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The Radical Versus Non-radical Reactive Intermediates in the Iron(III) Porphyrin Catalyzed Oxidation Reactions by Hydroperoxides, Hydrogen Peroxide and Iodosylarene

Arunava Agarwala · Debkumar Bandyopadhyay

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Abstract In the catalytic reaction of an iron(III) porphyrin with *t*-BuOOH, CumOOH, H_2O_2 and C_6F_5IO, cyclohexene was used as a probe substrate. The selective hydroxylation of cyclohexene by hydroperoxides proceeds through radical path and this has been utilized for successful dioxygen activation/autooxidation. For other oxidants epoxide was the major product and the reactions proceed through non-radical path.

Keywords Iron porphyrin · Catalysis · Oxidation · Hydroperoxide

1 Introduction

The iron(III) porphyrin catalyzed epoxidation and hydroxylation reactions have been extensively studied in the last several decades [1–5]. In the studies where the electronegatively substituted iron(III) porphyrins were used as the catalysts and iodosylarenes or peracids were used as the terminal oxidants, the high yield epoxidations and hydroxylations have indeed been achieved. However such hydroxylation of sp^3 hybridized C–H bonds in particular by ROOH and H_2O_2 remained as a challenge till date [6–18]. In these oxidation reactions it has been proposed that the oxo-iron(IV) porphyrin(**1**), oxo-iron(IV) porphyrin cation radical(**2**), and iron(III) porphyrin-oxidant adduct(**3**) were the potential reactive intermediates. In case of hydroperoxides the homolytic cleavage of ROOH in non-polar solvents such as benzene and dichloromethane were proposed earlier [19, 20]. However these were questioned in the later studies and the topic remained debatable [7]. In our recent study on F_{20}TPPFe(III)Cl catalyzed hydroxylation of cyclohexene by *t*-BuOOH the evolution of F_{20}TPPFe(IV)=O (**1**) through Eqs. 1–3 and that of **2** via Eq. 4 have been proposed [21].

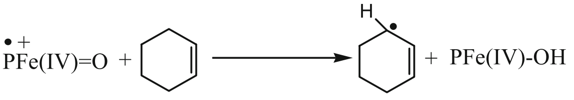
$$\mathrm{PFe(III)Cl} \xrightarrow[-\mathrm{Cl}^-]{\mathrm{H_2O}} \mathrm{PFe(III){-}OH} + \mathrm{H}^+ \quad (1)$$

$$\mathrm{PFe(III){-}OH} + t\mathrm{BuOOH} \rightarrow \mathrm{PFe(III){-}OO}^t\mathrm{Bu} + \mathrm{H_2O} \quad (2)$$

$$\mathrm{PFe(III){-}OO}^t\mathrm{Bu} \rightarrow \mathrm{PFe(IV){=}O} + {}^t\mathrm{Bu}\dot{\mathrm{O}} \quad (3)$$

$${}^t\mathrm{Bu}\dot{\mathrm{O}} + \mathrm{PFe(IV){=}O} \xrightarrow{-{}^t\mathrm{BuO}^-} \overset{\bullet\,+}{\mathrm{P}}\mathrm{Fe(IV){=}O} \quad (4)$$

In this reaction the non-oxidizable $CH_3CN–H_2O$ medium seems to stabilize the alkoxy radical. The linear product formation by this oxidizing system was explained by assuming the hydroxylation to proceed through **2** only (Eqs. 5, 6).



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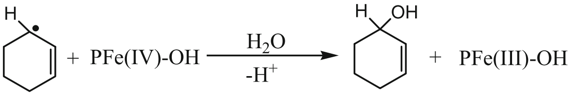

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However in order to establish that the alkoxy radical is involved in this reaction required further studies. Secondly the possible utilization of this alkoxy radical either in the dioxygen activation or autooxidation looked to be interesting and doable. Herein we present detailed demonstration that in presence of dioxygen, the high yield selective hydroxylation of cyclohexene to 2-cyclohexen-1-

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A. Agarwala · D. Bandyopadhyay (✉)
Department of Chemistry, Indian Institute of Technology Delhi, New Delhi 110016, India
e-mail: dkbp@chemistry.iitd.ac.in

ol was inhibited and this was supplemented by the formation of the keto and epoxide products in reasonably high yields. Similar results were also observed for cumene hydroperoxide, and not for hydrogen peroxide and iodisylbenzene. Attempts have been made to rationalize the results and the scope for further studies has also been discussed.

2 Experimental Section

2.1 Materials

Dichloromethane and acetonitrile were distilled under argon from P_4O_{10}. Methanol was distilled under argon from sodium metal. Cyclohexene was distilled under argon to remove the inhibitor and passed through silica gel column prior to any reaction. All the oxidation product standards, dodecane (internal standard) and iodopentafluorobenzene (internal standard) were purchased from Aldrich and were used as received without further purification. Pentafluoroiodosylbenzene (explosive [22]) was prepared by reported method [23]. The *t*-BuOOH was purchased from Aldrich as ~70% solution in water and CumOOH was purchased from Fluka as ~80% solution in cumene. H_2O_2 was obtained from Merck as ~30% solution in water. The exact active oxygen content of all these oxidants were determined iodometrically prior to use. All the iron-porphyrin catalysts were synthesized according to literature procedures [24–26].

2.2 Instruments

The UV-visible spectra were recorded using Perkin-Elmer Lambda (2S) spectrophotometer. The product analysis for cyclohexene oxidation was performed using Perkin-Elmer AutoSystemXL gas chromatograph equipped with flame ionization detector (FID) and carbowax capillary column of 30 m length.

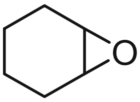
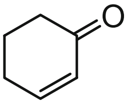
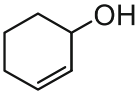
2.3 Catalytic Oxidation and Product Analysis

In all the experiments the iron-porphyrin catalyst (50 μM) and cyclohexene (200 mM) were first dissolved in 1.1 ml of a solvent mixture of $CH_3CN–H_2O$ (9.09%) or in 1.5 ml of CH_2Cl_2–MeOH (2:1) or in 1.6 ml of CH_3CN–MeOH (25%) in a 4 ml screw caped vial fitted with PTFE septa. The oxidation reactions were initiated by adding the oxidants (2 mM) at the end to the vial. This was followed by stirring the reaction mixture with a small magnetic bar and the reactions were carried out either under argon or under oxygen depending upon the objective of the study. After the reaction was over the reaction mixture was diluted with 2 ml of CH_2Cl_2 and 1 μL C_6F_5I was added to this diluted reaction mixture and an aliquot (~1 μL) was injected into the preheated GC column. The product identification and quantification were done from the known retention times of the products and the response factors of the products with the standards respectively. In case of samples containing water, the pre-treatment of such solutions with anhydrous solid $MgSO_4$ before injection into the GC column were done. In the product analysis of the oxidation reactions by C_6F_5IO, dodecane was used as the internal standard.

3 Results and Discussion

The oxidation reactions of cyclohexene (200 mM) with *t*-BuOOH (2 mM) in presence of F_{20}TPPFe(III)Cl (50 μM) were conducted in $CH_3CN–H_2O$ (9.09%) at 25 ± 2 °C under argon and under dioxygen and the product profiles were monitored by GC with time. In absence of any catalyst there was no oxidation of cyclohexene in any medium by C_6F_5IO, *t*-BuOOH, cum-OOH and H_2O_2 in 30 min. In presence of F_{20}TPPFeCl the oxidation of cyclohexene by *t*-BuOOH was completed in only 10 min when the reaction was conducted under argon and 2-cyclohexen-1-ol was the product (Table 1, entry 1). However in this reaction the characteristic band of **1** at 546 nm, formed immediately on the reaction of the catalyst with the oxidant, took only 4–5 min for it's complete decay to the known spectrum F_{20}TPPFe(III)-OH (Fig. 1) [19]. The characteristic UV-vis spectrum of F_{20}TPPFe(IV)=O has already been reported recently [21]. In presence of substrate (cyclohexene) the broad Q band of **1** was shifted by only 1 nm from 547 to 546 and there was no other change in this spectrum (not shown). Compound **1** was less stable if the quantity of water in the solvent was reduced as has also been observed by Nam et al. [8]. The rates of the formation of 2-cyclohexen-1-ol (~0.004 s^{-1}) and that of the decay of **1** (~0.012 s^{-1}) were very different from each other. This result indicates that only **1** could not be the major reactive intermediate responsible for the high yield hydroxylation reaction observed in this reaction. In case this reaction was conducted under dioxygen, the formation of 2-cyclohexen-1-ol was reduced and 2-cyclohexen-1-one was the major product (Table 1, entry 2). In this latter reaction the characteristic band of **1** at 546 nm remained very much stable while the product formation was continued (Fig. 2). In separate experiments we have noted that **1** was stable at least up to 1 h either in presence of argon or dioxygen and in absence of any substrate. In absence of oxygen the alkoxy radical formed via reaction 3 is utilized fully in reaction 4 for the formation of $F_{20}TPPFe^{+}$(IV)=O, which is the prime oxidant for alcohol formation (via Eqs. 5 and 6) [21]. In the system traces of water are present, therefore the

Table 1 F_{20}TPPFe(III)Cl catalyzed oxidation of cyclohexene in CH_3CN–H_2O (9.09%) at 25 ± 2 °C[a]

Entry	Catalyst	Oxidant	Atm. O_2/Ar	Rxn. time (min)	Products (% yields)[b]		
							
1	F_{20}TPPFeCl	*t*-BuOOH	Ar	10	0	0	97
2	F_{20}TPPFeCl	*t*-BuOOH	O_2	10	55	163	33
				30	54	215	45
3	F_{20}TPPFeCl	CumOOH	Ar	10	0	20	70
4	F_{20}TPPFeCl	CumOOH	O_2	10	18	145	35
				30	30	230	50
5	F_{20}TPPFeCl	H_2O_2	Ar	90	70	9	1
6	F_{20}TPPFeCl	H_2O_2	O_2	90	70	9	1
7	F_{20}TPPFeCl	C_6F_5IO	Ar	10	80	5	6
8	F_{20}TPPFeCl	C_6F_5IO	O_2	10	72	6	5

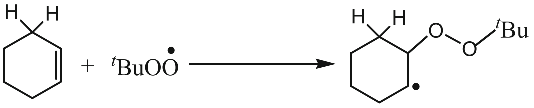
[a] Concentration of catalyst = 50 ± 2 μM; oxidant = 2 mM; cyclohexene = 200 mM in all the reactions

[b] Yields were based on total oxidant. Averages of duplicate sets of experiments are given

formation of alcohol is also possible via R-OO^{t}Bu. In presence of dioxygen, the alkoxy radical reacts with dioxygen faster than it reacts with F_{20}TPPFe(IV)=O and this could be the reason the F_{20}TPPFe(IV)=O spectrum remained stable under dioxygen. The most rational way to understand the product profile under dioxygen would be through a radical path as given in the Eqs. 7–13 [27].

$$ {}^t\mathrm{Bu}\dot{\mathrm{O}} + \mathrm{O}_2 \xrightarrow{\text{Fast}} {}^t\mathrm{BuOO}\dot{\mathrm{O}} \tag{7}$$

$$ 2\,{}^t\mathrm{BuOO}\dot{\mathrm{O}} \rightarrow {}^t\mathrm{BuO}\dot{\mathrm{O}} + \mathrm{O}_2 \tag{8}$$



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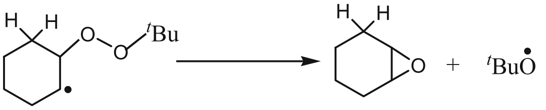

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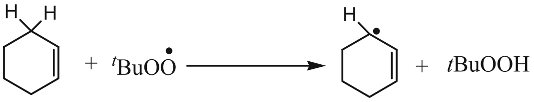

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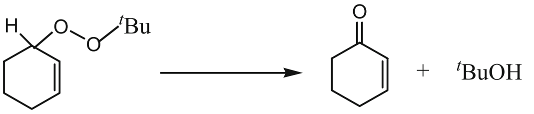


(13)

Thus Eqs. 7–10 explains the formation of the epoxide through the intermediacy of the alkoxy radical by consuming dioxygen and without any involvement of the porphyrin catalyst or the hydroperoxide. The formation of the ketone is understandable through Eqs. 11–13. For the formation of ketone *t*-BuOO radical is important and this is mainly formed in presence of dioxygen (Eq. 7) so we do not observe much ketone under argon. Here the hydrogen abstraction from cyclohexene by hydroperoxide radical (Eq. 12) may also be possible by more reactive alkoxy radical (not shown). Here also the formation of 2-cyclohexen-1-one does not require any porphyrin catalyst or the externally added hydroperoxide. This proposition is supported by our observation that the spectrum of **1** remained

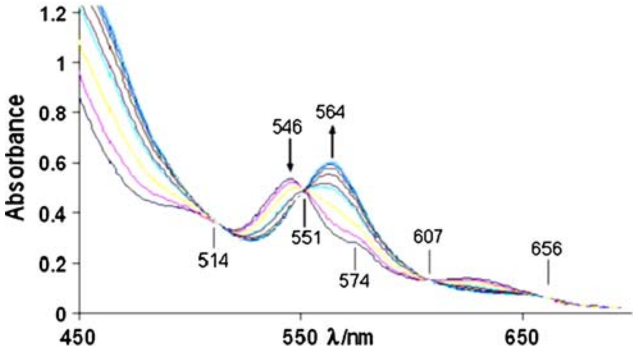


Fig. 1 Spectral change of F_{20}TPPFeCl during cyclohexene oxidation reaction under argon. Concentration of catalyst = 50 μM, *t*-Bu-OOH = 2 mM, cyclohexene = 200 mM. Path length of the cell = 1 cm. Spectral changes were taken at 1 min interval up to 10 min

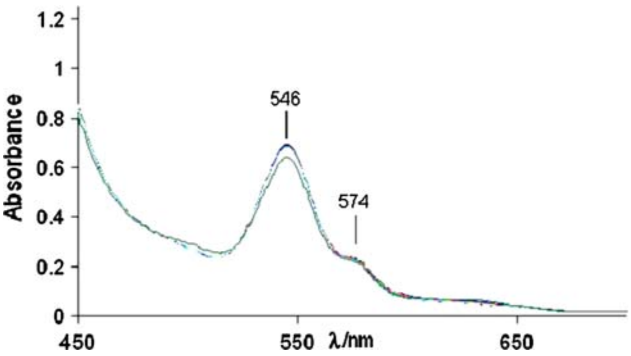


Fig. 2 Spectral change of F_{20}TPPFeCl during cyclohexene oxidation reaction under oxygen. Concentration of catalyst = 50 μM, *t*-BuOOH = 2 mM, cyclohexene = 200 mM. Path length of the cell = 1 cm. Spectral changes were taken at 1 min interval up to 10 min

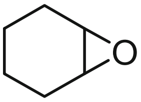
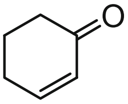
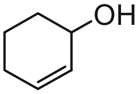
unchanged in presence of dioxygen, when product formation was continued and more than 100% (with respect to the *t*-BuOOH used) of the ketone was formed under dioxygen. The stability of similar oxo-iron(IV) porphyrin species in presence of dioxygen is not very surprising [28]. We believe that 1 atm of dioxygen is not sufficient enough to trap all the alkoxy radicals formed via Eq. 7, so the formation of alcohol via Eqs. 1–6 was indeed inhibited but it still remained operational. These reactions were then studied with cumene hydroperoxide (CumOOH), H_2O_2 and C_6F_5IO and the results are given in Table 1.

In case of CumOOH, the en-ol was the major product when the reaction was conducted under argon, however in presence of dioxygen the yield of the en-ol was diminished and the en-one was increased appreciably as in case of *t*-BuOOH (Table 1, entry 3, 4). In this reaction also the formation of **1** was observed spectroscopically.

In case of H_2O_2 the product profile was very different and dioxygen did not play any role on the product profile. Here the epoxide was the major product, secondly the time required for the formation of maximum product was longer (90 min, Table 1, entry 5, 6). This observation indicates the epoxidizing species is probably non-radical in nature and it is sluggish in its reactivity too. Thus it will be more rational to anticipate such intermediate as the catalyst-oxidant adduct rather than **2** [29]. The oxidation of cyclohexene with C_6F_5IO was completed within 10 min and in this reaction also no role of dioxygen was observed. In case of iodosylarenes the active involvement of **2** and the catalyst-oxidant adduct are proposed [30]. We believe the epoxidation of cyclohexene by C_6F_5IO under our experimental conditions was progressing through **2**.

These oxidation reactions were then conducted with two more catalysts: F_{16}TPPFe(III)Cl (F_{16}TPP = *meso*-tetrakis(2,3,5,6-tetrafluorophenyl)porphinato dianion) and F_8TPPFe (III)Cl (F_8TPP = *meso*-tetrakis(2,6-difluorophenyl) porphinato dianion) and the results are given in Table 2.

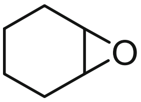
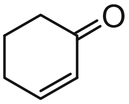
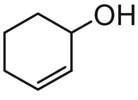
Table 2 Oxidation of cyclohexene in $CH_3CN–H_2O$ (9.09%) at 25 ± 2 °C[a]

Entry	Catalyst	Oxidant	Atm. O_2/Ar	Rxn. time (min)	Products (% yields)[b]		
							
1	F_{16}TPPFeCl	*t*-BuOOH	Ar	10	5	10	74
2	F_{16}TPPFeCl	*t*-BuOOH	O_2	10	7	98	24
3	F_8TPPFeCl	*t*-BuOOH	Ar	10	5	5	86
4	F_8TPPFeCl	*t*-BuOOH	O_2	30	53	169	32
5	F_{16}TPPFeCl	CumOOH	Ar	10	0	9	70
6	F_{16}TPPFeCl	CumOOH	O_2	10	0	90	20
				30	15	169	34
7	F_8TPPFeCl	CumOOH	Ar	10	0	9	65
8	F_8TPPFeCl	CumOOH	O_2	10	0	38	11
				30	0	64	17
9	F_{16}TPPFeCl	H_2O_2	Ar	90	60	7	2
10	F_{16}TPPFeCl	H_2O_2	O_2	75	62	7	2
11	F_8TPPFeCl	H_2O_2	Ar	90	34	7	2
12	F_8TPPFeCl	C_6F_5IO	Ar	10	70	3	4

[a] Concentration of catalyst = 50 ± 2 μM; oxidant = 2 mM; cyclohexene = 200 mM in all the reactions

[b] Yields were based on total oxidant. Averages of duplicate sets of experiments are given

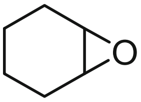
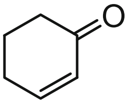
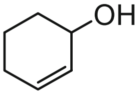
Table 3 Oxidation of cyclohexene in CH_2Cl_2–MeOH (2:1) at 25 ± 2 °C[a]

Entry	Catalyst	Oxidant	Atm. O_2/Ar	Rxn. time (min)	Products (% yields)[b]		
							
1	F_{20}TPPFeCl	*t*-BuOOH	Ar	30	66	13	08
2	F_{20}TPPFeCl	*t*-BuOOH	O_2	30	70	16	09
3	F_{20}TPPFeCl	CumOOH	Ar	30	40	20	10
4	F_{20}TPPFeCl	CumOOH	O_2	30	38	24	13
5	F_{20}TPPFeCl	H_2O_2	Ar	15	87	2	1
6	F_{20}TPPFeCl	H_2O_2	O_2	30	85	2	1
7	F_{20}TPPFeCl	C_6F_5IO	Ar	10	80	9	10
8	F_{20}TPPFeCl	C_6F_5IO	O_2	10	63	7	6

[a] Concentration of catalyst = 50 ± 2 μM; oxidant = 2 mM; cyclohexene = 200 mM in all the reactions

[b] Yields were based on total oxidant. Averages of duplicate sets of experiments are given

Table 4 Oxidation of cyclohexene in 25%MeOH in CH_3CN at 25 ± 2 °C[a]

Entry	Catalyst	Oxidant	Atm. O_2/Ar	Rxn. time (min)	Products (% yields)[b]		
							
1	F_{20}TPPFeCl	*t*-BuOOH	Ar	10	9	7	20
2	F_{20}TPPFeCl	*t*-BuOOH	O_2	60	34	46	16
3	F_{20}TPPFeCl	CumOOH	Ar	30	16	32	20
4	F_{20}TPPFeCl	CumOOH	O_2	75	23	43	14
5	F_{20}TPPFeCl	H_2O_2	Ar	15	81	3	2
6	F_{20}TPPFeCl	H_2O_2	O_2	30	74	3	1
7	F_{20}TPPFeCl	C_6F_5IO	Ar	10	67	10	8
8	F_{20}TPPFeCl	C_6F_5IO	O_2	10	68	9	8

[a] Concentration of catalyst = 50 ± 2 μM; oxidant = 2 mM; cyclohexene = 200 mM in all the reactions

[b] Yields were based on total oxidant. Averages of duplicate sets of experiments are given

This is clear from the results that all the three catalysts give similar results.

We recall that the *exo*-norbornene oxide was formed exclusively in 93% yields from norbornene in the F_{20}TPPFeCl catalyzed oxidation by *t*-BuOOH when the reaction was carried out in CH_2Cl_2–MeOH (2:1) solvent and that the reaction was very slow [11]. The involvement of catalyst-oxidant adduct was proposed as the major reactive intermediate in this reaction. Thus the F_{20}TPPFeCl catalyzed oxidation reactions of cyclohexene with the hydroperoxides, hydrogen peroxide and C_6F_5IO were conducted in this solvent and the results are given in Table 3. The data shows that in this solvent system (i) the epoxide was the major product irrespective of the oxidant was a hydroperoxide, hydrogen peroxide or iodosylarene, (ii) the reactions of hydroperoxide were still slower than that of hydrogen peroxide and (iii) there was absolutely no role of dioxygen on product profile.

In CH_2Cl_2–MeOH (2:1), the selectivity of all the oxidants were the same and neither of the hydroperoxides nor the hydrogenperoxide was suitable for hydroxylation reaction. There was no significant role of dioxygen in these oxidation reactions too. In this medium the non-radical catalyst-oxidant adducts seems to be stable and it could be the predominant reactive intermediate. It remained a question whether the solvent polarity was the reason for the selectivity. We measured the solvent polarity (E_T^N solvent polarity scale) by the reported method of Reichardt for $CH_3CN–H_2O$ (9.09%) and CH_2Cl_2–MeOH (2:1). The E_T^N values for these two solvents were 0.705 and 0.636 respectively [31]. In case the higher solvent polarity to be the reason for the observed hydroxylation, similar solvent mixture but of higher polarity should support hydroxylation. The CH_3CN–MeOH (25%) solvent was thus prepared to test this proposition because the measured polarity of this solvent mixture was 0.739, the value that is higher than that of $CH_3CN–H_2O$ (9.09%). In this solvent the oxidation reactions of cyclohexene were then conducted with all the four oxidants with F_{20}TPPFeCl as the catalyst and the results are given in Table 4. The results show that the solvent polarity is not the reason for the hydroxylation reaction. We believe that the relative strength of ligation of the components of the solvent mixture and the concerned oxidant is probably responsible to dictate the nature of the reaction.

4 Conclusions

In the iron(III) porphyrin catalyzed hydroxylation reactions by hydroperoxides the alkoxy radicals are involved and this alkoxy radical mediated oxygenation by dioxygen has been clearly demonstrated using cyclohexene as the probe substrate. We also conclude that in the reaction of iron(III) porphyrins with H_2O_2 and C_5F_5IO non-radical intermediates were evolved in aqueous acetonitrile and there was no observable hydroxylation reaction. We are investigating whether the radical generation from H_2O_2 could be the crucial step to achieve hydroxylation from this relatively bio-friendly oxidant.

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