Iron(II)-Induced Activation of 1:1 HOOH/HCl for the Chlorohydroxylation of Olefins and the Chlorination of Hydrocarbons: Chlorinated Fenton Chemistry

Donald T. Sawyer,* John P. Hage, and Andrzej Sobkowiak

Contribution from the Department of Chemistry, Texas A&M University,
College Station, Texas 77843-3255

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Abstract: Iron complexes [$Fe^{II}(OPPh_3)_4{}^{2+}$, $Fe^{II}(bpy)_2{},^{2+}$, $Fe^{II}(OH_2)_6{}^{2+}$, and $Fe^{III}Cl_3$] catalytically activate 1:1 HOOH/HCl combinations for the efficient chlorohydroxylation of olefins. The reactive intermediate **7** is not HOCl, but appears to be formed via a Fenton process $Fe^{II}L_x{}^{2+} \rightleftarrows$ (B) [$L_x{}^{+}Fe^{II}OOH(BH^+)$] (**1**) → (HCl) [$L_xFe^{IV}(OH)Cl$] (**7**) + H_2O}. Although the major product from the reaction of **7** with olefin substrates (e.g., cyclohexene, c-C_6H_{10}) is the chlorohydroxo derivative [c-C_6H_{10} + HOOH + HCl → ($Fe^{II}L_x$) c-$C_6H_{10}(OH)Cl$ + H_2O], significant amounts of the dihydroxo [c-$C_6H_{10}(OH)_2$] and traces of the dichloro [c-$C_6H_{10}Cl_2$] derivatives are produced. The reaction efficiency with respect to HOOH/HCl ranges from 51% for norbornene to 31% for cyclohexene to 10% for 1-hexene. The presence of dioxygen (O_2) with c-C_6H_{10} results in the production of some ketone [c-$C_6H_8(O)$] via oxygenated Fenton chemistry, but does not inhibit the chlorohydroxylation process. The catalyzed process is equally efficient and selective in a biphasic H_2O/substrate solution as in acetonitrile. With *cis*-stilbene (*cis*-PhCH=CHPh) the major product is the epoxide (>80%); the reaction efficiency is 63% relative to HOOH/HCl. These systems chlorinate saturated hydrocarbons (c-C_6H_{12} → c-$C_6H_{11}Cl$) and hydroxylate benzene (PhH → PhOH). Because **7** chlorohydroxylates olefins and chlorinates hydrocarbons in aqueous media much more efficiently than HOCl, its in-vivo analogue may be a reasonably reactive intermediate for "oxy-radical" damage in biological systems.

The conventional method for the chlorohydroxylation of olefins involves a direct one-to-one combination of hypochlorous acid (HOCl) and olefin via an uncatalyzed reaction[1]

$$\mathrm{RCH{=}CHR' + HOCl \rightarrow RCH(OH)CH(Cl)R'} \qquad (1)$$

To our surprise, iron(II) complexes catalyze one-to-one HOOH/HCl combinations for reaction with olefins to give their chlorohydroxylates also. However, rather than via the initial formation of HOCl and subsequent reaction with the olefin (eq 1), this is a direct reaction with a reactive intermediate

$$\mathrm{RCH{=}CHR' + (HOOH/HCl) \xrightarrow{Fe^{II}L_x} RCH(OH)CH(Cl)R'} \qquad (2)$$

This discovery occurred during investigations (a) to extend the characterization of iron-based Fenton systems [$L_xFe^{II}OOH(BH)^+$ (**1**), reactive intermediate][2] and oxygenated Fenton systems [L_x-$Fe^{III}(O_2)(OOH)(BH^+)$ (**5**), reactive intermediate][3] and (b) to ascertain their relevance to the biological transformation of HOOH/HCl to HOCl[4] and the "oxy-radical" theory of aging and human disease.[5]

Earlier studies demonstrated that $Fe^{III}Cl_3$ activates HOOH to epoxidize olefins in dry acetonitrile (MeCN) {probably via a [$Cl_3Fe^{V}(O)$] reactive intermediate}.[6] When the solvent is wet (about 0.2 M H_2O/MeCN) this system reacts with cyclohexene (c-C_6H_{10}) to yield twice as much allylic alcohol (c-C_6H_9OH) as epoxide [c-$C_6H_{10}O$].[7]

Experimental Section

Equipment. The reaction products were separated and identified with a Hewlett-Packard 5880A Series gas chromatograph equipped with a HP-1 capillary column (cross-linked methyl silicone gum phase, 12 m × 0.2 mm i.d.) and by gas chromatography−mass spectrometry (Hewlett-Packard 5790A Series gas chromatograph with a mass-selective detector).

Chemicals and Reagents. The reagents for the investigations and syntheses were the highest purity commercially available and were used without further purification. Burdick and Jackson "distilled in glass" grade acetonitrile (MeCN, 0.004% H_2O) and pyridine (py, 0.014% H_2O) were used as solvents. High-purity argon gas was used to deaerate the solutions. All compounds were dried in vacuo over $CaSO_4$ for 24 h prior to use. Ferrous perchlorate [$Fe^{II}(OH_2)_6$]$(ClO_4)_2$ was supplied by GFS Chemicals, and ferric chloride ($Fe^{III}Cl_3$, anhydrous, 98%), 2,2′-bipyridine (bpy, 99+%), and triphenylphosphine oxide ($OPPh_3$, 98%) were obtained from Aldrich. Hydrogen peroxide (50% H_2O) was obtained from Fisher. The organic substrates included: Cyclohexane (Aldrich, anhydrous, 99+%), cyclohexane-d_{12} (Aldrich, 99.5 atom % D), cyclohexene (Fisher, 99%), and 1-hexene, *cis*-stilbene, norbornene (C_7H_{10}), and benzene (all from Aldrich).

[$Fe^{II}(MeCN)_4$]$(ClO_4)_2$. The [$Fe^{II}(MeCN)_4$]$(ClO_4)_2$ complex was prepared by multiple recrystallizations of [$Fe^{II}(OH_2)_6$]$(ClO_4)_2$ from MeCN.

Iron(II) Tetrakis(triphenylphosphine oxide) Solutions. The $Fe^{II}(OPPh_3)_4{}^{2+}$ complex was prepared in-situ by mixing [$Fe^{II}(MeCN)_4$]$(ClO_4)_2$ in MeCN with a stoichiometric ratio of the $OPPh_3$ ligand.

Iron(II) Bis(2,2′-bipyridine). The $Fe^{II}(bpy)_2{}^{2+}$ complex was prepared in-situ by mixing [$Fe^{II}(MeCN)_4$]$(ClO_4)_2$ in MeCN with a stoichiometric ratio of bpy.

Methods. The investigation of HOOH/HCl activation by the iron complexes (FeL_x) combined substrate (RH) and FeL_x in the solvent

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Table 1. Chlorohydroxylation of c-C_6H_{10} with HOOH/HCl and $Fe^{II}(OPPh_3)_4^{2+}$ [or FeL_x] in MeCN [or H_2O] under Argon

	products (mM ± 5%)[a]				
$Fe^{II}L_4^{2+}$/HOOH/HCl(mM)	c-$C_6H_{10}(OH)Cl$	c-$C_6H_{10}(OH)_2$	c-$C_6H_{10}Cl_2$	others (mM)	efficiency (%)[b]
5/10/10	3.7 [2.4][c]	1.6 [1.6][c]	0	c-$C_6H_8(O)$ (0.3)	53 [40][c]
5/20/20	6.4 [5.8]	2.5 [4.2]	0.5 [0]	c-C_6H_9OH (1.2) c-$C_6H_8(O)$ (0.5)	47 [50]
5/50/50	10 [16]	4.8 [12]	0.5 [0.5]	c-$C_6H_8(O)$ (0.3) R−R (0.6)	31 [57]
5/50/50 [$Fe^{II}(bpy)_2^{2+}$]	19 [9.7]	5.6 [8.6]	0.6 [1.7]	c-C_6H_9OH (4.6) c-$C_6H_8(O)$ (0.4)	50 [40]
5/50/50 [$Fe^{II}(OH_2)_6^{2+}$]	[8.6]	[6.3]	[1.1]		[32]
5/50/50 [$Fe^{III}Cl_3$]	[16]	[8.6]	[1.7]		[47]
10/10/10	3.5	1.7	0	0	52
10/20/20	6.1	2.2	0	c-C_6H_9OH (1.5) c-$C_6H_8(O)$ (0.5)	42
10/50/50	14 [12]	6.6 [8.5]	1.0 [0.5]	c-C_6H_9OH (2.0) c-$C_6H_8(O)$ (0.4) R-R (0.6)	43 [42]
10/50/50 [$Fe^{II}(bpy)_2^{2+}$]	15	3.6	0.3	c-C_6H_9OH (1.5) c-$C_6H_8(O)$ (0.2)	38
0/50/50	4.6 [0]	2.5 [0]	0 [0]		14 [0]

[a] Substrate (1 M) and $Fe^{II}(OPPh_3)_4^{2+}$ combined in solvent (MeCN or H_2O) to which an aliquot of 1:1 HOOH/HCl(500 mM/500 mM) was added to give the indicated initial concentrations in a total volume of 5.0 mL. The product solutions were analyzed by capillary-column gas chromatography and GC-MS after a reaction time of 3 h at 24 ± 2 °C. [b] Millimoles of c-$C_6H_{10}(OH)Cl$, c-$C_6H_{10}(OH)_2$, and c-$C_6H_{10}Cl_2$ produced per millimole of HOOH/HCl. [c] Aqueous media.

(MeCN or H_2O) with an aliquot of 1:1 HOOH/HCl (500 mM/500 mM) to give initial concentrations of 1 M substrate, 0−10 mM FeL_x, and 10−50 mM HOOH/HCl in a total volume of 5 mL. After 3 h with constant stirring at room temperature (24 ± 2 °C), samples of the reaction solutions were injected into a capillary-column gas chromatograph for analysis. In some cases, the reaction was quenched with water, and the product solution was extracted with diethyl ether. Product species were characterized by GC-MS. Reference samples were used to confirm product identifications and to produce standard curves for quantitative assays of the product species.

The kinetic isotope effect [$K = k_H/k_D$] was determined with a 1:1 cyclohexane/cyclohexane-d_{12} mixture (0.5 M/0.5 M) as the substrate; the k_H/k_D ratios were determined from the product ratios of c-$C_6H_{11}Cl$/c-$C_6D_{11}Cl$.

Results

Chlorohydroxylation of Olefins. Table 1 summarizes the reactivities and product profiles for the combination of $Fe^{II}(OPPh_3)_4^{2+}$, 1:1 (HOOH/HCl), and cyclohexene (c-C_6H_{10}) in MeCN and in H_2O (two-phase system). Limited data (Table 1) indicate that $Fe^{II}(bpy)_2^{2+}$, $Fe^{II}(OH_2)_6^{2+}$, and $Fe^{III}Cl_3$ also are effective catalysts. The dominant product is 1,2-c-$C_6H_{10}(OH)Cl$, with lesser amounts of 1,2-c-$C_6H_{10}(OH)_2$ and 1,2-c-$C_6H_{10}Cl_2$. In MeCN the 5 mM $Fe^{II}(OPPh_3)_4^{2+}$/10 mM HOOH/10 mM HCl combination is the most efficient (53%, moles of product per mole of HOOH/HCl). The efficiency decreases as the reagent concentrations are increased. In the absence of the iron catalyst the reaction efficiency is reduced by a factor of 3 in MeCN. The presence of 20−30% pyridine in the MeCN-solvent matrix inhibits the chlorohydroxylation reaction by about 80%.

Although the c-C_6H_{10} substrate is immiscible with H_2O, the iron-catalyzed reaction is rapid and equally efficient (Table 1). In the absence of catalyst the substrate is unreactive in an aqueous matrix. If pyHCl is substituted for HCl in an aqueous matrix, the reaction efficiency for c-C_6H_{10} decreases from 57 to 38%, and ketonization becomes a second reaction path [c-C_6H_{10} → c-$C_6H_8(O)$] (Table 2).

Table 2. Products from the Reaction of the $Fe^{II}(OPPh_3)_4^{2+}$ (5 mM)/HOOH (50 mM)/HCl (50 mM) in MeCN [or H_2O] with Various Organic Substrates

		products (mM, ±10%)	
substrate (1 M)		MeCN	H_2O (2-phase)
c-C_6H_{10}[a,b]	c-$C_6H_{10}(OH)Cl$	10	16
	c-$C_6H_{10}(OH)_2$	4.8	12
	c-$C_6H_{10}Cl_2$	0.5	0.5
norbornene (c-C_7H_{10}, R)	R(OH)Cl	15	
	$R(OH)_2$	7	
	RCl_2	3	
1-hexene (C_6H_{12}, R)	R(OH)Cl	4	
	$R(OH)_2$	1	
	RCl_2	0.4	
cis-PhCH=CHPh(R)	epoxide [R(O)]	25	
	PhCH(O)	4	
	RCl_2	3	
c-C_6H_{12}[c]	c-$C_6H_{11}Cl$	18	8
PhH	PhOH	5	19
	Ph−Ph	0	1

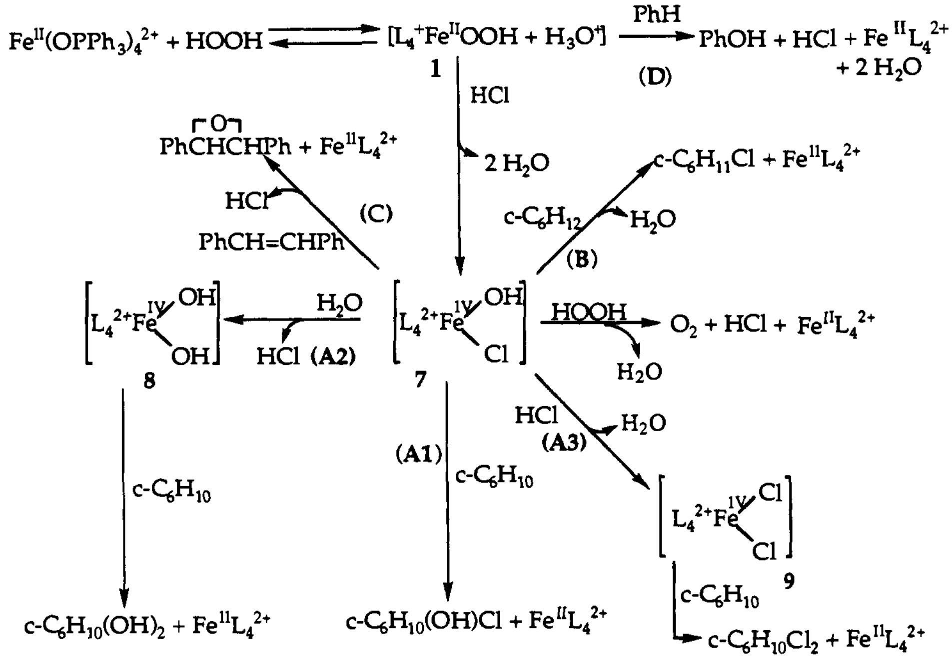
[a] With 50 mM pyHCl in place of HCl the product profile in H_2O includes c-$C_6H_{10}(OH)Cl$ (5 mM), c-$C_6H_{10}(OH)_2$ (4 mM), and c-$C_6H_8(O)$ (5 mM) [38% efficiency]. [b] With $(py)_2HOAc$ as the solvent, the only substrate product is c-$C_6H_{10}(OH)Cl$ (1.7 mM), but there is extensive reaction with the solvent. [c] With 0.5 M c-C_6H_{12}/c-C_6D_{12} in MeCN the kinetic-isotope-effect [$K = k_{c\text{-}C_6H_{12}}/k_{c\text{-}C_6D_{12}}$] for production of c-$C_6H_{11}Cl$ is 1.8 ± 0.1.

The reactivity of the $Fe^{II}(OPPh_3)_4^{2+}$/(HOOH/HCl) system with other substrates (olefins, cyclohexane, and benzene) is summarized in Table 2. The efficient and selective chlorohydroxylation of cyclic olefins [c-C_6H_{10} and norbornene (C_7H_{10})] is in sharp contrast with the results when HCl is absent from the reaction system. In MeCN a 5 mM $Fe^{II}(OPPh_3)_4^{2+}$/100 mM HOOH system reacts with (a) 1 M cyclohexene to yield 3 mM cyclohexen-3-one [c-$C_6H_8(O)$] and 2 mM cyclohexen-3-ol (c-C_6H_9OH), and (b) 1 M *cis*-PhCH=CHPh to yield 29 mM PhCH(O), 7 mM PhC(O)C(O)Ph, and no epoxide.[7] Also in MeCN a 5 mM $Fe^{III}Cl_3$/HOOH system reacts with 1 M c-C_6H_{10} to yield 18 mM c-C_6H_9OH, 9 mM epoxide, and 5 mM c-$C_6H_8(O)$.[7]

Hydrocarbons and Benzene. The $Fe^{II}(OPPh_3)_4^{2+}$(5 mM)/[HOOH/HCl](50 mM) system chlorinates hydrocarbons (c-C_6H_{12} → c-$C_6H_{11}Cl$; 36% reaction efficiency in MeCN and 16% in H_2O), hydroxylates benzene (PhH → PhOH, 10% efficient in MeCN and 38% in H_2O), and oxygenates toluene [$PhCH_3$ → PhCH(O), 20% efficient in H_2O].

Hypochlorous Acid. The known ability of HOCl to produce 1,2-chlorohydroxy derivatives of olefins,[1] the knowledge that a heme-centered protein (myeloperoxidase) forms HOCl from

Scheme 1. Iron-Induced Activation of HOOH/HCl for Reaction with Olefins and Hydrocarbons



HOOH/HCl,[4] and the possibility that the present system may accomplish its chemistry via initial formation of HOCl has prompted a study of the reactivity of HOCl with 1 M c-C_6H_{10} in H_2O (a two-phase system). The combination of 100 mM HOCl with 1 M c-C_6H_{10} yields 22 mM 1,2-C_6H_{10}(OH)Cl as the only detectable product [50 mM HOCl yields 5 mM 1,2-C_6H_{10}(OH)Cl]. In the presence of 5 mM $Fe^{II}(OPPh_3)_4^{2+}$ the HOCl/substrate reaction is completely suppressed. Instead, the iron(II) complexes catalyze the rapid decomposition of HOCl (2 HOCl → O_2 + 2 HCl). Hence, HOCl is not the reactive intermediate for the $Fe^{II}L_x$/(HOOH/HCl) systems (Tables 1 and 2).

Discussion and Conclusions

Because the dominant chemical characteristic of HOOH is nucleophilic addition,[2,3,8] this is a reasonable initial step in the iron(II)-induced activation of HOOH/HCl (Scheme 1). Subsequent reaction of **1** with HCl yields the reactive intermediate $[L_4^{2+}Fe^{IV}(OH)Cl]$ (**7**) is a reasonable possibility], which chlorohydroxylates olefins (path A1, Scheme 1). Hydrolysis of **7** via path A2 would give **8**, which could account for the dihydroxy product [c-$C_6H_{10}(OH)_2$]. Reaction of **7** with a second HCl via path A3 would give **9** and facilitate the formation of the dichloro product (c-$C_6H_{10}C_{12}$).

The reaction of species **7** with saturated hydrocarbons (c-C_6H_{12}) to give the chloro derivative as the only detectable product (path **B** in Scheme 1; kinetic-isotope-effect [$K = k_{c\text{-}C_6H_{12}}/k_{c\text{-}C_6D_{12}}$], 1.8 ± 0.1) is consistent with its formulation in Scheme 1. Thus, the stabilized HO• of **7** attacks a C−H bond of the substrate to give a carbon radical that is stabilized via bond formation with the iron center prior to its collapse to product (eq 3). This process is analogous to the proposed pathway for the hydroxylation of hydrocarbons by Fenton reagents.[2] In contrast, the $Fe^{III}Cl_3$/HOOH/MeCN system reacts with c-C_6H_{12} to yield approximately equal amounts of c-C_6H_{11}-OH and c-C_6H_{11}Cl {apparently via an iron(V) reactive intermediate $[Cl_3Fe^V(OH)_2]$; [*K*] = 2.9 ± 0.3} (eq 4).[6,7] The smaller kinetic-isotope-effect value for **7** indicates that it is significantly more reactive than species **8** (eq 4) [that is, the Fe-OH bond in **7** is weaker than that in **8** (lower valence-electron-density)]. Thus, the pathways of Scheme 1 and the reactivity of **7** with saturated hydrocarbons (c-C_6H_{12}) might be classified as *chlorinated Fenton chemistry.*

$$\underset{7}{[L_4^{2+}Fe^{IV}(OH)Cl]} + c\text{-}C_6H_{12} \xrightarrow[H_2O]{} [L_4^{2+}Fe^{IV}(c\text{-}C_6H_{11})Cl] \longrightarrow c\text{-}C_6H_{11}Cl + Fe^{II}L_4^{2+} \qquad (3)$$

$$\underset{8}{[Cl_3Fe^V(OH)_2]} + c\text{-}C_6H_{12} \xrightarrow[H_2O]{} [Cl_3(HO)Fe^V\text{-}C_6H_{11}] \longrightarrow c\text{-}C_6H_{11}Cl + Fe^{III}(OH)Cl_2 \qquad (4)$$
$$(\text{or } c\text{-}C_6H_{11}OH + Fe^{III}Cl_3)$$

In the presence of *cis*-PhCH=CHPh species **7** appears to act as an effective epoxidizing agent via path **C**, possibly first being transformed to $[L_4^{2+}Fe^{IV}(O)]$ by elimination of HCl (Scheme 1). Although the $Fe^{II}(OPPh_3)_4^{2+}$/(HOOH/HCl)/H_2O system hydroxylates benzene with an impressive 38% efficiency, essentially the same efficiency is achieved for a system without HCl. Hence, species **1** appears to be the reactive intermediate via path **D**.

Perhaps the most noteworthy attribute of the present systems is their ability to catalytically and selectively chlorohydroxylate olefins (via HOOH/HCl) without the use of HOCl or Cl_2. Also, effective chlorination of hydrocarbons by an HOOH/HCl combination in place of Cl_2 may have advantages in some syntheses. There should be substantial environmental benefits to the extent that HOOH/HCl can replace Cl_2/HOCl in synthetic and process chemistry.

A final point to ponder is whether the in vivo combination of dysfunctional iron, hydrogen peroxide, and HCl/Cl^- leads to the reactivity with organic substrates that is outlined in Scheme 1. The present results indicate that species **7** is much more reactive than HOCl (the biological oxidant from myeloperoxidase)[4] with organic substrates in an aqueous matrix. The

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uncontrolled formation of **7** in a biological matrix via chlorinated Fenton chemistry may be a more reasonable basis for the "oxy-radical" theory for aging and disease states (rather than the generation of free hydroxyl radicals).[2,5]

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