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## COMMUNICATION

## Oxoiron(IV)-mediated Baeyer-Villiger oxidation of cyclohexanones generated by dioxygen with co-oxidation of aldehydes.

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In this communication we describe a detailed mechanistic studies on the  $[\text{Fe}^{\text{II}}(\text{CH}_3\text{CN})(\text{N4Py})(\text{ClO}_4)]\text{ClO}_4$ -catalyzed (N4Py = *N,N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine) Baeyer-Villiger oxidation of cyclohexanones by dioxygen with cooxidation of various aldehydes, including the kinetics on the formation and the reactivity of the trapped and spectroscopically characterized oxoiron(IV) intermediate.

Baeyer-Villiger oxidation is one of the most important reactions in organic chemistry because the lactones or esters are important industrial intermediates in the production of polymers, pharmaceuticals and herbicides.<sup>1</sup> The most common oxidants used for this reaction are peroxyacetic acids.<sup>2</sup> Over the past four decades transition metal complexes of a variety of ligand systems like porphyrins, Schiff bases, isoindolines, polypyridines etc. have been reported as active catalysts for the catalytic oxygen transfer reactions,<sup>3</sup> and their catalytic cycles often involve oxoiron(IV) intermediates as oxidants.<sup>4</sup> Within the past decade more than 60 oxoiron(IV) complexes, including  $\text{S}=\text{1}^{4\text{f}}$  and  $\text{S}=\text{2}^{5}$  ground states, have been produced by reactions of precursor complexes with externally prepared oxidizing compounds (in which oxygen is already partly reduced) such as iodosylbenzene (PhIO), *m*-chloroperoxybenzoic acid (*m*-CPBA), and hydroperoxides ( $\text{H}_2\text{O}_2$  and  $\text{RO}_2\text{H}$ ). However, only few examples exist for their generation by activating dioxygen.<sup>6</sup> Since the molecular oxygen is a cheap, environmentally clean and readily oxidant, the use of  $\text{O}_2$  as the primary oxidant is of fundamental importance. Oxoiron(IV) species can be prepared in solvent mixtures of  $\text{CH}_3\text{CN}$ /alcohols<sup>6a</sup> or  $\text{CH}_3\text{CN}$ /ethers<sup>6b</sup>, furthermore in the presence of an electron donor (dihydroxynicotinamide adenine dinucleotide (NADH)<sup>6c</sup> analogue or  $\text{BPh}_4^-$ ) and proton source ( $\text{HClO}_4$ ). Dioxygen activation using an aldehyde as a reductant is a very simple and practical oxidative system that is able to

epoxidize alkenes,<sup>7</sup> Baeyer-Villiger oxidation of ketones<sup>8</sup> and oxidation of alcohols and of some hydrocarbons.<sup>9</sup> These processes proceed via a free radical chain mechanism, and without transition metal catalyst are often of low efficiency and selectivity. Metal complexes depending on their reduction power can accelerate or inhibit the above processes.<sup>10</sup> There are some reports on the aerobic Baeyer-Villiger oxidation of ketones to esters or  $\varepsilon$ -lactones catalysed by iron catalysts with aldehyde as reductant, but until now, no direct evidence for the involvement of a high-valent oxoiron species in the catalytic process.<sup>11</sup>

We have found that complex  $[\text{Fe}^{\text{II}}(\text{CH}_3\text{CN})(\text{N4Py})](\text{ClO}_4)_2$  (**1**) (N4Py = *N,N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methylamine) highly selectively and efficiently catalyse the Baeyer-Villiger (B.-V.) oxidation of cyclohexanone derivatives to  $\varepsilon$ -caprolactones with molecular oxygen in the presence of various aldehydes such as isobutyraldehyde and benzaldehyde (Fig. 1, and Table S1, ESI†).

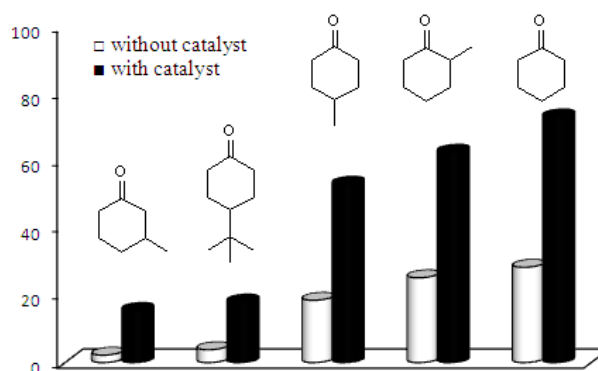


Fig. 1. Yields without and with catalyst for the **1**-catalysed B.-V. oxidation of cyclohexanones with benzaldehyde in MeCN at 60°C under oxygen atmosphere for 15 hours.  $[\mathbf{1}]_0 = 1.00 \times 10^{-5}$  M,  $[\text{cyclohexanone derivatives}]_0 = 1.00 \times 10^{-2}$  M,  $[\text{benzaldehyde}]_0 = 1.50 \times 10^{-1}$  M.

The reactions were carried out in MeCN at 298, 323, 333 and 343 K. The optimum conditions used for the cyclohexane oxidation were: catalyst, substrate and aldehyde in a molar ratio of 1 : 1000 : 15000, respectively at 333 K in acetonitrile solution under dioxygen. The consumption of the starting ketones and formation of oxidized products were monitored by GC or GC-MS in the presence of inert internal standard (naphthalene) (Fig. S1-S6, ESI†). The oxidation in the presence of isobutyraldehyde occurs with moderate conversion (6.2% (5h) and 16.4% (15h) at 333 K). The highest conversions are attained with benzaldehyde, 34% and 73% after 5 and 15 h, respectively. In case of the Fe/(*m*-CPBA)-containing system the oxidation occurs with much higher yields (59.1% (5h) and 100% (15h) at 333 K), the yields without catalyst are 16.8 and 92.3% after 5 and 15h, respectively (Table S1, ESI†). It means that the conversion can be increased in both cases by the use of **1**, compared to the classical B.-V. reaction (Fig. S7 and S8, ESI†). Complex **1** may have a dual effect, it can serve as an initiator and catalyst too. The relative reactivity of substrates is in the following order: cyclohexanone (73%) > 2Me-cyclohexanone (62.5%) > 4Me-cyclohexanone (53%) > 4<sup>t</sup>Bu-cyclohexanone (18%) > 3Me-cyclohexanone (15.5%, 3- and 5-methyl- $\epsilon$ -caprolactone (1:1)<sup>11d</sup>). The reactivities of *para*-substituted benzaldehydes relative to that of benzaldehyde were determined in the presence or in the absence of **1**. Hammett treatments of relative reactivities ( $k_{rel} = (\log(X_f X_i)/(\log(Y_f Y_i))$ , where  $X_i$  and  $X_f$  are the initial and final concentrations of *para*-substituted benzaldehydes, and  $Y_i$  and  $Y_f$  are the initial and final concentration of benzaldehyde) of various substituents against  $\sigma$  gave  $\rho$  values of -0.71 ( $r = 0.997$ ,  $n = 5$ ), and -0.68 ( $r = 0.998$ ,  $n = 5$ ) for **1**, and no metal complex, respectively (Fig. 2, and Table S1-2, ESI†). The  $\rho$  values obtained with **1** and no catalyst were the same within experimental error, suggesting that the formation of the PBA is the key step in both cases. It is pertinent to mention that the 4-hydroxy- and 4-methylaminobenzaldehyde are able to block both reactions, probably via a hydrogen abstraction and electron transfer processes.

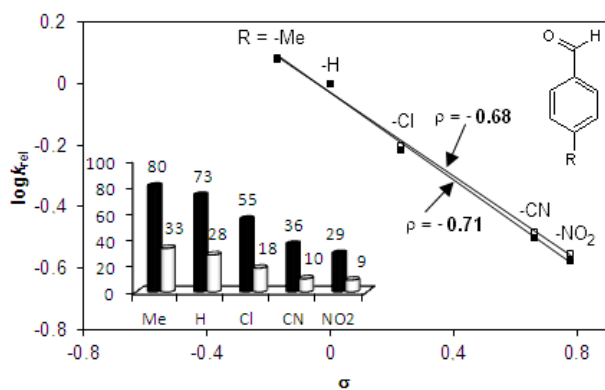


Fig. 2. Hammett plot for the *para*-substituted benzaldehydes in the B.-V. reactions without **1** ( $\square$ ), and with **1** ( $\blacksquare$ ) in MeCN at 60 °C. Inset: yields in the reactions without **1** (white), and with **1** (black).  $[1]_0 = 1.00 \times 10^{-5}$  M,  $[\text{cyclohexanone}]_0 = 1.00 \times 10^{-2}$  M,  $[\text{aldehyde}]_0 = 1.50 \times 10^{-1}$  M under  $O_2$ .

In order to prove that cyclohexanone has been oxygenated, we carried out the reaction with a mixture of  $^{18}O_2$  and  $^{16}O_2$  60 : 40%). Analysis of the GC-MS spectra of the products using  $^{18}O$ -labeled compounds gave an answer to this question. After 24 h of stirring the reactants at 298 K, GC-MS analysis of the reaction mixture shows the presence of  $^{18}O$ - and  $^{16}O$ - $\epsilon$ -lactone in the appropriate ratio:  $m/z$  116( $M^+$ , 7.7), 114( $M^+$ , 4.8). The  $^{18}O$ - $\epsilon$ -lactone derivative gave a molecular ion at  $m/z$  116 ( $114 + 2$ ), showing that one of the  $^{18}O$  atom of  $^{18}O_2$  are incorporated into the cyclohexanone ring. The relative abundance of  $m/z$  116 to that at  $m/z$  114 (~62%) parallels the  $^{18}O_2$  enrichment used in the experiment (Fig. S2, and Table S1, ESI†). The second  $^{18}O$  atom of  $^{18}O_2$  can be found in the forming benzoic acid:  $m/z$  124( $M^+$ , 64.6), 122( $M^+$ , 54.7). The smaller value of the relative abundance (54% compared to 62%) can be explained by water exchanged reaction. Spectral investigations on the catalytic system above have confirmed the formation of oxoiron(IV) species (Fig. 3, and Fig. S9, ESI†). The steady-state concentration of  $[Fe^{IV}=O(N4Py)]^{2+}$  (**2**) was determined to be ~20% by comparing the intensity of the absorption band at 693 nm with the known  $\epsilon$  value of **2**.<sup>12a,b</sup>

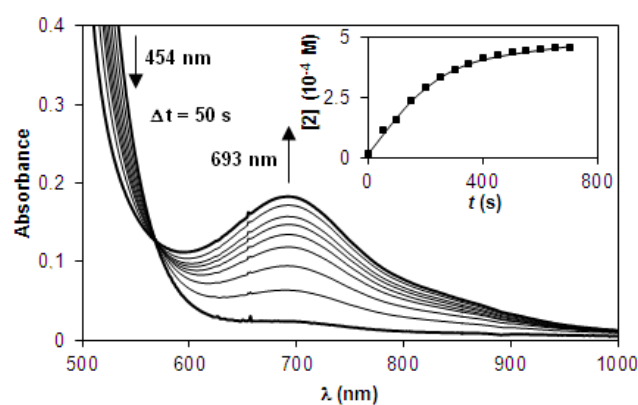
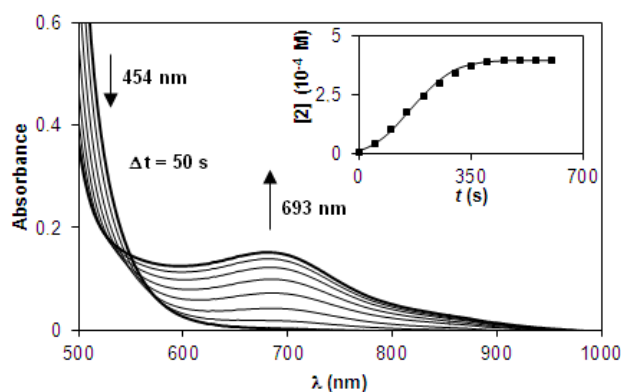


Fig. 3. Visible spectral change for the formation of  $[Fe^{IV}=O(N4Py)]^{2+}$  (**2**) species (at 693 nm) derived from the B.-V. oxidation of cyclohexanone catalysed by **1** in MeCN at 298 K. Inset: Time dependent formation of **2** under the conditions described above.  $[1]_0 = 2.00 \times 10^{-3}$  M,  $[\text{benzaldehyde}]_0 = 8.00 \times 10^{-2}$  M,  $[\text{cyclohexanone}]_0 = 1.00 \times 10^{-1}$  M.

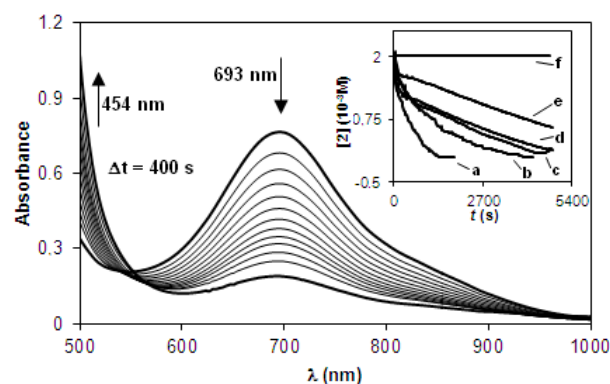
To get insight into the formation of **2** generated by dioxygen plus benzaldehydes, which serve as oxygen acceptors, detailed kinetic studies were carried out at 293 K, in MeCN, without cyclohexanones. The kinetic profile of the reaction is given in Fig. 4. Addition of benzaldehyde at room temperature to acetonitrile solution of the complex **1** under air results in rapid changes in colour from red to green. Similar spectral behaviour can be observed during the reaction of **1** with *m*-CPBA (Fig. S10, ESI†), where the formation of **2** can be drawn by oxene transfer between the precursor complex and the oxidant. Influence of the structure and electronic properties of the aldehyde was also studied on the formation reaction of **2**. Isobutyraldehyde gave ~10% yield of **2** (Fig. S11, ESI†). Upon using *para*-benzaldehydes with electron donating groups the yields were increased remarkably (Fig. S11, ESI†). Rate constants ( $k_{obs}$ ) determined from these plots showed a good

linear correlation ( $r = 0.99$ ,  $n = 4$ ) with the Hammett substituent parameters ( $\sigma = -1.61$ , Fig. S12, ESI†).

enthalpies and the large negative activation entropies are typical of associative processes.



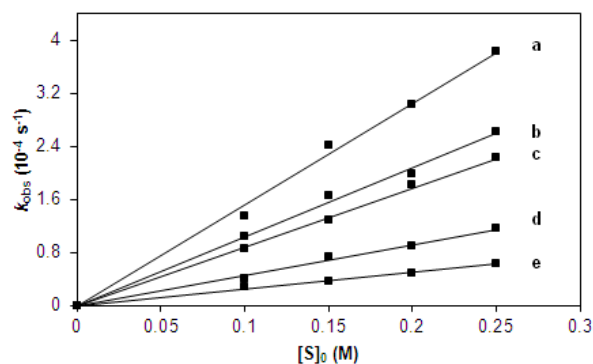
**Fig. 4.** Visible spectral change for the formation of **2** (at 693 nm, yield = ~45 %) derived from the reaction of **1** and benzaldehyde in MeCN under air at 298 K.  $[1]_0 = 1.00 \times 10^{-3}$  M,  $[\text{benzaldehyde}]_0 = 8.00 \times 10^{-2}$  M.



**Fig. 5.** Visible spectral change for the decay of **2** (at 693 nm) derived from the reaction of **2** with 2-methyl-cyclohexanone. Inset: The change of  $\text{Fe}^{\text{IV}}=\text{O}$  concentration (at 693 nm) derived from the reaction of  $\text{Fe}^{\text{IV}}=\text{O}$  and cyclohexanone (a), 2-methyl- (b), 4-methyl-(c), 4-*tert*-butyl-(d), 3-methyl-cyclohexanone (e) and without substrate (f,  $t_{1/2} = 60$  h) in MeCN at 298 K.  $[2]_0 = 2.00 \times 10^{-3}$  M,  $[\text{cyclohexanone}]_0 = 2.50 \times 10^{-1}$  M.

Time analysis of these reactions showed an induction period (lengths are dependent on the amount of dioxygen, benzaldehyde, and complex **1** concentration), and after that a first order rate law was observed. The partial rate orders of the reaction were investigated by plotting the initial concentrations against the reaction rates, which gave straight lines, suggesting an overall third order rate law of  $d[2]/dt = k_3 [\text{aldehyde}][1][\text{O}_2]$  with a third-order rate constant  $k_3 = 34 \pm 2 \text{ M}^{-2}\text{s}^{-1}$  in MeCN at 298 K (Fig S13-S18, Table S2 and S3, ESI†). The dependence of  $k_3$  on temperature ( $T = 293$  to  $308$  K) gave the activation parameters  $\Delta H^\ddagger = 44 \text{ kJ mol}^{-1}$  and  $\Delta S^\ddagger = -109 \text{ J mol}^{-1}\text{K}^{-1}$  (Table S3, Fig. S19, ESI†).

Finally, to get direct evidence for the involvement of the high-valent oxoiron(IV) species in the Baeyer-Villiger oxidation, the reaction of **2** with various cyclohexanone derivatives was investigated. The oxoiron(IV) was generated by reaction of **1** with PhIO,<sup>12</sup> and its reaction with cyclohexanones was measured as a function of the concentration of added cyclohexanone derivatives (Fig. 5 and 6). It was found that the electrophilic oxoiron(IV) is able to oxidize the cyclohexanone derivatives to the corresponding  $\epsilon$ -caprolactones, excluding its nucleophile attack on the carbonyl group. Since no reaction has been observed for acetophenone and benzophenone, this indicates clearly that the conjugation of the carbonyl group decreases the reactivity of the ketone.<sup>11a</sup> The traces could be fitted with a first-order kinetic law, with respect to **2**, and the calculated  $k_{\text{obs}}$  values for different concentrations of the appropriate substrate are reported in Table S4 (ESI†). The relative reactivity of substrates is in the following order: cyclohexanone > 2Me-cyclohexanone > 4Me-cyclohexanone > 4<sup>t</sup>Bu-cyclohexanone > 3Me-cyclohexanone, which is the same trend, that was found for the catalytic system (Fig. 5, and Table S4, ESI†). Kinetic experiments revealed 1st-order dependence on both the oxoiron(IV) and the substrate concentration with  $k_2 = 1.48 \pm 0.04 \text{ M}^{-1} \text{ s}^{-1}$ ,  $\Delta H^\ddagger = 41 \text{ kJ mol}^{-1}$  and  $\Delta S^\ddagger = -111 \text{ J mol}^{-1} \text{ K}^{-1}$  at 298 K (Table S4, Fig. S20-21, ESI†). The low activation



**Fig. 6.** Dependence on the reaction rate values ( $k_{\text{obs}}$ ) on the substrate concentrations for the decay of **2** in the presence of cyclohexanone derivatives: cyclohexanone (a), 2-methyl- (b), 4-methyl-(c), 4-*tert*-butyl-(d), and 3-methyl-cyclohexanone (e) in MeCN at 298 K.  $[2]_0 = 2.00 \times 10^{-3}$  M.

In summary, a mechanism for the iron(II)-catalysed Baeyer-Villiger oxidation of cyclohexanones by  $\text{O}_2$  and aldehyde has been proposed (Scheme 1). It is well known that autoxidation rates of aldehydes are very high with long propagation chains even at room temperature. In the absence of **1** the formation of the  $\epsilon$ -caprolactones can be drawn from the reaction between the forming peroxybenzoic acid and cyclohexanone via Criegee adduct (Route A in Scheme 1). We have found that complex **1** exhibited high catalytic performance for the oxidation of cyclohexanone to  $\epsilon$ -caprolactone comparing with that in blank experiment, indicating that iron is crucial for the aerobic oxidation of cyclohexanones. It has a dual effects in the catalytic cycle, firstly to aid in the generation of the peroxy-carboxylic acid (side effect) which is necessary for transforming the iron(II) complex into the active high-valent oxoiron(IV) species, and secondly to mediate the oxygen transfer into the substrate via an electron transfer mechanism (main effect) between the ketone and the electrophilic





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Mechanistic studies on the Fe(II)-catalyzed Baeyer-Villiger oxidation is described, including the formation and the reactivity of the trapped oxoiron(IV) intermediate.

