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# Mechanistic diversity of the selective oxidations mediated by supported iron phthalocyanine complexes

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**Selective oxidations of (i) phenols and condensed aromatics to quinones and (ii) alkynes to α,β-acetylenic ketones mediated by supported iron phthalocyanine complexes exhibit very different mechanistic features as evidenced by $^{18}O$ labelling and kinetic isotope effect studies.**

Catalytic homogeneous oxidation of alkanes and olefins using metal complexes has been an object of numerous studies.[1,2] By contrast, the reports on the selective catalytic oxidation of aromatic compounds and alkynes are rather scarce. The oxidation of aromatics provides quinones used for the preparation of drugs and vitamins.[3] α,β-Acetylenic ketones obtained *via* selective oxidation of alkynes are valuable precursors for the enantioselective total syntheses and preparation of heterocyclic compounds, nucleosides, *etc.*[4,5] Halogen or heavy metal based stoichiometric oxidants are usually applied to perform these oxidations thus leading to severe environmental problems. The quest for efficient catalytic methods that use clean oxidants such as dioxygen or peroxides and heterogeneous catalysts still remains an important challenge. The catalysts immobilized on solid supports are especially attractive because they allow easy separation from the reaction mixture and possible recycling. Phthalocyanine metal complexes resemble porphyrin complexes widely used by Nature in the active sites of oxygenases. By contrast to porphyrins, a cheap and facile preparation of phthalocyanines, their availability at a large scale as well as their chemical and thermal stability make them industrially viable candidates for oxidation catalysis. Indeed, we have recently shown that iron tetrasulfophthalocyanine (FePcS–$SiO_2$) and iron hexadecachlorophthalocyanine (FePc$Cl_{16}$–$SiO_2$) covalently supported onto silica are efficient catalysts in the selective oxidation of phenols[6–8] and alkynes[9] by $^t$BuOOH (TBHP). Beyond the synthetic utility, in particular a high product yield and an easy separation and recycling of catalyst, mechanistic aspects of these oxidations are also of importance, especially when hydroperoxide oxidant is involved. We report herein the selective oxidation of condensed aromatics to quinones with high yields and experimental evidence for multiple pathways in the FePc–$SiO_2$ catalyzed oxidation of aromatic compounds and alkynes.

The heterogeneous catalysts FePcS–$SiO_2$ and FePc$Cl_{16}$–$SiO_2$ were prepared as previously described[6] and characterized by chemical analysis, surface area determination and the diffuse reflectance UV-Vis spectroscopy that evidenced the effective complex grafting. The contents of complexes were determined by metal analysis using an inductively coupled plasma-mass spectroscopy method to be 21–25 μmol $g^{-1}$ (for FePc$Cl_{16}$–$SiO_2$) and 35–40 μmol $g^{-1}$ (for FePcS–$SiO_2$). Results of the oxidations of three types of substrates, condensed aromatics, phenols and alkynes are listed in Table 1. Except for the very demanding oxidation of 2-methylnaphthalene, the FePcS–$SiO_2$ catalyst in combination with TBHP was very efficient in aromatic oxidation, providing quinones in 84–91% yields. Importantly, even phenols containing other oxidizable groups, *e.g.* methyl and acetamide groups, could be oxidized into corresponding valuable quinones with high selectivity. For example, trimethyl-1,4-benzoquinone, obtained by oxidation of 2,3,6-trimethylphenol, is the precursor of vitamin E. A high selectivity of this catalytic system was further demonstrated in the α-oxidation of alkynes while the triple bond was left intact (Table 1). Highly useful α,β-acetylenic ketones were obtained in up to 84% yield. Such conjugated α,β-acetylenic ketones are usually prepared by multistep synthesis. Only a few homogeneous methods have been reported using direct alkyne oxidation.[9] To the best of our knowledge this is the first heterogeneous catalytic system for the selective oxidation of alkynes to α,β-acetylenic ketones.

Then the question arises: what mechanism is operating to provide such a high selectivity in the oxidation of these polyfunctionalized substrates? It should be noted that mechanism(s) of oxidation by peroxides in the presence of iron complexes is an important topic in oxidation catalysis and a subject of numerous studies and discussions.[10] We used $^{18}O$ labelling[11,12] and isotope effects[13] to gain insight on the mechanism of the heterogeneous oxidation.

The oxidation of several substrates by $^t$BuOOH was performed in the presence of $^{18}O_2$ (Table 1). Isotopic compositions of products and dioxygen in the gas phase were constant during all reaction courses indicating no side reactions, *e.g.* dioxygen evolution from $^t$BuOOH or oxygen exchange between dioxygen and products. A dramatic difference of $^{18}O$ labelling in two groups of substrates was observed. The oxidation of alkynes occurred with significant $^{18}O$ incorporation from $^{18}O_2$ in both oct-4-yn-3-one (61.7%) and 4-phenylbut-3-yn-2-one (85.1%). To the contrary, a very low labelling of products was observed during oxidation of anthracene **A** to anthraquinone **AQ** (8.3%), 2,3,6-trimethylphenol to trimethylquinone (2.3%) and xanthene to xanthone (1.6%). GC-MS analysis of the oxidation products of **A** indicated that anthrone, the first oxidation product of **A**, contained only $^{16}O$. Importantly, the isotopic molecular cluster in the mass spectrum of **AQ** consisted of 208 $[M]^+$ and 210 $[M + 2]^+$ meaning that the $^{18}O$ atom was unambiguously located only in one carbonyl group of this quinone. These results are quite surprising since radicals, easily formed *via* 1 $e^-$ oxidation of these substrates, were expected to result in a significant $^{18}O$ content in oxidation products. Two key points emerge from the systematic labelling study: (i) a very small percentage of $^{18}O$ in oxidation products of anthracene, trimethylphenol and

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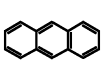
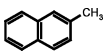
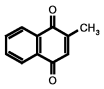
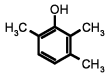
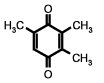
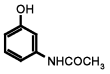
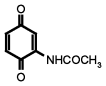
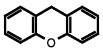
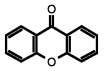
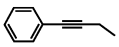
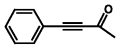
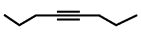
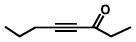
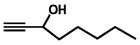
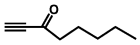
**Table 1** Oxidations of aromatics and alkynes by $^{t}$BuOOH catalyzed by FePcS–$SiO_2$[a]

| Substrate | Product | Conversion (%) | Yield (%) | $^{18}$O Content (%) |
|---|---|---|---|---|
|  |  | 100[b] | 90 | 8.3 ± 0.4 |
|  |  | 70[c] | 45 | n.d. |
|  |  | 97[b] | 84 | 2.3 ± 0.8 |
|  |  | 100[d] | 91 | n.d. |
|  |  | 100[d] | 99 | 1.6 ± 0.1 |
|  |  | 75[d,e,f] | 62 | 85.1 ± 2.0 |
|  |  | 80[d,e,f] | 71 | 61.7 ± 0.3 |
|  |  | 84[d,e,f] | 84 | n.d. |

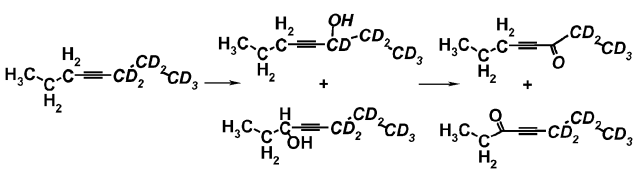
[a] Reaction conditions: 4 μmol catalyst, 0.4 mmol substrate, 2.24 mmol $^{t}$BuOOH in $CH_3CN$ at 40 °C. Reaction time: 2 h for phenols, 7 h for xanthene, 24 h for other substrates. n.d. = not determined. [b] In 1,1-dichloroethane. [c] With 16 μmol catalyst. [d] With 8 μmol catalyst. [e] In $^{t}$BuOH. [f] With 1.6 mmol $^{t}$BuOOH.

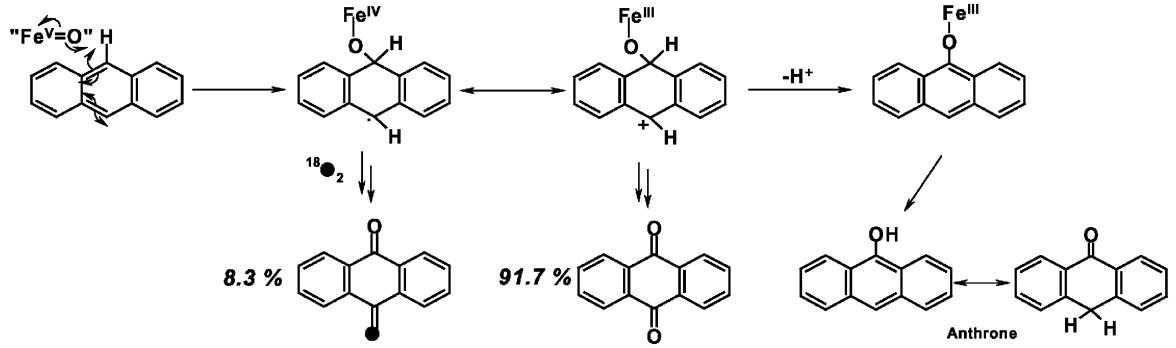
xanthene is consistent with the involvement of iron phthalocyanine centered species; and (ii) a large $^{18}$O incorporation in acetylenic ketones suggests a possible involvement of free radicals.

To further probe the mechanisms of oxidation of the two types of substrates, we have determined deuterium kinetic isotope effects (KIE) in the oxidations of anthracene and oct-4-yne. The KIE in anthracene oxidation was determined in intermolecular competitive experiments using a 50 : 50 **A-*h*$_{10}$–A-*d*$_{10}$** mixture. Isotopic compositions of compounds were determined by GC-MS, substrate conversions were obtained by HPLC and KIEs were calculated as described.[14] Analysis of the reaction mixture after 2 h reaction (conversion being 68%) indicated a preferential consumption of **A-*d*$_{10}$** resulting in a KIE of 0.90 ± 0.02 for the initial reaction step. This inverse KIE cannot be interpreted as a primary KIE involving C–H(D) bond cleavage in the rate determining step and excluded an oxygen rebound type mechanism which involves H atom abstraction from the substrate by an electrophilic high-valent oxo-iron complex to give a short-life radical followed by a rapid recombination step. Inverse KIEs are usually associated with secondary KIEs when no C–H(D) is cleaved, but this bond located at the reaction site itself (α-secondary KIE) changes its parameters in the transition state (TS).[14] Based on calculations with model systems, the α-secondary KIEs have been interpreted as reflecting the changes in the out-of-plane bending motion, *i.e.* hybridization change or differences in the loose/tight character of the TS.[15,16] The activation energy for sp$^2$-to-sp$^3$ hybridization change is lower for the deuterated substrate compared to the non-deuterated analogue, creating then an inverse KIE.[17] The aromatic hydroxylation of *o*- and *p*-xylene, catalyzed by cytochrome P-450, showed also an inverse α-secondary KIE (0.83–0.94) which has been explained by an addition reaction of an oxo-iron species onto an sp$^2$-hybridized carbon atom.[18] Similarly, the inverse KIE observed in anthracene oxidation strongly suggests the formation of a σ-complex between the substrate and putative oxo-iron phthalocyanine species. It should be noted that, in contrast with well-documented iron porphyrin chemistry relevant to cytochrome P-450, where intermediate active species in the catalytic cycle were identified and characterized by different spectroscopic techniques, the catalytic chemistry of metallophthalocyanines is practically not developed in terms of oxidation mechanisms and active species involved. When using $^{t}$BuOOH as an oxidant one can suggest the initial formation of PcSFe$^{III}$–OO$^{t}$Bu. By analogy with iron porphyrin chemistry, this peroxo complex can undergo homolytic cleavage of the O–O bond to give PcSFe$^{IV}$=O and a $^{t}$BuO$^{\bullet}$ radical, or to produce PcSFe$^{V}$=O *via* heterolytic O–O cleavage. A low incorporation of $^{18}$O in **AQ** and no $^{18}$O labelling of anthrone (the first oxidation product of **A**) observed by GC-MS, coupled with an inverse KIE in the first oxidation step favor an FePcS-based active species having two redox equivalents above the Fe$^{III}$ state. An electrophilic attack of this species at an sp$^2$ $C_9$ atom of **A** to give a σ-complex is probably the first step (Scheme 1).

The inverse KIE indicative of a sp$^2$-to-sp$^3$ rehybridization in the TS, no $^{18}$O incorporation into anthrone and the location of 8.3% of labelled oxygen only in one carbonyl position of quinone are consistent with the proposed mechanism. An intramolecular e$^-$ transfer can lead to an intermediate carbocation which cannot react with $^{18}O_2$ and should be further oxidized by $^{t}$BuOOH or FePcS-based species to give 91.7% of unlabelled **AQ**. Otherwise, the intermediate radical σ-complex can be trapped by $^{18}O_2$ to produce a small amount of labelled **AQ**. A similar mechanism should also be operating in the oxidations of 2,3,6-trimethylphenol and xanthene where smaller $^{18}$O incorporations, 2.3 and 1.6%, respectively, were observed suggesting shorter lifetimes for intermediate radical species.

Oct-4-yne-1,2,3-$d_7$ (98% isotope purity) having C–D and C–H bonds in the same stereochemical environments was prepared from pent-1-yne and 1-iodopropane-$d_7$ for intramolecular KIE determination:






**Scheme 1** Proposed mechanism of anthracene oxidation. "Fe$^{V}$=O" stands for FePcS-based species having two redox equivalents above the Fe$^{III}$ state.

The intrinsic KIEs of the first oxidation step were measured by GC-MS using the ratio of oct-4-yn-6-ol-$d_7$ (C–H oxidation product, major ion at $m/z$ = 104 corresponding to $[M - C_2H_5]^+$) and oct-4-yn-3-ol-$d_6$ (C–D oxidation product, major ion at $m/z$ = 98: $[M - C_2D_5]^+$). The KIEs for the acetylenic ketone formation were determined using the ratio of oct-4-yn-6-one-$d_7$ (C–H oxidation product, major ion $m/z$ = 102: $[M - C_2H_5]^+$) and oct-4-yn-3-one-$d_5$ (C–D oxidation product, major ion $m/z$ = 95: $[M - C_2D_5]^+$). High KIEs obtained with the two catalysts are consistent with C–H bond cleavage in the rate limiting step (Table 2). The dependence of intramolecular KIE on the catalyst structure strongly suggests the involvement of FePc-based active species. The formation of ketone proceeds *via* the cleavage of two C–H bonds. Higher KIE on ketone formation indicates that oxidation of alcohol to ketone also proceeds with significant isotope effect. These results, coupled with high $^{18}O$ incorporation in the reaction products from $^{18}O_2$ (61.7% for oct-4-yne), may be rationalized as follows. At the first rate limiting step, an FePc-based active species abstracts an H atom from an α-position of the alkyne (Scheme 2). The radical formed reacts with $O_2$ to give an intermediate peroxo radical leading to acetylenic ketones. The alkyne radical could also react with an FePc-based species to give unlabelled propargylic alcohol that can be rapidly converted to ketone.

To summarize, the oxidation of anthracene, 2,3,6-trimethylphenol and xanthene by the FePcS–$SiO_2$–$^t$BuOOH catalytic system occurs with a very low $^{18}O$ incorporation from $^{18}O_2$ to products and an inverse KIE, indicating 2 $e^-$ oxidation as a principal pathway consistent with a high yield of quinones, while coupling products should be obtained if a 1 $e^-$ pathway is operating. The oxidation of alkynes occurs with a significant $^{18}O$ incorporation from $^{18}O_2$ to reaction products and a high KIE, suggesting an involvement of radical intermediates corresponding to one electron oxidation. The reason for this dual reactivity is not yet clear. This finding might be reminiscent of the involvement of multiple reaction pathways in the cytochrome P-450 mediated oxidations explained by two-oxidants[19] and two-state reactivity models.[20] The results obtained indicate that a complexity of oxidation reactions is a feature not only for porphyrin[19,20] or non-heme complexes[21] but probably a more general phenomenon. Further research is in progress in order to understand whether two different species could be involved or if one active species would be able to adapt its mechanism of action depending on the substrate.

**Table 2** KIEs in the oxidation of oct-4-yne-$d_7$ by $^t$BuOOH[a]

| Catalyst | Alcohol $k_H/k_D$ | Ketone $k_H/k_D$ |
|---|---|---|
| FePcS–$SiO_2$ | 3.5 ± 0.7 | 9.3 ± 0.7 |
| $FePcCl_{16}$–$SiO_2$ | 6.5 ± 0.3 | 18.1 ± 0.6 |

[a] $T$ = 40 °C, $^t$BuOH, 2 h, catalyst : substrate : oxidant = 1 : 100 : 400.

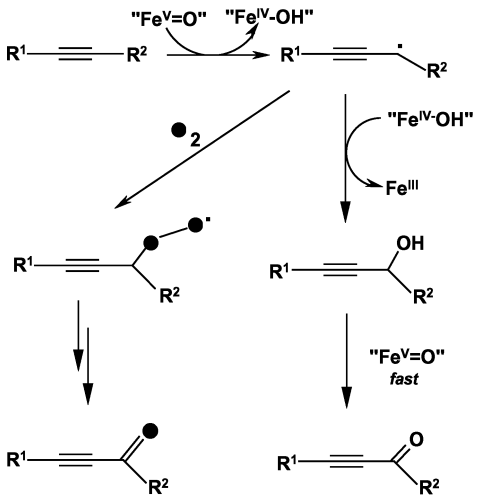
## Experimental

Solvents and chemicals were obtained from Sigma-Aldrich and used without purification unless indicated. Anthracene-$d_{10}$ (Acros, 99+ atom% D) was purified by sublimation. 1-Iodopropane-$d_7$ (Eurisotope, 98% isotope purity) was used as received. $^{18}O_2$ (98.5 atom%) was purchased from Eurisotope.

The reaction products were identified and quantified by NMR spectroscopy (AM 250 Bruker spectrometer), GC-MS (Hewlett Packard 5973/6890 system; electron impact ionization at 70 eV, He carrier gas, 30 m × 0.25 mm cross-linked 5% PHME siloxane [0.25 μm coating] capillary column, HP-5MS), GC (Agilent 4890D system, $N_2$ carrier gas, 15 m × 0.25 mm cross-linked 5% PHME siloxane [0.25 μm coating] capillary column, HP-5MS) and HPLC (Agilent Series 1100, Eclipse XDB-C8 column, MeCN–water = 70 : 30, 0.8 mL $min^{-1}$, UV-Vis detection) methods. The reaction courses were monitored by GC and substrate conversions and product yields were determined using an internal standard. Control experiments in the absence of FePc under otherwise identical reaction conditions showed a minor non-selective oxidation of oct-4-yne (13% conversion, 5% ketone yield), 1-phenylbut-1-yne (15% conversion, 8% ketone yield), anthracene (after 7 h: no reaction; after 24 h: 30% conversion, 8% quinone yield), trimethylphenol (21% conversion, 4% quinone yield). Other substrates were completely stable under the reaction conditions in the absence of the catalyst.

### Preparation of oct-4-yne-$d_7$

To a cold (−78 °C) stirred solution of pent-1-yne (600 μL, 6.1 mmol) in anhydrous THF (25 mL) was added *n*-BuLi (1.6 M in hexane, 4 mmol) under argon. The solution was allowed to




**Scheme 2** Proposed mechanism for alkyne oxidation.

warm to room temperature before adding 1-iodopropane-$d_7$ (328 mg, 1.9 mmol). The reaction mixture was stirred for two hours at room temperature, then heated to 38 °C for 42 hours until 1-iodopropane-$d_7$ was consumed (GC control). The mixture was cooled to 0 °C and quenched with saturated $NH_4Cl$. The product was then extracted with diethyl ether and purified by distillation to give a pure product. GC-MS analysis indicated 98% isotope purity (98.0% of oct-4-yne-$d_7$ and 2.0% of oct-4-yne). MS (EI) $m/z$ (*relative int.*): 117 (100, $[M]^+$), 102 (11, $[M - CH_3]^+$), 99 (14, $[M - CD_3]^+$), 88 (41, $[M - C_2H_5]^+$), 83 (57, $[M - C_2D_5]^+$).

### $^{18}O_2$ experiments

$^{18}O$ incorporations in products were corrected on $^{18}O$ natural abundance and purity of $^{18}O_2$. Reactions were carried out in triplicate using an $^{18}O_2$ (98.5 atom%) mixture with argon in a ratio of 45 : 55 according to the following procedure. A 25 mL flask was charged with 2 mL of 20 mM substrate solution in acetonitrile and solid catalyst [1 mol% for anthracene and trimethylphenol oxidation and 2 mol% for oxidation of xanthene and alkynes]. The reaction mixture was submitted to 3 freeze–pump–thaw cycles and the reaction flask was filled up with the mixture containing about 45% of $^{18}O_2$ (98.5 atom%) and 55% of argon. The reaction was started by the addition of 3.5 M TBHP solution in PhCl. The reaction temperature was 30 °C for TMP oxidation and 40 °C for other substrates. The substrate conversion was monitored by HPLC or GC and isotopic compositions of products and gas phase were analyzed by GC-MS. Isotopic compositions were determined from the intensities of molecular peaks at $m/z = 194/196$ for anthrone (tautomeric form of 9-hydroxyanthracene), $m/z = 210/212$ for oxanthrone (tautomeric form of 9,10-dihydro-9,10-dihydroxyanthracene), $m/z = 208/210$ for anthraquinone, $m/z = 150/152$ for trimethylquinone and $m/z = 196/198$ for xanthone (9-xanthenone). Isotopic compositions of the oxidation of oct-4-yne and 1-phenylbut-1-yne were calculated as described.[9]

### Determination of kinetic isotope effects

KIEs were determined by GC-MS using $m/z$ intensities of *h*- and *d*-containing molecules. Each sample was analyzed three times and $m/z$ intensities of each peak were obtained by an integration of all scans of the peak.[13]

### Oxidation of anthracene

Reactions were carried out in triplicate using an anthracene-$h_{10}$/anthracene-$d_{10}$ mixture in 50 : 50 molar ratio. A 25 mL flask was charged with 2 mL of 20 mM anthracene solution in 1,1-dichloroethane and 1 mol% of solid catalyst. The reaction was started by the addition of 3.5 M TBHP solution in PhCl. The substrate conversion was monitored by HPLC and isotopic compositions of products and gas phase were analyzed by GC-MS. Isotopic compositions of substrates left were determined during 2 h of the reaction from the intensities of molecular peaks at $m/z = 178/188$.

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