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Catalytic oxidation of alkanes by iron bispidine complexes and dioxygen: oxygen activation *versus* autoxidation†

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Organic substrates (specifically *cis*-1,2-dimethylcyclohexane, DMCH) are oxidized by O_2 in the presence of iron(II)–bispidine complexes. It is shown that this oxidation reaction is not based on O_2 activation by the nonheme iron catalysts as in Nature but due to a radical-based initiation, followed by a radical- and ferryl-based catalytic reaction.

Nonheme iron oxidation and oxygenation enzymes, *e.g.* methane monooxygenase,[1] naphthalene dioxygenase,[2] bleomycin,[3] taurine dioxygenase[4] and cysteine dioxygenase,[5] activate O_2, leading to a putative superoxido Fe^{III} intermediate which, in subsequent steps, is reduced (and protonated) to yield (hydro)peroxido Fe^{III} species, which are generally converted to the high-valent iron-oxo active oxidant (an exception with known Fe^{III} reactivity is bleomycin). However, the key superoxido Fe^{III} intermediate has so far not been trapped and characterized, and for nonheme iron model systems, evidence for superoxido Fe^{III} complexes is extremely scarce, *i.e.* the reactive intermediate so far remains elusive.[6–9] It is expected that the ligand sphere has a significant effect on the $Fe^{III/II}$ potential and hence on the O_2 activation by the ferrous center, with a predicted barrier for the activation of O_2 by nonheme iron centers of less than −0.10 V *vs.* Fc/Fc^+.[7,10] Interestingly, preliminary experiments indicated that iron bispidine complexes with $Fe^{III/II}$ potentials much higher than the −0.10 V limit [*i.e.* +0.84 V for complex **1** (Fig. S1, ESI†) and +0.76 V for **2**,[11] see Scheme 1 for complex structures] catalyze the oxidation of *cis*-1,2-dimethylcyclohexane (DMCH) with O_2. Importantly, DMCH has a significantly higher C–H bond dissociation energy (BDE, *ca.* 96.5 kcal mol^{-1})[12] than the substrates used in similar experiments (*e.g.*, cyclohexene, *ca.* 88.8 kcal mol^{-1})[6,12,13] and, under ambient conditions in MeCN, conversion of cyclohexane (BDE, *ca.* 105 kcal mol^{-1})[12] to cyclohexanol was also observed.[14] With iron bispidine complexes under ambient conditions in acetonitrile (MeCN) and with DMCH as the substrate, formation of a stable purple intermediate (characterized as the corresponding alkylperoxido-Fe^{III} species, *vide infra*) and oxidation products was observed (alcohols as well as ketones with similar yields and in similar ratios as with H_2O_2 as the oxidant, see ESI,† Fig. S2). Here, we present an alternative reaction mechanism for the oxidation of organic substrates in the presence of iron–bispidine complexes and dioxygen.

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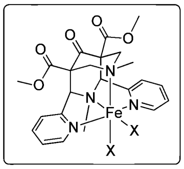

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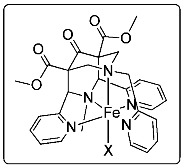

Scheme 1 Bispidine complexes **1** and **2**; X = solvent molecule.

The assumed mechanism of alkane oxygenation by a superoxido Fe^{III} complex involves H atom abstraction by the superoxido complex, producing a hydroperoxido Fe^{III} intermediate which then forms an $Fe^{IV}{=}O$ complex.[6] This is known to be a strong enough oxidant for the substrates studied here. Moreover, preliminary DFT calculations indicated that the putative superoxido Fe^{III} complex **2′** is able to abstract H atoms from cyclohexadiene,[15–17] and electronic spectra of the supposedly emerging ferryl complexes **1″** and **2″** are well-known[18,19] and are observed upon reaction of DMCH with the Fe^{II} complexes **1** and **2** in MeCN under ambient conditions (see ESI,† Fig. S3). The fact that Fe^{III} hydroperoxido intermediates could also be trapped and characterized by EPR[20] indicated that the assumed superoxido-Fe^{III}-based mechanism might operate – although the $Fe^{III/II}$ potentials of our "catalysts" are much too high.[10] We therefore studied the kinetics of the formation and decay of the ferryl intermediate in detail.‡ Interestingly, with all substrates used, the kinetic traces were sigmoidal with a substantial lag phase,

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† Electronic supplementary information (ESI) available: The synthesis of complexes **1** and **2** was reported previously.[33–35] Full description of the experiments describing all relevant experimental and simulated spectra. See DOI: 10.1039/c3cc47013j

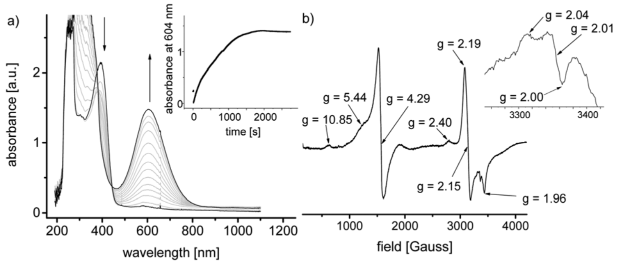


Fig. 1 (a) UV-vis-NIR spectral change observed in the reaction of 1.0 mM **2** with 200 equiv. of DMCH^{aged} in O_2-saturated DCM at −80 °C; the inset shows the time profile of the absorbance at 604 nm. (b) The EPR spectrum of the solution obtained in a reaction of 1.0 mM of **2** with 200 equiv. of DMCH^{aged} in O_2-saturated DCM at −80 °C (9.4369 GHz, 5 K, 3.0 × 10^{-4} T modulation amplitude, 100 kHz modulation frequency, see ESI,† Fig. S8 for **1**); the inset shows a magnification of the signals at g_c = 2.04, 2.01 and 2.00.

which was irreproducible in length. After thorough purification of the substrates by filtration over magnesium sulfate, alumina and silica, the duration of the lag phase increased (but not fully reproducible); with an older batch of DMCH (DMCH^{aged}), the start of the formation of ferryl species was very fast (see ESI,† Fig. S3). This indicates that DMCH might be oxidized prior to the exposure to the iron bispidine compounds (from diethylether it is well known that in an oxygen atmosphere there is formation of peroxo compounds *via* hydrogen abstraction by dioxygen[21]). Solutions of Fe^{II} complexes with DMCH^{aged} and O_2 at −80 °C in dichloromethane (DCM) are bluish with electronic transitions at 604 nm and EPR signals of at least three different species (g_a = 4.29; g_b = 2.19, 2.15 and 1.96; g_c = 2.04, 2.01 and 2.00; see Fig. 1 for **2** and ESI,† Fig. S8 for **1**). The EPR spectrum with g_b = 2.19, 2.15 and 1.96 resembles that of the previously published $S = 1/2$ hydroperoxido and alkylperoxido Fe^{III} bispidine compounds.[20,22] It indicates that the observed iron–bispidine-assisted oxidation might be initiated by organic radicals.

To test this assumption we investigated the reactions of DMCH, methylcyclohexane (MCH) and 1,4-dimethylcyclohexane (1,4-DMCH) with added radical scavengers [2,6-bis(*tert*-butyl)-4-methylphenol as an antioxidant (A), bromotrichloromethane as a carbon radical scavenger (C) and diphenylamine as an oxygen radical scavenger (O)] as well as with the radical starter azobis-isobutyronitrile (AIBN; otherwise identical experimental conditions, see Table 1). The BDEs of the three substrates used are very similar but they have different hydrogen abstraction reactivities, as observed before for *cis*- and *trans*-1,2-dimethylcyclohexane.[23]

For the reactions provided in Table 1, **1** was preferred over **2** because of the simple and fast visual detection of an activation and its beneficial reaction characteristics, *i.e.* **1**″ is a faster and stronger oxidant than **2**″ and is therefore expected to increase the probability of a positive reaction.[11,18,19,24] From Table 1 it can be observed that carbon-based radicals initiate the oxidation sequence. Therefore, for **2** we studied the iron species that form during the sigmoidal activation and the exponential decay phase in the presence of AIBN and DMCH (Fig. 2; note that for **1** the corresponding EPR spectra did not reveal any low-spin ferric complexes). As the reaction proceeds, the $Fe^{IV}{=}O$ intermediate is generated (UV-vis-NIR, 735 nm) along with three different species with EPR signals for Fe^{III} $S = 5/2$, $S = 1/2$ and a species of almost axial symmetry at g = 2.03, 2.01 and 2.00 (see Fig. 2). In the reaction of **1** with *tert*-butylhydroperoxide, we first observed the formation of an oxygen-based radical; after the decomposition, according to mass spectrometry a *tert*-butylalkoxido Fe^{III} compound emerged (see ESI,† Table S1).

Based on these observations, we propose a reaction mechanism initiated by organic radicals and involving ferrous bispidine complexes, O_2 and organic substrates (Scheme 2): (A) The EPR and UV-vis-NIR spectra of **2** with DMCH^{aged} in DCM at −80 °C (Fig. 1) are due to the alkylperoxido Fe^{III} intermediate with an

Table 1 Comparison of the reactivities of 1.0 mM of **1** and various substrates (18 h reaction time under ambient conditions in MeCN; 180 equiv. of AIBN was used as a radical starter; (A), (O) and (C) [see text] were used as radical scavengers, 9.0, 4.5 and 4.5 equiv., respectively; see ESI, Fig. S9 for UV-vis-NIR spectra of entries a–d, f, and h)

Entry	Substrate	Radical starter	Radical scavenger	Fe^{III}-OOR observed[a]
a	DMCH (200 eq.)	—	—	✓
b	DMCH (200 eq.)	—	✓ A	—
c	DMCH (200 eq.)	—	✓ C	(✓)[b]
d	DMCH (200 eq.)	—	✓ O	—
e	MCH (200 eq.)	—	—	—
f	MCH (200 eq.)	✓	—	✓
g	1,4-DMCH (400 eq.)	—	—	—
h	1,4-DMCH (400 eq.)	✓	—	✓
i	—	✓	—	—

[a] Reactions are considered positive when a purple alkylperoxido Fe^{III} species was observed; note that so far only complexes with tetradentate bispidines have been shown to form stable alkylperoxido Fe^{III} species.[22]
[b] A strong increase of intensity in the UV region but no well-resolved electronic transition at around 520 nm, see ESI, Fig. S9c.

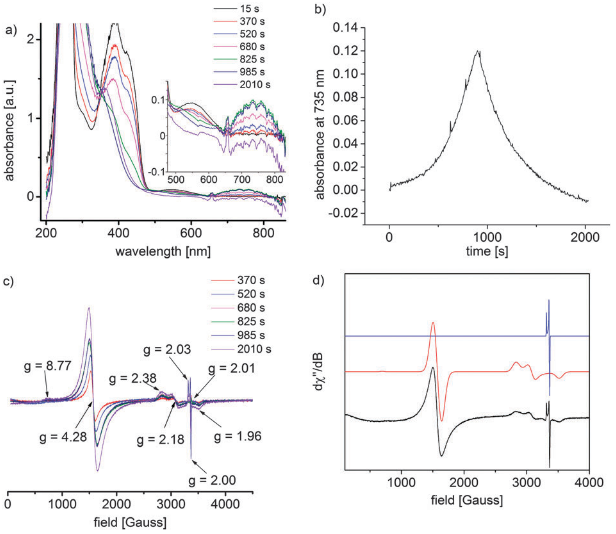
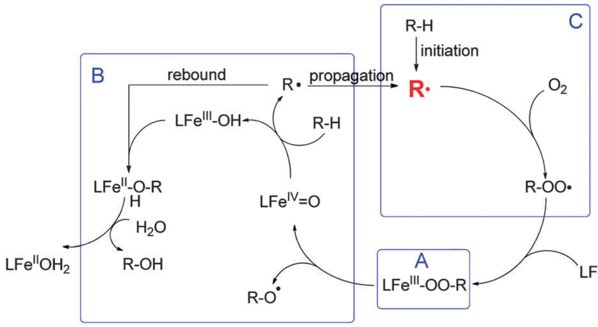


Fig. 2 (a) UV-vis-NIR spectra of 1.0 mM of **2** with 200 equiv. of DMCH and 75 equiv. of AIBN in MeCN at 25 °C; the inset shows the magnification of the increasing ferryl band; (b) time-dependent generation and decomposition of the ferryl species at 735 nm; (c) EPR spectra, 9.4375 GHz, 110 K, 3.0 × 10^{-4} T modulation amplitude, 100 kHz modulation frequency; (d) simulation of the EPR spectra after 985 s (black: experimental spectrum).[25–27]



Scheme 2 Proposed autocatalytic radical chain mechanism.

electronic transition at 604 nm and g = 2.19, 2.15 and 1.96. The assignment of these spectra to a metastable hydroperoxido Fe^{III} derivative is ruled out because addition of a base to these solutions did not lead to the corresponding peroxido complex (whose spectroscopic signature is known[20]), and addition of acid did not[20,22] yield the expected Fe^{V} complex,[22] *i.e.* no conversion was observed under these conditions (see also ESI,† Fig. S10 and S11). (B) The continuous formation and decomposition of the alkylperoxido Fe^{III} species (see Fig. 2) with AIBN at 25 °C yields the ferryl complex with a UV-vis-NIR feature at 735 nm, responsible for the oxygenation of the organic substrate, and an oxygen-based radical with g = 2.03, 2.01 and 2.00. This interpretation is supported by EPR spectra observed after the reaction of **1** with *tert*-butylhydroperoxide.[22] The alkoxy radical may react in different ways: (i) oxidative reaction with Fe^{II} to yield a ferric alkoxido complex with $S = 5/2$ and g = 4.29 and also supported by mass spectrometry (see ESI,† Table S1), followed by acid/base decomposition to yield the alcohol product and a hydroxido Fe^{III} complex, which has an EPR transition at approx. g = 4.3;[18] (ii) the alkoxy radical may react as a hydrogen atom abstracting species to pursue the radical chain mechanism (this pathway is unlikely due to the relatively low efficiency of the reaction; also, the observed product ratio, which is similar to that with H_2O_2 as the oxidant, indicates that an Fe^{IV}=O based alkane oxidation mechanism is likely). (C) The ferryl complex as well as the alkoxy and alkylperoxido radicals may produce alkyl radicals needed for the formation of the ferryl species.[28,29]

In conclusion, we present evidence that the iron–bispidine-assisted oxygenation of alkanes is initiated by organic radicals – a similar autoxidation pathway has recently been proposed.[30] We cannot exclude that formation of these radicals may involve Fe^{II} and O_2 but with our ligand systems initiation by superoxido Fe^{III} intermediates is very unlikely.[10] We believe that the pathway presented here is quite general, and one needs to be very cautious when studying Fe-catalyzed oxidation reactions of organic substrates in an ambient atmosphere – and this includes reactions with various oxidants such as peracids, peroxides and iodosylbenzene, and alkanes as well as olefins.[24,31,32]

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