthermore, the oxidation rates measured for alkylbenzenes were lower than those obtained for benzene (Fig. 1) and this is not consistent with the higher reactivity expected for activated substrates in electrophilic aromatic substitutions (the initial turnover frequencies, TOF, reported in Fig. 1 only refer to the ring oxidation and were calculated as described in the experimental section; anisole was not included, because of the prevalence of over-oxidation products). This phenomenon could be explained by: (i) the lower

solubility of alkylbenzenes in the aqueous phase, in which the reaction takes place (benzene: 142.3 mmol/l, toluene: 98.9 mmol/l, ethylbenzene: 77.4 mmol/l, *tert*-butylbenzene: 44.0 mmol/l, as determined by HPLC); (ii) the lower number of reactive C–H bonds, which, are reduced from 6 to 3 (*ortho* and *para* positions) in

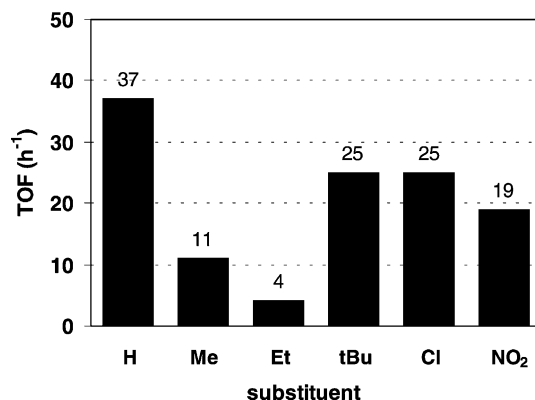


Fig. 1. Catalyst efficiencies. Turnover frequency (TOF) = moles of phenols/(moles of Fe × hour).

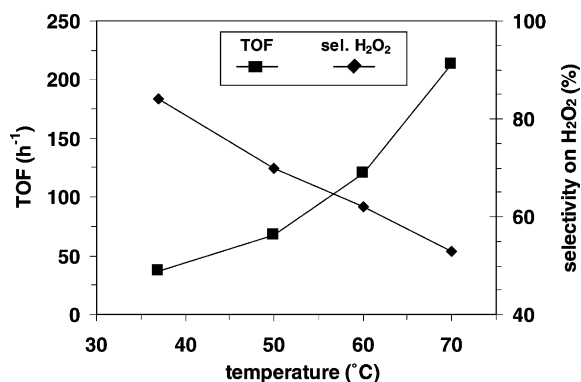


Fig. 2. Effect of the temperature. The oxidation of benzene to phenol was chosen as a model reaction. Turnover frequency (TOF) = moles of phenol/(moles of Fe × hour). Selectivity based on H₂O₂: moles of phenol × 100/moles of reacted hydrogen peroxide.

the case of toluene and ethylbenzene, and to 1 (*para* positions) for *tert*-butylbenzene; (iii) the competition with the benzylic oxidation (when possible).

The predominance of the *para* substituted phenols (up to 97% in *tert*-butylbenzene oxidation) confirms that, as already observed in the toluene oxidation [8b], the oxidizing species is sterically demanding, at least to some extent. Moreover, it is noteworthy that the presence of biphenyl derivatives, typically formed by the radical dimerization in the classical Fenton system [16], was never observed for all the tested substrates.

At higher temperatures, the TOF of the catalyst increased, while the selectivity on hydrogen peroxide sharply decreased, as shown in Fig. 2, for the benzene oxidation to phenol.

Operating in the water/acetonitrile/aromatic substrate biphasic system, the iron complex and the excess of the ligand were confined in the aqueous phase, keeping the iron concentration in the organic phase close to the detection limit. Conversely, the organic phase allowed the *in situ* products extraction, with an average distribution of the produced phenols in the organic layer ranging from 88 (measured for nitrophenols) to 99% (measure for *tert*-butylphenols). So, in this system, the products, largely confined into the organic phase, can be easily separated, by simple decantation, from the aqueous phase. The latter, containing the catalyst, can be reused as a “working solution” in consecutive reaction cycles. Operating

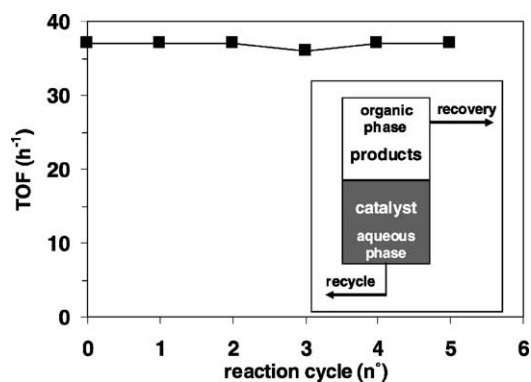


Fig. 3. Recycle of the catalyst. The oxidation of benzene to phenol was chosen as a model reaction. The oxidation was carried out in a semi-batch reactor as described in the Section 2. At the end of each cycle, the aqueous phase, containing the catalyst, was separated, added to a fresh mixture of benzene and acetonitrile and reused in a new reaction. Turnover frequency (TOF) = moles of phenol/(moles of Fe × hour).

under the standard reaction conditions, the ligand, which is protected as *N*-oxide in the most sensitive position, did not undergo any chemical modification, showing a long term stability.

As reported in Fig. 3, the oxidation of benzene to phenol was carried out in a semi-batch reactor, recycling the aqueous phase for six consecutive reaction cycles, detecting a complete retention of the catalytic activity, and a loss of the catalyst (determined as iron concentration) lower than 5%.

4. Conclusions

The study has proved that the complex with pyrazine-3-carboxylic acid *N*-oxide is an efficient catalyst for the direct hydroxylation of a wide range of aromatic substrates, to the corresponding phenols.

An attractive feature of the process is the operation in a particular biphasic system, with the quantitative distribution of the catalyst in the aqueous phase, that can be separated and reused in several consecutive cycles without any appreciable loss of activity.

However, the new system shows some limitations for a general application, due to the low selectivity displayed in the case of very electron-rich substrates and to the possible competition with the oxidation of aliphatic moieties.

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