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The Importance of Carboxylate Ligands in the Differentiation of Catalase Reactivity from Gif Ketonization Systems.

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***Abstract:** The presence or absence of certain chelating carboxylic acids such as picolinic acid permits the distinction between ketonization (Gif Chemistry) and oxygen formation (catalase reaction). In the presence of such an acid, evidence is provided for the possible involvement of a* $^{III}Fe\text{-}O\text{-}O\text{-}Fe^{III}$ *species as a key intermediate in this hydrocarbon activation chemistry.*

The selective activation of saturated hydrocarbons is an industrial and biochemical problem of importance.[1] Gif Chemistry permits the selective functionalization of saturated hydrocarbons at ambient temperatures under mild conditions giving ketones (up to 30 % conversion, nearly quantitative yield) using a pyridine - acetic acid solvent matrix.[2,3] The mononuclear Fe^{III}- picolinic acid complex **4** was crystallized and identified by X-Ray spectroscopy.[4] However, little is known about the catalyst in solution and the role of the carboxylic acids. Here we distinguish between catalase activity (O_2 formation) and Gif Chemistry (ketonization) and provide evidence for a possible μ-peroxo-dimer in solution.

The recognition that there are two (Fe^{II}-Fe^{IV} and Fe^{III}-Fe^{V}) manifolds in Gif Chemistry is of fundamental importance.[5] The Fe^{II}-Fe^{IV} manifold (Fe^{II} + H_2O_2) involves an Fe^{IV} species which attacks saturated hydrocarbons selectively at secondary positions and then gives carbon radicals ($R^{\bullet}$), characterized by reaction with Fe^{III}-Cl to furnish R-Cl. In the absence of chloride ion and of oxygen $R^{\bullet}$ couples with the solvent pyridine. In contrast in the Fe^{III}-Fe^{V} manifold R-Cl is never seen however much chloride anion is added. With cyclohexane and its congeners, there is no coupling to pyridine. Chemical reactions in the Fe^{II}-Fe^{IV} manifold are much faster than those in the Fe^{III}-Fe^{V} manifold.[5]

To study the effect of carboxylic acids, we simplified the Gif system by leaving out the acetic acid and by working in pyridine alone. An Fe^{III}/H_2O_2/acid ratio of 1:4:4 was found to be efficient for ketone formation. Simple iron salts like $FeCl_3 \bullet 6\ H_2O$ alone were shown to give O_2 quantitatively. Then $CBrCl_3$ was reacted under the conditions shown in Table 1 with and without picolinic acid **1**. In the absence of **1**, dioxygen was also formed exclusively (Table 1, entry 1). Neither alkyl bromide nor carbon dioxide were produced (n.d. indicates not detected). However, in the presence of four equivalents of **1**, both, cyclooctylbromide and carbon dioxide were formed in almost equimolar amounts,[6] as already known from previous studies in pyridine-acetic acid.[7] No dioxygen was detected. Diphenyl sulfide showed an inverse behavior: without **1**, diphenyl sulfoxide was formed with only minor amounts of cyclohexanone (ratio 20:1), but in the presence of **1**, cyclohexanone was produced almost exclusively (ratio 1:20) (Table 1, entry 3). The oxidation of a saturated hydrocarbon in preference to Ph_2S is indeed remarkable (the Gif paradox).[2]

Table 1. Chemoselectivity study in presence or absence of picolinic acid 1[a,e]

entry	Fe^{III},[a] mmol	trap, mmol	H_2O_2 mmol	products [mmol] without 1	products [mmol] with 1[b]	eff.[f] wo/w 1
1[c]	1	$CBrCl_3$, 20	4	R-Br [n.d.], CO_2 [n.d.], O_2 [1.65], R=O [n.d.]	R-Br [1.43], CO_2 [1.33], O_2 [n.d.], R=O [n.d.]	83 / 36
2[c]	3	$CBrCl_3$, 20	1.5	R-Br [0.08], CO_2 [n.d.], O_2 [0.67], R=O [n.d.]	R-Br [1.26], CO_2 [0.99], O_2 [n.d.], R=O [n.d.]	95 / 84
3[d]	1	Ph_2S, 10	4	Ph_2SO [2.05], O_2 [0.71], R=O [0.10]	Ph_2SO [0.08], O_2 [0.05], R=O [1.57]	92 / 83

[a] Conditions: $FeCl_3{\bullet}6H_2O$, pyridine 33 ml, hydrocarbon 20 mmol, 0°C → room temp., overnight; [b] 4 equivalents of 1 with respect to the ferric chloride used (4 or 12 mmol, respect.); [c] cyclooctane used, expt. carried out under slow argon stream, CO_2 was trapped and quantified as $BaCO_3$; [d] cyclohexane used; [e] dioxygen was quantified manometrically. [f] efficiency [%] with respect to $H_2O_2 = 2 \times [R{=}O + O_2] + R\text{-}Br + Ph_2SO$. CO_2 is a side product from R-Br formation and can therefore not be considered.

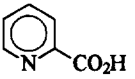
These dramatic changes in chemoselectivity upon the addition of picolinic acid led us to investigate the influence of other carboxylic acids on the chemistry of the iron catalyst. The results of typical experiments are depicted in Table 2. In this system using picolinic acid 1 (without acetic acid) oxygen is scarcely evolved or absorbed. A free hydroperoxide is not an intermediate. The experiments in entries 1, 6, 7 and 8 gave ketone as the dominant product with little O_2 formed. The requirements for this chemoselectivity become clear when comparing isoquinoline-1-carboxylic acid **3** (entry 6) with quinaldic acid **2** (entry 5). Obviously, the adjacent aromatic ring α to the nitrogen atom in **2** provides enough steric hindrance to prevent chelation of this carboxylic acid, and hence O_2 is formed exclusively. On the other hand, when chelation of the carboxylic acid is possible, a species is formed, which reacts with high chemoselectivity with saturated hydrocarbons (see Table 1). This conclusion is confirmed by the results obtained with the known ferric complex **4** (Table 2, entry 8), comparable with those for picolinic acid **1** (entry 1) or isoquinoline-1-carboxylic acid **3** (entry 6). An important change in the product distribution was observed in experiments under an argon stream or in vacuum (entries 2, 3 and 9). Significant amounts of alkyl chloride were formed, accompanied by Fe^{II} formation (typically 15 %).[8] Furthermore, reducing agents such as PPh_3 in association with H_2O_2 (entry 4) lead to formation of alkyl chloride[9] and Fe^{II} (11 %). It is important to mention that in all other experiments in the presence of H_2O_2 no Fe^{II} could be detected. Also $FeCl_3{\bullet}$ 6 H_2O alone in pyridine with an argon stream is not reduced and affords no chloride. In the reaction of H_2O_2 with Fe^{III} in the presence of picolinic acid (entry 1) the removal of traces of free oxygen or the passage of oxygen has no effect on the yield of the ketone. The reduction of Fe^{III} to Fe^{II} involves the evolution of oxygen as determined by the Winkler-method.[10,11] Although a one electron change per iron could be envisaged, it seems to us more probable that two one electron changes are concerted to give oxygen and two Fe^{II}.

Table 2. Effect of various carboxylic acids, vacuum and PPh_3 on O_2 and ketone formation.[a]

entry	carboxylic acid[b]	oxygen [mmol]	ketone [mmol]	alkyl chloride [mmol]	efficiency [%][c]
1	picolinic acid **1**	0.06	1.28	0.00	67
2	picolinic acid **1**[d]	-	0.88	1.00	94[g]
3	picolinic acid **1**[e]	-	0.53	0.55	54[g]
4	picolinic acid **1**[f]	0.00	0.07	1.18	63
5	quinaldic acid **2**	2.01	0.00	0.00	100
6	isoquinoline-1-carboxylic acid **3**	0.05	1.57	0.00	81
7	isoquinoline-3-carboxylic acid	0.13	1.42	0.00	78
8	$[(pic)_2FeCl_2]^{\ominus}$ $[pyr_2H]^{\oplus}$ **4**	0.16	0.81	0.00	49
9	$[(pic)_2FeCl_2]^{\ominus}$ $[pyr_2H]^{\oplus}$ **4**[d]	-	0.51	0.65	58[g]
10	picolinic acid **1**[h]	-	(0.43)[h]	(0.33)[h]	(38)[g,h]
		-	1.31	0.33	82[g]

[a] To a stirred solution of $FeCl_3 \bullet 6\ H_2O$ (1 mmol) (exception for entries 8 and 9: 1 mmol of **4** was used) in pyridine (33 ml), cyclooctane (20 mmol) and the appropriate acid[b] was added. The reaction flask was made gastight and connected to a manometric burette filled with brine saturated with oxygen prior to use. Then, 30 % aqueous H_2O_2 (4 mmol) were added dropwise within 10 seconds at 0°C; [b] 4.0 mmol acid were used in each experiment, except entries 8 and 9; [c] with respect to H_2O_2, eff. = 2 x [R=O + O_2 + R-Cl]; [d] Performed under a constant argon stream; [e] Performed under vacuum (0.1 mm Hg); [f] PPh_3 (4 mmol) added; [g] Oxygen development not determined and hence not taken into account; [h] 2 hrs argon stream, then oxygen stream until completion of the reaction; ( ) = amounts of product after 2 hrs.

Therefore, the results are possibly best rationalized by a μ-peroxo-dimer **5**, formed by reaction of H_2O_2 and the ferric iron *in situ* in solution, which loses dioxygen reversibly.[12] Another molecule of H_2O_2 is necessary to afford R-Cl by radical chemistry (anionic trapping). This conclusion is in harmony with the findings of a previous study,[5] where Fe^{II} was found to be responsible for anionic trapping to divert the usual ketonization towards R-Cl formation. The reversibility of the loss of O_2 from **5** is demonstrated in entry 10 of Table 2. Flushing O_2 after a 2 hrs argon stream stops the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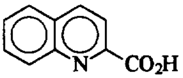
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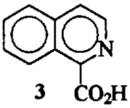
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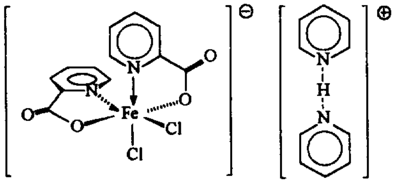
4


$$^{III}Fe{-}O{-}O{-}Fe^{III} \underset{+O_2}{\overset{-O_2}{\rightleftharpoons}} 2\,Fe^{II}$$

5

Scheme 1

chlorination and results in ketone formation due to the peroxide complex **5**.

In summary we have shown the importance of chelating carboxylic acids such as **1** or **3** for the generation of an Fe species, which only in their presence exhibits an extraordinary affinity towards saturated hydrocarbons. In either the Fe^{II}-Fe^{IV} or the Fe^{III}-Fe^{V} manifolds Gif chemistry is not observed in the absence of a suitable carboxylate ligand. Evidence for the possible formation of a μ-peroxo-dimer **5** is based on the reversible removal of O_2 and simultaneous Fe^{II} formation. From these results, Gif type chemistry may be related to non-heme-type oxygenases such as methane monooxygenase (MMO).[13]

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