Cytochrome P-450 model compound catalyzed selective hydroxylation of C–H bonds: Dramatic solvent effect

Arunava Agarwala and Debkumar Bandyopadhyay*

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Selective hydroxylation of cyclohexane and cyclohexene by *t*-BuOOH in presence of F_{20}TPPFe(III)Cl as the catalyst has been achieved at room temparature in high yields.

Among all the reactions catalyzed by the cytochrome P-450 family of enzymes the hydroxylation and epoxidation reactions have been studied very extensively.[1] The studies of the last few decades have indicated that the electronegatively substituted iron(III) porphyrin compounds such as F_{20}TPPFe(III)Cl, Cl_8TPPFe(III)Cl and Cl_8Br_8TPPFe(III)Cl are oxidatively very robust and are very good model compounds of this enzyme.[2,3] Such model compound catalyzed high yield epoxidation of alkenes by ArIO and MCPBA were achieved rather easily, but it remained very difficult with ROOH and HOOH for quite a long time.[4–6] It was the Traylor group who first reported the high yield epoxidations of alkenes by hydroperoxides and hydrogen peroxide and his conclusions are very useful still today.[7–9] Similarly the iron(III) porphyrin catalyzed hydroxylation of several C–H bonds have been achieved by ArIO and MCPBA, but it has not been so easy to date with ROOH or HOOH.[10–12] Herein we report the hydroxylation of cyclohexane to cyclohexanol in 47% yield and the selective hydroxylation of cyclohexene to 2-cyclohexen-1-ol in 97% yield by *t*-BuOOH in presence of F_{20}TPPFe(III)Cl as a catalyst. To the best of our knowledge these are the highest yield conversions of C–H bonds to C–OH bonds where the carbon is sp^3 hybridized and the terminal oxidant is a hydroperoxide.

It has been noted that in achieving the successful hydroxylation of alkanes by hydroperoxides the Traylor group used mixed solvents, such as CH_2Cl_2–MeOH–H_2O and CH_2Cl_2–MeOH.[10] These and similar other mixed solvents such as CH_3CN–H_2O, CH_2Cl_2–CH_3CN and CH_3CN–CH_2Cl_2–H_2O have also been used by others in hydroxylating various C–H bonds.[11] We observed that CH_3CN containing only 9.09% of H_2O is one of the best solvent systems to facilitate hydroxylation of cyclohexene and cyclohexane by *t*-BuOOH in presence of F_{20}TPPFeCl. For example, when a reaction mixture containing 50 μM of F_{20}TPPFe(III)Cl (F_{20}TPP = *meso*- tetrakis(pentafluorophenyl)porphinato dianion), 2 mM of *t*-BuOOH and 200 mM of cyclohexene in argon saturated CH_3CN containing 9.09% of water at 25 °C was allowed to react for only 10 min and then analyzed by GC, 2-cyclohexen-1-ol was found to be the only product formed in 96–98% yields. To the best of our knowledge this is the first report of cyclohexene oxidation by this oxidising system where hydroxylation is prevailed over epoxidation. In the above reaction when cyclohexane was used as the substrate, cyclohexanol was formed exclusively in 46–48% yields, however in this case the product formation was extended to 30 min. When these two substrates were taken together in the reaction mixture, both products, 2-cyclohexen-1-ol and cyclohexanol, were detected. The product distribution has certainly reflected the competitive rates of hydroxylation of these two substrate. However when the above oxidation reactions were carried out in MeOH–CH_2Cl_2 (1 : 2), cyclohexene was converted mainly to the epoxide as expected.[13] The conversion of cyclohexane to cyclohexanol was very poor in this latter medium. These results are given in Table 1.†

The above reactions were then carried out with another two 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), in order to follow the role of peripheral electronegative substituents on the product profile. These results are given in Table 2.† The data clearly indicate that there is not much difference in the product distribution from F_8TPPFe(III)Cl to F_{20}TPPFe(III)Cl. However F_{20}TPPFe(III)Cl gives better selectivity in the oxidation of cyclohexene. TMPFe(III)Cl gives very poor yields both in the hydroxylation and epoxidation reactions and these results are not shown here.

The UV-visible spectra of a 15.2 μM solution of F_{20}TPPFe(III)Cl in CH_3CN and that in CH_3CN–H_2O are not very different. All four electronic transitions of F_{20}TPPFeCl are only blue shifted with variable intensities (Fig. 1). The pyrrole β-proton signals of the F_{20}TPPFeCl in CD_3CN–D_2O is observed at 70.14 ppm. In CH_3CN–MeOH solvent the β-pyrrole protons of

Table 1 F_{20}TPPFe(III)Cl catalyzed oxidation of cyclohexene and cyclohexane by *t*-BuOOH at 25 °C[a]†

Substrate[b]	Solvent[c]	Reaction time (min)	Products (% yields)[d]
Cyclohexene	CH_3CN–H_2O	10	2-cyclohexen-1-ol (97)
	CH_2Cl_2–MeOH	30	epoxide(50) 2-cyclohexen-1-ol (14) 2-cyclohexen-1-one (8)
Cyclohexane	CH_3CN–H_2O	30	Cyclohexanol (47)
	CH_2Cl_2–MeOH	30	Cyclohexanol (06)
Cyclohexene + Cyclohexane	CH_3CN–H_2O	30	2-cyclohexen-1-ol (76) cyclohexanol (17)

[a] Concentrations of catalyst: 50 ± 2 μM; *t*-BuOOH = 2 mM; in all the reactions. [b] The cyclohexene and cyclohexane concentrations were 200 and 400 mM respectively. [c] CH_3CN–H_2O represents CH_3CN containing 9.09% of H_2O, and CH_2Cl_2–MeOH represents CH_2Cl_2 containing 33% of MeOH. [d] Yields were based on total oxidant. Averages of duplicate sets of experiments are given.

Department of Chemistry, Indian Institute of Technology, New Delhi, India. E-mail: dkbp@chemistry.iitd.ac.in; Fax: 911126584715; Tel: 911126591509

Table 2 F_{16}TPPFe(III)Cl and F_8TPPFe(III)Cl catalyzed oxidation of cyclohexene and cyclohexane by *t*-BuOOH at 25°C[a]†

Catalyst	Substrate[b]	Solvent[c]	Products (% yields)[d]
F_{16}TPPFeCl	Cyclohexene	CH_3CN–H_2O	2-cyclohexen-1-ol (74) 2-cyclohexen-1-one (10) epoxide (05)
		CH_2Cl_2–MeOH	epoxide (55) 2-cyclohexen-1-ol (14) 2-cyclohexen-1-one (05)
	Cyclohexane	CH_3CN–H_2O	cyclohexanol (47)
F_8TPPFeCl	Cyclohexene	CH_3CN–H_2O	2-cyclohexen-1-ol (86) 2-cyclohexen-1-one (05) epoxide (05)
		CH_2Cl_2–MeOH	epoxide (58) 2-cyclohexen-1-ol (14) 2-cyclohexen-1-one (08)
	Cyclohexane	CH_3CN–H_2O	cyclohexanol (43)

[a] Concentrations of catalyst: 50 ± 2 μM; *t*-BuOOH = 2 mM; in all the reactions. [b] The cyclohexene and cyclohexane concentrations were 200 and 400 mM respectively. [c] CH_3CN–H_2O represents CH_3CN containing 9.09% of H_2O, and CH_2Cl_2–MeOH represents CH_2Cl_2 containing 33% of MeOH. [d] The products of the hydroxylation reactions of cyclohexene and cyclohexane were measured after 10 and 30 min of the reaction respectively, and those of epoxidation reactions of F_{16}TPPFeCl and F_8TPPFeCl were measured after 30 and 90 min of the reaction respectively Yields were based on total oxidant. Averages of duplicate sets of experiments are given.

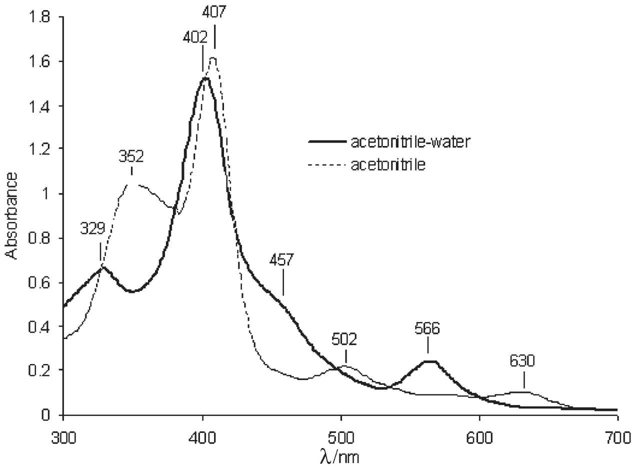


Fig. 1 UV-vis spectra of F_{20}TPPFeCl in acetonitrile and in acetonitrile–water. Concentration of catalyst = 15.2 μM; path length of the cell = 1 cm.

F_{20}TPPFeCl are observed at 65 ppm where the formation of F_{20}TPPFe(III)–OMe has been proposed.[9] These observations indicate the spin state of Fe(III) in CH_3CN–H_2O did not change and only the exchange of axial chloro to hydroxo ligand took place. Thus we represent eqn (1) as themost probable structural change of the catalyst in CH_3CN–H_2O. To this solution when *t*-BuOOH (2 mM) was added, the distinctly identifiable spectrum of PFe(IV) = O (**1**) was evolved (Fig. 2).[14,15]This spectral change represented by eqn (2) and (3) is hypothetical but seems reasonable. In MeOH–CH_2Cl_2 (1 : 2) such evolution of oxo iron(IV) has not been observed.

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

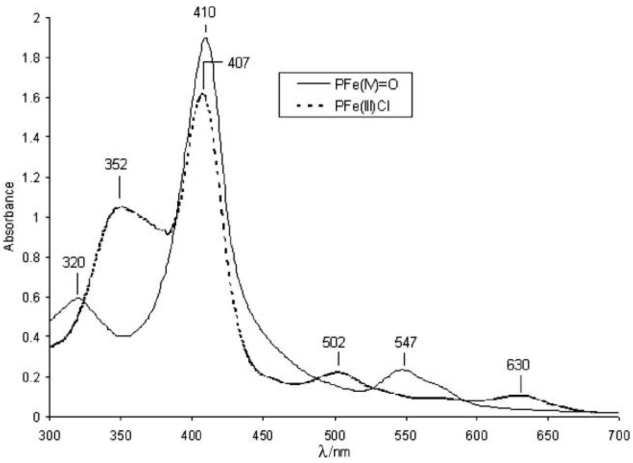


Fig. 2 UV-vis spectra of F_{20}TPPFeCl in acetonitrile and that of F_{20}TPPFe(IV)=O in acetonitrile–water. Concentration of catalyst = 15.2 μM; *t*-BuOOH = 2 mM; path length of the cell = 1 cm.

$$\mathrm{F_{20}TPPFe(III)\text{–}OH} + t\text{-BuOOH} = \mathrm{F_{20}TPPFe(III)\text{–}OO^{\mathit{t}}Bu + H_2O} \qquad (2)$$

$$\mathrm{F_{20}TPPFe(III)\text{–}OO^{\mathit{t}}Bu} \rightarrow \mathrm{F_{20}TPPFe(IV) = O} + t\text{-BuO}^{\bullet} \qquad (3)$$

In another set of experiments **1** was first generated *in situ* by reacting the oxidant (2 mM) with the catalyst (50 μM) in CH_3CN–H_2O and then it was reacted with cyclohexene of variable concentrations for only 10 min. The yields of 2-cyclohexen-1-ol were: 31, 42, 51, 71 and 97% when the cyclohexene concentrations were 25, 50, 100, 150 and 200 mM respectively. This linear increase of the single product from 31 to 97% (Fig. 3) indicates that probably only one oxidant is primarily involved in this hydroxylation reaction. In all such reactions the spectra of PFe(III)–OH (bold line, Fig. 1) before and after the reaction remained unchanged, showing that there was no degradation of catalyst during these reactions and F_{20}TPPFe–OH is the active catalyst. We propose that the reactions shown in eqn (4)–(6) are mainly responsible for the hydroxylations, and oxo-iron(IV) porphyrin cation radical (**2**) is the only hydroxylating species.

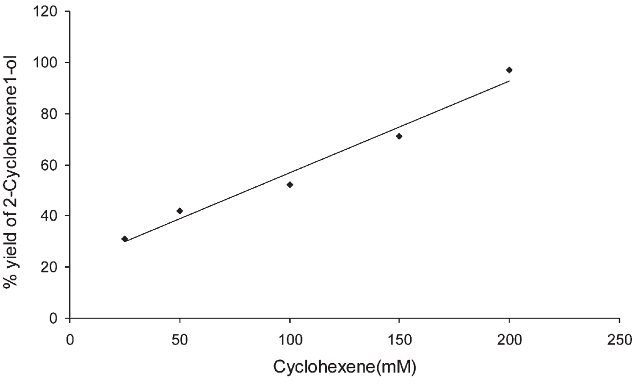
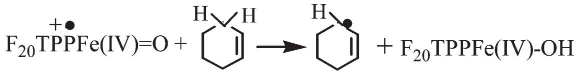


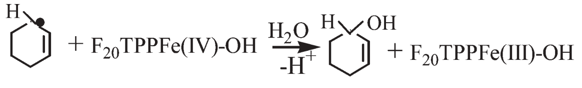
Fig. 3 Linear increase of 2-cyclohexen-1-ol yield with increasing cyclohexene concentration. Concentration of catalyst = 50 ± 2 μM; concentration of *t*-BuOOH = 2 mM. Yields are based on the total oxidant

This proposition is in accord with the literature reports that **1** cannot epoxidize alkenes and hydroxylate alkanes that efficiently and that **2** is more reactive than **1**.[14–17] The formation of **2** (eqn (4)) is extremely crucial in achieving the hydroxylation reaction and this step seems to be highly solvent sensitive. In $CH_3CN–H_2O$ neither component is that easily oxidizable, so in this solvent system **2** abstracts a hydrogen atom from the substrate only (eqn (5)). This could be the reason for theobserved hydroxylation in $CH_3CN–H_2O$ and not in CH_2Cl_2–MeOH. The final hydroxylation step (eqn (6)) may be progressing by the rebound type mechanism originally proposed by Groves. We believe that the PFe(III)–OO^tBu (**3**) is mainly responsible for the slow epoxidation of cyclohexene in CH_2Cl_2–MeOH (2 : 1). However its slow transformation to **1** or **2** and their immediate reaction with MeOH cannot be overruled. This probably explains the slow and inefficient transformation of cyclohexene to the epoxide in methanolic solvent. The H^+ and t-BuO^- evolved from eqn (6) and (4) respectively recombines to give t-BuOH (eqn 7) as the reduced product of t-BuOOH consumedin eqn 2. The catalytic cycle will thus start from eqn (1) and will proceed up to eqn (6) where F_{20}TPPFe(III)–OH will be regenerated, so that the next cycle will start from eqn (2) and not from eqn (1). In order to get the full utility of the oxo-iron(IV) porphyrin cation radical the most obvious side reactions represented by eqn (8) to (10) are to be suppressed. Increasing the substrate concentration was one of the options, and this has been the case in the hydroxylation reactions of cyclohexene in $CH_3CN–H_2O$ medium (Fig. 3). In order to test the importance of eqn (3), when we conducted hydroxylation of cyclohexene in $CH_3CN–H_2O$ but in the presence of O_2, the major product was 2-cyclohexen-1-one and the yield of 2-cyclohexen-1-ol was dramatically reduced. This was expected because the t-$BuO^{\bullet}$ radical will initiate auto oxidation of cyclohexene, 2-cyclohexen-1-one will be the major product and formation of **2** (eqn (4)) will be disrupted.

$$F_{20}TPPFe(IV){=}O + t{-}BuO^{\bullet} \xrightarrow[-tBuO^{-}]{} F_{20}\,\overset{+}{T}\,\overset{\bullet}{P}\,PFe(IV){=}O \quad (4)$$



(5)



(6)

$$H^+ + t\text{-}BuO– = t\text{-}BuOH \quad (7)$$

$$t\text{-}BuO^{\bullet} + t\text{-}BuOOH = t\text{-}BuOO^{\bullet} + t\text{-}BuOH \quad (8)$$

$$F_{20}\,\overset{+}{T}P\,\overset{\bullet}{P}F\,e(IV){=}O + t{-}BuOOH = t{-}BuOO^{\bullet} + F_{20}TPPFe(IV){-}OH \quad (9)$$

$$2\ t\text{-}BuO^{\bullet} = t\text{-}BuOO^tBu \quad (10)$$

In summary the F_{20}TPPFe(III)Cl catalyzed selective and efficient hydroxylation of cyclohexene to 2-cyclohexen-1-ol has been achieved by t-BuOOH at room temperature from aqueous acetonitrile medium. The shifting of medium to CH_2Cl_2–MeOH has produced epoxide as the major product. The hydroxylation of cyclohexane to cyclohexanol has also been achieved by the same oxidizing system in 47% yields from the same aqueous acetonitrile medium. Studies in this laboratory are focused understanding the reason of this remarkable solvent effect and to further improve the efficiency of hydroxylation of cyclohexane and its possible industrial application.

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Notes and references

† Experimental Section: In a typical reaction 50 μM of catalyst and 200–400 mM of substrate were dissolved in 1.1 ml of argon saturated solvent mixture of $CH_3CN–H_2O$ in a small screw capped vial fitted with PTFE septa. The oxidation reaction was initiated by adding 2 mM of t-BuOOH and the contents were magnetically stirred for 10–30 min under argon. The standard solution of C_6F_5I was added to this reaction mixture and an aliquot was injected into a capillary column (carbowax, 30 meter) of a preheated GC. The identification and the quantitation of the products were done from the response factors of standard product samples as usual.

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