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Efficient iron(III) porphyrins-catalyzed oxidation of guanidoximes to cyanamides in ionic liquids

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Abstract. Water soluble iron(III) porphyrins immobilized in imidazolium ionic liquids serve as an effective catalyst for the H_2O_2 mediated oxidation of guanidoximes to selectively give corresponding cyanamides in good yields. The use of ionic liquid with non-coordinating counter anion PF_6 affords the product in high yield by facilitating the formation of anionic iron peroxo intermediate.

Keywords. Cyanamide; guanidoxime iron(III) porphyrins; ionic liquids; nitric oxide synthase.

1. Introduction

Guanidoxime (*N*-hydroxyguanidine) (**1**) is a model substrate of nitric oxide synthase (NOS) that plays a key role in the physiological activities of mammals and plants.[1] The NOS catalyzes the oxidation of the guanidine group of *L*-arginine with intermediate formation of *N*-hydroxy-*L*-arginine (NOHA) that requires heme, FAD, FMN and tetrahydrobiopterine (BH_4) as co-factors, and NADPH and O_2 as co-substrates.[2,3] The NOS fully saturated with BH_4 oxidises NOHA to *L*-citrulline, whereas BH_4-free NOS catalyzes the oxidation of NOHA to a mixture of *L*-citrulline and *N*-cyano-*L*-ornithine (scheme 1). Cytochrome P450-dependent monooxygenases (P450) have also been reported to catalyze the oxidative transformation of NOHA and its analogues to corresponding carbonyl and nitrile products.[4,5] It has been observed that the product distribution (nitrile/carbonyl yield ratio) in enzymatic or chemical systems varies on changing the substrate (NOHA, ketoximes, aldoximes, amidoximes or guanidoximes), nature of oxidants and catalysts used in the reactions.[6–9] For instance, the oxidation of *N*-aryl derivatives of guanidoximes with KO_2[6] or by microperoxidase 8 (MP 8) in combination with H_2O_2[7] selectively afford *N*-aryl cyanamides as the main products with formation of only minor amounts of *N*-arylureas (scheme 1). The N-alkyl derivative of guanidoxime such as NOHA also oxidises by MP 8 to *N*-cyano-*L*-ornithine (cyanamide) along with a little amount of *L*-citrulline. However, *N*-cyano-*L*-ornithine being unstable could not be isolated.[7] The oxidation of guanidoximes by potassium ferricyanide, silver carbonate or lead oxide is also known to yield cyanamide as the main product.[10]

Various chemical models have been developed to understand the heme enzymes catalyzed oxidative transformations of NOHA and their analogues to corresponding carbonyl products in recent years.[8,11–13] However, the reports on their selective transformation to corresponding nitrile products are limited.[14,15] Nitriles are very important synthetic intermediates for pharmaceuticals, agricultural chemicals, dyes and material sciences.[16] Despite the recent progress, there is still a strong need to develop a preparative, efficient and biomimetic catalytic system for the selective conversion of oximes to nitriles under mild conditions.

The combination of iron(III) porphyrins and monooxygen donors have been used as chemical models of P450 and related heme enzymes to mimic various oxygenation and oxidation reactions.[17] Ionic liquids (ILs) are potential green solvents for various chemical and biochemical transformations.[18] Metalloporphyrinoids catalyzed various reactions have also been studied in ILs whereby ILs act as catalyst, co-catalyst, ligand source or reaction media.[19–22] Recently, we have reported the iron(III) porphyrin catalyzed oxidation of aldoximes and ketoximes to corresponding carbonyl products in ILs.[11] Thereafter, we aimed to prepare aromatic analogues of NOHA *i.e.*, *N*-aryl-*N*-hydroxyguanidines and to study their oxidations with H_2O_2 catalyzed by iron(III) porphyrins to present a precise biomimetic system. We expected to obtain corresponding carbonyl products, but to our surprise,

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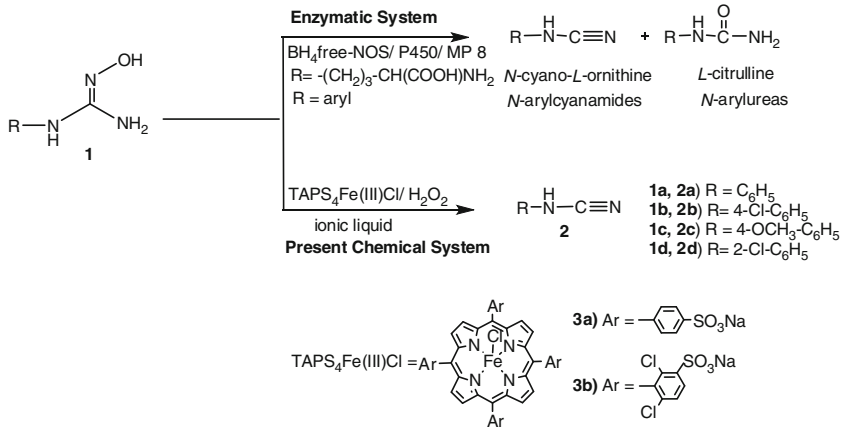


Scheme 1. Oxidation of guanidoximes by enzymatic and present chemical system.

nitrile products (cyanamides) were obtained selectively after oxidation reactions. The results stimulated us to study these reactions in detail to understand the mechanism of formation of cyanamides from guanidoximes. Herein, we report the oxidation of different *N*-aryl guanidoximes (**1a–1d**) to corresponding cyanamides (**2a–2d**) with H_2O_2 catalyzed by water soluble anionic iron(III) porphyrins [$TAPS_4Fe(III)Cl$] (**3a–3b**) in imidazolium ILs under different conditions (scheme 1).

2. Experimental

The ionic liquid [bmim][Br] has been synthesized by refluxing the mixture of *N*-methyl imidazole and *n*-butyl bromide at 70°C for 24 hr.[19] The ionic liquids [bmim][BF_4] and [bmim][PF_6] have been prepared from [bmim][Br] by treatment with $NaBF_4$ and KPF_6 respectively. The iron(III) 5,10,15,20-tetrakis(4-sulfonatophenyl) porphyrin (**3a**) and iron(III) 5,10,15,20-tetrakis(2,6-dichloro-3-sulfonatophenyl) porphyrin (**3b**) have been synthesized by metallation of corresponding free base porphyrins with ferrous chloride in dimethyl formamide solvent as reported in literature.[23] The guanidoximes (**1a–1d**) have been prepared by following the literature procedure which involves the reaction of corresponding aromatic amine with BrCN followed by treatment with hydroxylamine hydrochloride.[1,24]

2.1 *Representative procedure for the oxidation of guanidoximes (**1a–1d**) with H_2O_2 catalyzed by water soluble iron(III) porphyrins (**3a–3b**)*

Hydrogen peroxide (2.0 mmol, 226 μl, 30% v/v) was added with stirring to a solution of water soluble iron(III) porphyrins (**3**) (0.01 mmol) and guanidoxime (**1**) (1.0 mmol) in ionic liquid (3 mL). The reaction mixture was stirred for 5 h at room temperature. On completion of the reaction, the mixture was extracted with ethyl acetate (a mixture of ethyl acetate and diethyl ether was used in case of [bmim][PF_6] ionic liquid) and the ionic liquid containing **3** was recovered and reused for catalyzing further oxidation reactions. The ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The products were isolated by column chromatography over silica gel (60–120 mesh) using methanol/dichloromethane mixtures as eluents. The cyanamide products (**2a–2d**) were identified and characterized by ^{1}H NMR, IR and MS spectral data that concur with the reported data.[25,26]

3. Results and Discussion

The oxidation of guanidoxime (**1a**) with H_2O_2 in the absence of catalyst [$TAPS_4Fe(III)Cl$] (**3a–3b**) did not produce cyanamide (**2a**) (table 1) and **1a** was recovered in 99% yield even after 10 h. The reaction

Table 1. Oxidation of guanidoximes (**1a–1d**) with H_2O_2 catalyzed by **3** in ILs.

Entry	System[a]	Ionic Liquid	Yield of **2** (**a–d**) (%)[b]
1	**1a**/H_2O_2	[bmim][Br]	0
2	**1a/3a**/H_2O_2	[bmim][Br]	65
3	**1a/3b**/H_2O_2	[bmim][Br]	76
5	**1b/3b**/H_2O_2	[bmim][Br]	79
6	**1c/3b**/H_2O_2	[bmim][Br]	70
7	**1d/3b**/H_2O_2	[bmim][Br]	75
8	**1a/3b**/H_2O_2	[bmim][BF_4]	82
9	**1a/3b**/H_2O_2	[bmim][PF_6]	89

[a]Reaction conditions: guanidoxime (**1a–1d**) (1.0 mmol), H_2O_2 (2.0 mmol), iron(III) porphyrin (**3a–3b**) (0.01 mmol), IL (3.0 mL). The reaction mixture was stirred at room temperature for 5 h.
[b]yields refer to isolated products

of **1a** with H_2O_2 catalyzed by iron(III) 5,10,15,20-tetrakis(2,6-dichloro-3-sulfonatophenyl) porphyrin (**3b**) in [bmim][Br] gave product **2a** in 38% yield after 1 h. and yield improved to 76% on prolonging the reaction for 5 h. (table 1, figure 1). The use of catalyst **3a** in the reaction afforded **2a** in lesser yield (65%) in [bmim][Br] (table 1). The efficiency of the catalytic system improved on increasing the amount of H_2O_2, however, not much increase in yield of product **2a** was observed after using more than 3 mmol of H_2O_2 *vs.* **1a** (figure 2). The use of 2 mmol of H_2O_2 *vs.* **1** was preferred in the reaction as with excess of H_2O_2 an unidentified side product was observed in trace amount. The influence of the nature of the substituent at *para* position of the phenyl ring of **1** was studied by performing the oxidation of **1b** and **1c**. It was observed that **1c** bearing electron-donating groups -OCH_3 group exhibited lower oxidation potential (70% yield) than **1b** bearing electron-withdrawing group -Cl group (79% yield) (table 1). The present oxidative system worked well with guanidoxime bearing a substituent at *ortho* position in phenyl ring and (2-chlorophenyl)cyanamide (**2d**) was isolated in good yield after reaction with **1d** (table 1).

To study the effect of anion of imidazolium IL on the oxidation of **1**, two different ILs [bmim][BF_4] and [bmim][PF_6] were prepared from [bmim][Br] by anion exchange method.[19] The reaction conditions were also optimized for [bmim][BF_4] and [bmim][PF_6] by monitoring the reaction of **1a** with different concentration of H_2O_2 and at different time intervals (figures 1 and 2). The yield of **2a** increased with high concentration of

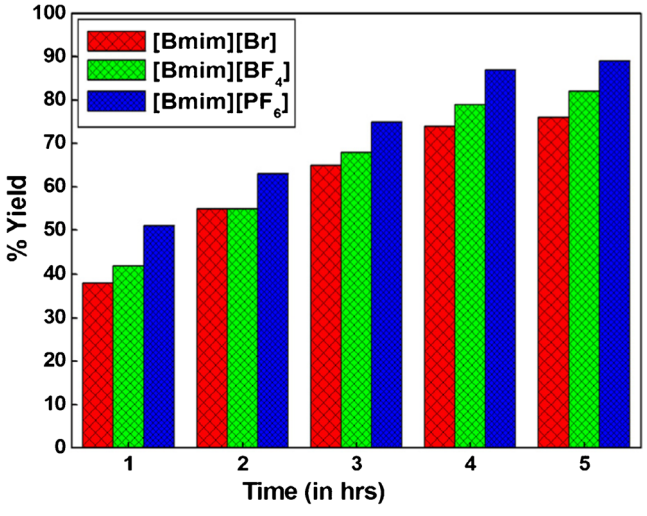


Figure 1. Oxidation of **1a** to give **2a** with H_2O_2 catalyzed by **3b** at different time intervals. Reaction conditions: guanidoxime (**1a**) (1.0 mmol), H_2O_2 (2.0 mmol), iron(III) porphyrin (**3b**) (0.01 mmol), IL (3.0 mL).

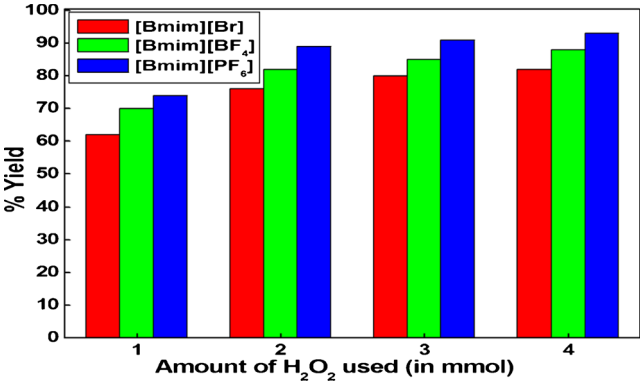


Figure 2. Effect of concentration of H_2O_2 on the yield of **2a** formed by the oxidation of **1a** with H_2O_2 catalyzed by **3b** after 5 hr. reaction conditions: guanidoxime (**1a**) (1.0 mmol), H_2O_2 (1.0–4.0 mmol), iron(III) porphyrin (**3b**) (0.01 mmol), IL (3.0 mL).

H_2O_2 on prolonging the reaction from 1 hr to 5 h. It is interesting to observe that the oxidation of **1a** to form **2a** increases with the change of anions of imidazolium IL in the line of Br (76% yield) <BF_4 (82% yield) < PF_6 (89% yield) (table 1). To study the impact of different ILs on catalyst, the UV-vis titration of **3b** were performed on addition of different ILs. A slight red shift with enhanced absorption intensity was observed in the Soret band at 423 nm after every addition of IL in the solution of **3b** in water (figure 3), indicating the ionic/π-π interaction between IL with iron-porphyrin.[27] It was noteworthy that the enhancement in the absorption intensity was more pronounced with [bmim][PF_6] which could be ascribed to the most non-coordinating nature of [bmim][PF_6] making the imidazolium part of IL more available to interact with porphyrin ring **3b**.[28] To support this interaction, ^{1}H-NMR titrations of ILs on addition of solution of **3b** in D_2O were performed. In ^{1}H-NMR spectrum of [bmim][Br]

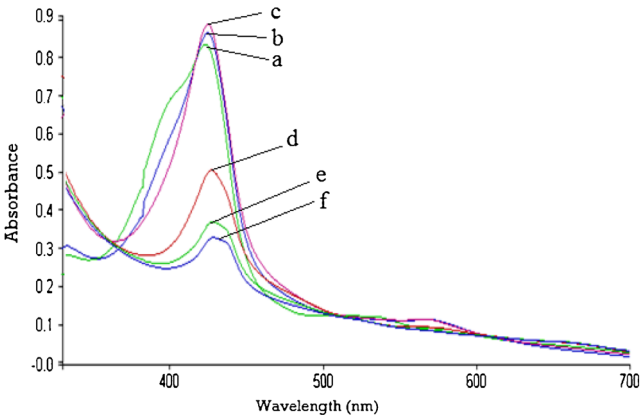


Figure 3. UV-Vis spectra of **3b** (a) with increasing concentration of [bmim][PF_6] (b-c) and after addition of H_2O_2 at time interval of 1 min (d-f).

and [bmim][BF_4], a significant up-field shift in the signals for all the protons was observed after addition of **3b** solution in D_2O, however, the signal for C-2 proton of [bmim][PF_6] exhibited down-field shift under similar conditions (figure 4). This diverse behaviour indicates that C-2 proton of [bmim][PF_6] with stronger H-bond tendency[29] is involved in interaction with anionic porphyrin ring **3b**. Considering the interaction of ILs with iron-corroles[30] and iron-porphyrins,[21] the C-2 proton of [bmim][PF_6] is believed to H- bonded with axial ligand –Cl of Fe-Cl bond of iron-porphyrin (**3b**), facilitating the formation of reactive reaction intermediate. The H-bonding interaction of C-2 proton of [bmim][Br] and [bmim][BF_4] with axial ligand –Cl could be relatively weak, making it difficult to be observed by ^{1}H-NMR spectral analysis.

To investigate the reusability of the present catalytic system, the stability and immobilization of **3b** in IL was studied by UV-vis spectroscopy. After isolation of product from the reaction mixture, the solution of **3b** in [bmim][PF_6] was extracted with ethyl acetate and diethyl ether and the extracts were screened with UV-vis spectroscopy. There was no characteristic Soret band for iron(III) porphyrins in the region of 410–430 nm, showing that the catalyst was completely immobilized in ILs without any appreciable leaching. The UV-vis spectrum of **3b** immobilized in [bmim][PF_6] exhibited a very less decrease in Soret band, suggesting the high stability of catalyst in ILs. Thereby, **3b** immobilized in [bmim][PF_6] was conveniently recycled after extraction of the product from first cycle and it retained good catalytic activity up to four consecutive cycles (figure 5).

In metalloporphyrin catalyzed oxidation reactions, similar to heme enzymes catalyzed various reactions in biological systems, different electrophilic and nucleophilic reactive intermediate species such as a ferric hydroperoxy complex (Fe^{III}–OOH), ferric peroxy anions (FeIII–OO^-) and high valent iron(IV)oxo porphyrin radical cation radicals ($Fe^{IV=}O^{\cdot+}$), have been postulated.[31] The nature of solvent used in the reaction and electronic effect of substituents as well as axial

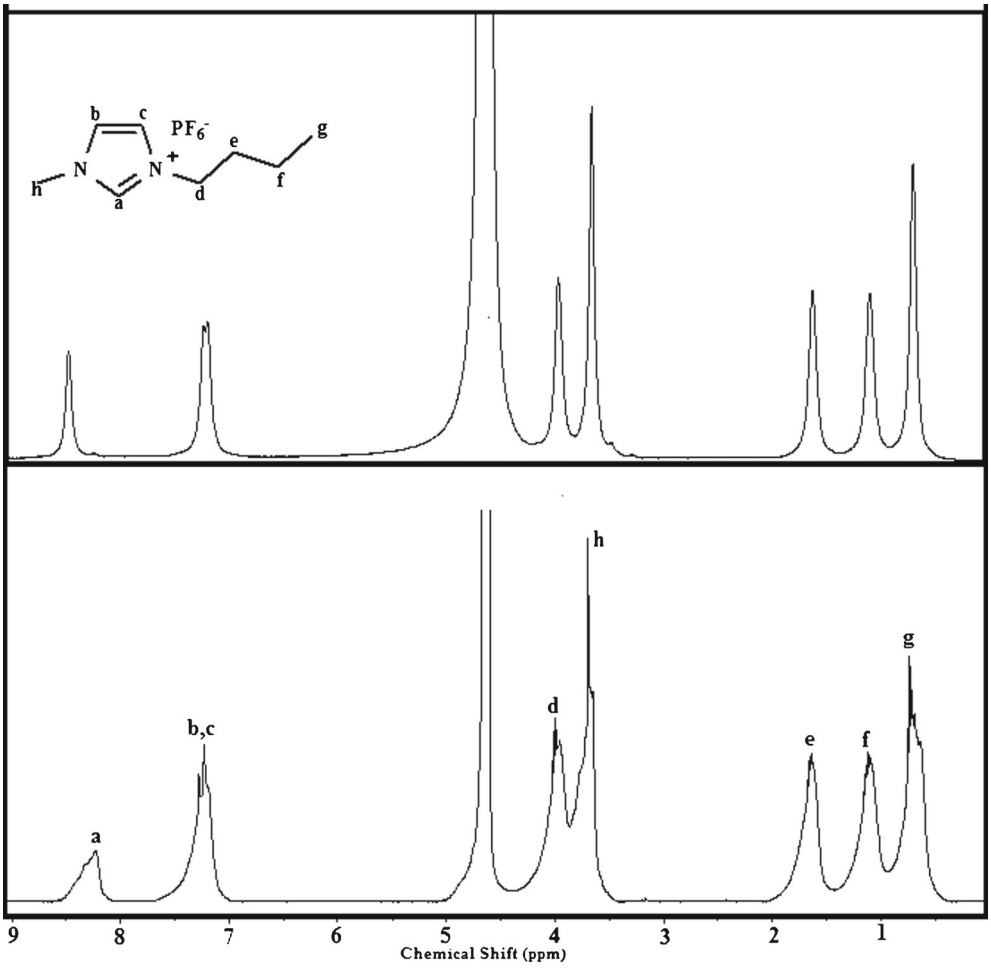


Figure 4. The ^{1}H-NMR spectra of [bmim][PF_6] in D_2O (resolution is low due to poor solubility) (a) on addition of solution of **3b** in D_2O (b).

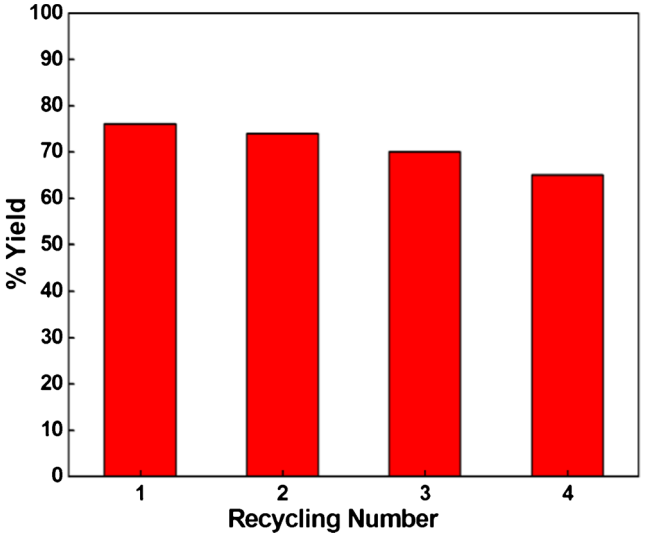
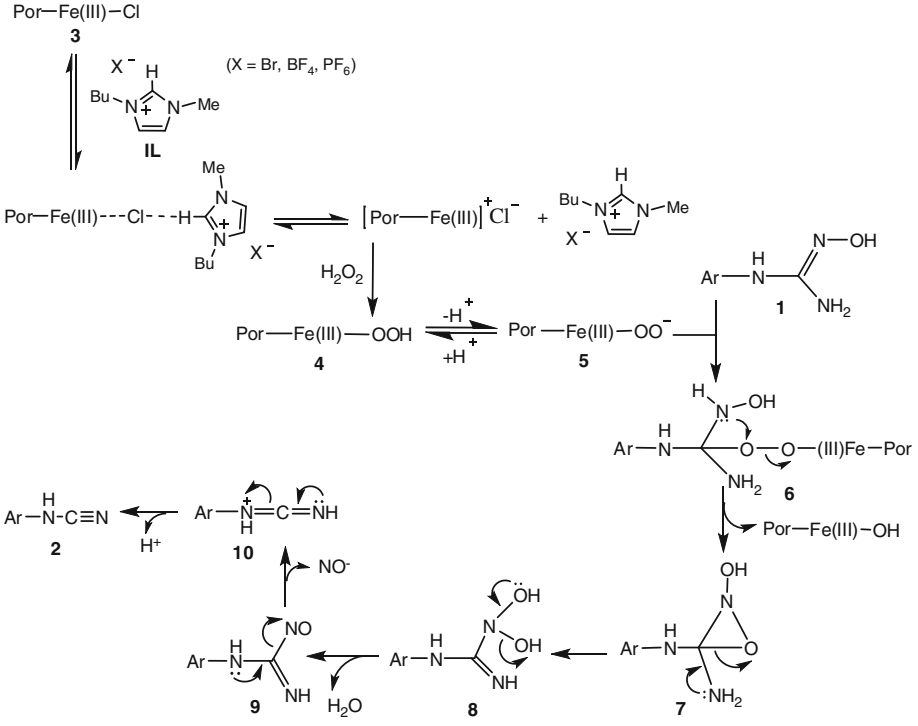


Figure 5. Reusability of iron(III) porphyrin (**3b**) on the oxidation of **1a** to **2a**. Conditions: **1a**: 1 mmol; catalyst: 0.01 mmol; H_2O_2: 2mmol; time = 5 h at r.t.

ligands in porphyrin ring play a vital role in directing the system to generate electrophilic or nucleophilic catalytic intermediate.[32] The H-bonding interaction of C-2 proton of imidazolium cation of ILs with Fe-Cl bond of iron(III) porphyrin catalyst [Por-Fe(III)Cl] (**3**) is believed to make Fe-Cl bond weak which may lead to the formation of transient $[Por\text{-}Fe(III)]^+$ species[30] (scheme 2). The formation of $[Por\text{-}Fe(III)]^+$ species is favoured more in [bmim][PF_6] IL as PF_6 anion is more available to stabilize $[Por\text{-}Fe(III)]^+$ species due to its low coordinative ability. This transient species promotes the rapid attack of H_2O_2 on iron centre of **3** leading to the formation of hydroperoxo complex (**4**) which equilibrate to anionic iron peroxo intermediate (**5**) (scheme 2). The effect of ILs on the conformation of porphyrins is also known.[33] The formation of intermediate **5** was confirmed by UV-vis spectrum of **3b** which showed a red shift in Soret band with deceased intensity on addition of H_2O_2 (figure 3).[20,22] The stabilization of anionic iron peroxo intermediate (**5**) by H-bond interaction of C-2 proton of non-coordinating imidazolium ILs[34] could be another governing factor for the generation of nucleophilic intermediate **5** which could attack at electrophilic carbon of >C=N-OH bond in **1**. The similar effect of non-coordinating nature of ILs to accelerate the reaction rate by stabilizing the highly charged iron-peroxo or iron-oxo intermediate generated in the rate-determining step for cytochrome-c, microperoxidase-11 and hemin has been reported.[35] The crucial role of ILs in stabilization of highly charged peroxo or oxo intermediates (compound 1 of cytochrome P450) generated in the reaction catalyzed by iron(III)porphyrins and manganese(III) porphyrins have also been described.[36,37]

The oxidative conversion of guanidoximes (**1**) to cyanamides (**2**) is believed to proceed with the nucleophilic attack of anionic iron peroxo species (**5**) on >C=N-OH bond of **1** to generate a peroxo complex



Scheme 2. Proposed mechanism for the oxidation of guanidoximes (**1a–1d**).

6. The iron peroxo complex **6** then cyclises to give *N*-hydroxyoxazirine ring **7** (scheme 2). The presence of aryl group in **7** could contribute towards the stabilization of oxazirine intermediate and may direct the regioselective amine-assisted oxazirine ring opening to give a dihydroxylated guanidinium species **8**. The elimination of water from **8** gives intermediate **9**. On release of nitroxyl anion (NO^-), **9** converts into **10** which then by loss of proton gives cyanamide product (**2**). This mechanism is in accordance with NOS catalyzed reactions of analogues substrates.[38]

4. Conclusion

The system of water soluble iron(III) porphyrin immobilized in ionic liquid presents a greener reusable chemical model of heme enzymes for the selective oxidation of guanidoximes to cyanamides with H_2O_2 at room temperature. The use of iron(III) porphyrins bearing electron withdrawing –Cl groups and high molar ratio of H_2O_2 gives excellent yield of cyanamide product. The activity of catalyst in ionic liquid [bmim][PF_6] is significantly high which can be ascribed to H-bonding interaction of C-2 proton of non-coordinating [bmim][PF_6] with axial ligand –Cl of iron-porphyrin favouring the formation of anionic iron-peroxo reactive intermediate.

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