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Ferroxime(II)-catalyzed oxygenation of nitroalkanes by *tert*-butyl hydroperoxide and its relevance to 2-nitropropane dioxygenase

József Kaizer [a], Zoltán Gréczi [b], Gábor Speier [a,b,*]

[a] *Research Group for Petrochemistry, Hungarian Academy of Sciences, 8201 Veszprém, Hungary*
[b] *Department of Organic Chemistry, University of Veszprém, 8201 Veszprém, Hungary*

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Abstract

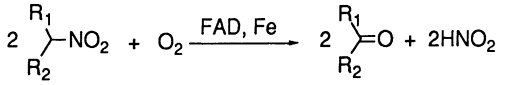
The complex $[Fe(Hdmg)_2(py)_2]$, referred to as ferroxime(II), was found to be a selective catalyst for the oxidative denitrification of nitroalkanes such as 1-nitroethane, 1-nitropropane, 2-nitropropane, 1-nitropentane and nitrocyclohexane to the corresponding aldehydes or ketones. The oxidation was performed in DMF and EtOH under Ar in the presence of various oxidants such as O_2, TBHP, H_2O_2 at room temperature, and was followed by glc. The substrate specificity of the catalyst either in DMF or EtOH solution shows that there are no significant differences in the conversions with the exception of 1-nitropentane and nitrocyclohexane. The effect of various oxidants shows that the catalytic oxidations were effective only with TBHP and H_2O_2. No oxidation products could be detected when O_2 was used. The best conversions (TN) have been obtained with TBHP in EtOH (up to 24%, TN = 9.3), followed by H_2O_2 (1.7%, TN = 0.5).

Keywords: 2-Nitropropane dioxygenase; Catalysis; Ferroxime; Nitroalkane oxidation; *tert*-Butyl hydroperoxide

1. Introduction

The conversion of nitro compounds to aldehydes or ketones can be carried out classically with the Nef reaction [1]. There are a fair number of stoichiometric reagents for this conversion. Treatment of nitroalkanes with aqueous $TiCl_3$ [2,3], cetyltrimethylammonium permanganate [4], tin complexes and $NaHSO_3$ [5], activated dry silica gel [6], 30% H_2O_2–K_2CO_3 [7], $KMnO_4$ [8], ceric ammonium nitrate [9], MoO_5–pyridine–HMPA [10] or ozone [11] leads to oxo compounds. A catalyst and tBuO$_2$H provide a catalytic process for the transformation [12].

Biological organisms can also transform aliphatic nitro compounds to the corresponding oxo species and nitrite ion. Oxygenated flavoenzyme species [13], glucose oxidase, D- and L-amino acid oxidase [14], flavoprotein nitroalkane oxidase from *Fusariam oxysporum* [15] and the intracellular enzyme 2-nitropropane dioxygenase of *Hanzenula mrakii* [16] accept nitroalkanes as substrates. The latter is believed to contain iron ions at its active center, and the action of this enzyme can be best described as an intermolecular dioxygenation reaction (Eq. (1)).



(1)

Only limited data on 2-nitropropane dioxygenase are available in the literature and the role of the metal

* Corresponding author. Tel.: +36-88-422-022; fax: +36-88-427-492.
E-mail address: speier@almos.vein.hu (G. Speier).

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ion at its active site is obscured. The question is put forward as how the reaction is accelerated and what is the role of the redox metal ion in terms of activation of either dioxygen or the substrate. Recently, we demonstrated the facile copper- and iron-assisted oxygenation of nitroalkanes, and proposed a mechanism for these curious reactions [17–19]. These systems provide the first metal-containing functional models for 2-nitropropane dioxygenase. As an extension of these works in this article, we will show that the iron(II) complex $[Fe(Hdmg)_2(py)_2]$ (H_2dmg: dimethylglyoxime) exhibits very important role in activating alkylperoxide, leading to oxygenation reaction of nitroalkane derivatives to the corresponding enzyme-like oxo products.

2. Experimental

2.1. General procedure

All manipulations were carried out under Ar atmosphere by using standard Schlenk technique. Ethanol and DMF were purified in the usual manner [20] and stored under argon. The iron(II) complex was synthesized by the procedure reported [21]. Nitroethane, 1-nitropropane, 2-nitropropane, nitrocyclohexane, 1-nitropentane, H_2O_2 (35% aqueous) and TBHP (70% aqueous) were Aldrich products. The GC analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a flame ionization detector with Carbowax 20 M, 30 m × 0.32 mm × 1 mm or ultra 1 cross-linked methyl silicone gum phase, 25 m × 0.32 mm × 0.52 mm columns. Quantification of the products was achieved by using cyclohexanone or benzene as internal standards and the peaks were identified by comparison with pure samples analyzed by GC–MS HP 5890II/5971 coupled system fitted with an ultra 1 cross-linked methyl silicone gum phase, 25 m × 0.32 mm × 0.52 mm column at 75 EV.

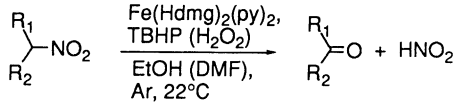
2.2. Oxidation procedure

Standard reactions were carried out at room temperature (25 °C) under inert atmosphere (Ar) as follows. The ferroxime(II) (0.5 mmol) was dissolved in DMF or ethanol (∼6.5 ml) containing either 15 mmol of nitroethane, 1-nitropropane, 2-nitropropane, nitrocyclohexane or 1-nitropentane. The reaction was started by adding 15 mmol of TBHP or H_2O_2. After 3 h stirring, an internal standard (cyclohexanone or benzene) was added to the reaction mixture and the products were quantified by GC and verified by GC–MS. The consumption of oxidants was determined by iodometry. After 3 h, the reactions practically ceased, the consumption of oxidants was about 70–80%. Unambiguous identification of the products was made by comparison with pure compounds, prepared independently or commercially available. In some experiments, the solutions were saturated with dioxygen.

3. Results and discussion

In the present work, we wish to report a study on the oxidative ferroxime(II)-catalyzed transformation of nitro compounds. Nitroalkane oxidation has been typically tested at room temperature in the presence of 0.5 mM of the catalyst with a 30-fold molar excess of the substrate and the oxidant [tBuO$_2$H (TBHP), H_2O_2 and O_2] under various conditions. Some representative experimental data are summarized in Table 1. The following conclusions may be drawn from these results.

- Primary and secondary nitro compounds are easily transformed to aldehydes or ketones by TBHP catalyzed by ferroxime(II) complex as catalyst (Eq. (2)). The substrate specificity of the catalyst in either DMF or EtOH solution shows that there are no significant differences in the conversions with the exception of 1-nitropentane and nitrocyclohexane. In the case of unbranched primary nitroalkanes such as 1-nitroethane and 1-nitropropane, the similarity in the conversions can be explained by the absence of steric strains, however, in the case of 1-nitropentane and nitrocyclohexane, this is not the case any more.



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a) $R_1 = CH_3$; $R_2 = H$
b) $R_1 = C_2H_5$; $R_2 = H$
c) $R_1 = R_2 = CH_3$
d) $R_1R_2 = C_5H_{10}$
e) $R_1 = C_4H_9$; $R_2 = H$ (2)

Table 1
Product distribution for the ferroxime(II)-catalyzed oxidation of nitroalkanes[a]

Run	Substrates	Oxidant	Solvents	Condition	Time (h)	Conversion[b] (%)	TN	TN/h[c]
1	**1a**	TBHP	DMF	Ar	3	9.8	3.0	1.0
2	**1a**	TBHP	EtOH	Ar	3	21.3	6.4	2.1
3	**1b**	TBHP	DMF	Ar	3	10.5	3.2	1.1
4	**1b**	TBHP	EtOH	Ar	3	22.0	6.6	2.2
5	**1c**	TBHP	DMF	Ar	3	9.2	2.8	0.9
6	**1c**	TBHP	DMF	Ar	3	16.5[d]	5.0	1.7
7	**1c**	TBHP	EtOH	Ar	3	24.0	7.2	2.4
8	**1c**	TBHP	EtOH	Ar	3	31.0[d]	9.3	3.1
9	**1c**	TBHP	EtOH	O_2	3	19.8	5.9	2.0
10	**1c**	O_2	DMF	Ar	20	–	–	–
11	**1c**	O_2	EtOH	Ar	20	–	–	–
12	**1c**	H_2O_2	DMF	Ar	3	0.6	0.2	0.06
13	**1c**	H_2O_2	EtOH	Ar	3	1.7	0.5	0.17
14	**1d**	TBHP	DMF	Ar	3	1.9	0.6	0.2
15	**1e**	TBHP	EtOH	Ar	3	11.6	3.5	1.2

[a] Oxidation were performed with 0.5 mmol of catalyst and 30-fold molar excess of TBHP and substrates at 25 °C.
[b] Conversions are based on nitroalkanes.
[c] TN/h, turnover number (calculated as mol of product per mol of catalyst per hour).
[d] 1.0 mmol catalyst was used.

- The effect of varying the oxidant was studied during 2-nitropropane oxidation in the presence of ferroxime(II). Catalytic oxidations were effective only with TBHP and H_2O_2. No oxidation products could be detected when O_2 was used. The best conversions have been obtained with TBHP in EtOH solution (up to 24%), followed by H_2O_2 (1.7%). Increasing the catalyst concentration (1 mM) led to a 16.5 and 31% conversion of 2-nitropropane in DMF and EtOH, respectively. Ménage et al. [22] in the iron-catalyzed alkane oxidation system have shown that in the absence of substrate, around 50% of total TBHP and 70% of total H_2O_2 was transformed into O_2 and *t*-butanol and H_2O, respectively. In the presence of substrate, the yield of O_2 dropped to 10% with TBHP but with H_2O_2 no significant change was observed. We believe that the low conversion with H_2O_2 as the oxidant was due to an efficiently catalyzed dismutation.
- Two sets of reaction conditions have been investigated in order to determine whether dioxygen plays a role during oxidation reactions: (i) solutions saturated with argon; (ii) solutions continuously saturated with dioxygen. As shown in Table 1, there was not a single anaerobic experiment in which oxidation was totally abolished. Dioxygen had a minor effect on the conversion of the reaction. The lower conversion can be explained by the formation of the moderately reactive μ-oxodiiron(III) dimer. In conclusion, our results unambiguously demonstrate that dioxygen is not required for the oxidation of nitroalkanes to oxo species. This fact is also supported by the experiments in which the dioxygen was used as the oxidant.
- We have found that the solvent has a profound effect on the effectivity of the reaction. When ethanol was replaced by more coordinating solvents such as DMF, the ferroxime(II) was much less active (9.2% conversion compared to 24% after 3 h reaction time). This can be rationalized by the fact that electron-donating ligands in the iron coordination sphere make TBHP more difficult to bind.
- During the oxidation of 2-nitropropane by TBHP in the presence of ferroxime(II) the characteristic band of the complex at 509 nm immediately disappeared due to the loss of coordinated py and a new species was formed signalled by the appearance of a broad absorption band at around 610 nm (Fig. 1). The spectroscopic characteristics (UV-visible) of the species absorbing at 610 nm is identical with

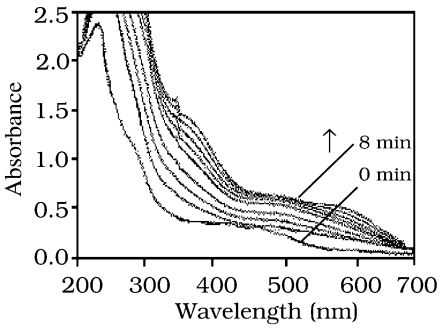
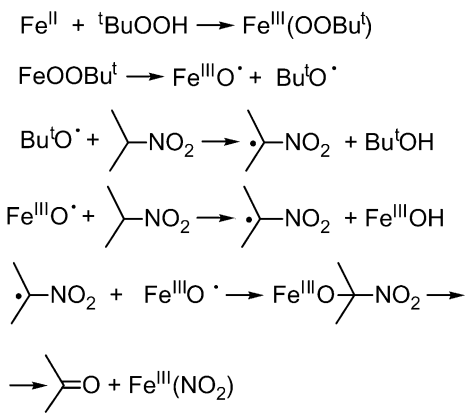


Fig. 1. Oxidation of 2-nitropropane by TBHP catalyzed by ferroxime(II) followed by UV-visible spectroscopy (catalyst/TBHP/2-nitropropane = 1:30:30, at 25 °C).

those of the mononuclear alkylperoxo-iron complex, Fe(III)(OOR) as reported earlier [23].

It is now well established that the function of the iron center is to activate the alkylhydroperoxide into a more reactive species. Without the catalyst, no reaction could be observed. The activation requires the presence of a labile site on the catalyst and the binding of the peroxide.

In the Scheme 1, we summarize our interpretation of the experimental data reported here. The first step of the reaction is the binding of the oxidant TBHP to the iron catalyst forming an alkylperoxo-iron(III) complex. After that the two possible candidates for the H-abstracting species are the high valent iron oxo complex Fe(III)O• or the alkoxyl radical derived from the homolytic cleavage of the O–O bond, respectively. We believe that in this reaction both radical species (^{t}BuO• and Fe(III)O•) are involved in the H-abstraction. The so formed 2-nitro-2-propanolatoiron(III) species decomposes to acetone and Fe(III)NO_2. The nitrito group may then be displaced by the oxidant TBHP to give Fe(III)OO^{t}Bu and HNO_2 to close the catalytic cycle.



Scheme 1.

As a conclusion, it can be said that while copper nitronate and some iron(III) nitronate complexes do react with dioxygen, the iron(II) complex does not react with O_2 at all. However, with TBHP or H_2O_2 as primary oxidants the oxygenation of nitropropanes is catalyzed by the iron complex. The catalytic process is rather similar to the enzyme catalyzed reaction. The compound 2-nitropropane dioxygenase is a flavoenzyme, where the flavin reacts with dioxygen to give peroxidic species, probably an H_2O_2, which as a secondary oxidant reacts with the nitroalkane substrates, possibly by the use of catalytic activity of iron ions. So the present iron(II) peroxide systems seem to mimic the enzyme reaction using conventional and easily accessible peroxidic species.

Acknowledgements

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