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Functionalization of Saturated Hydrocarbons in Gif-Type Systems Using 2-Methyl-1,4-Naphthoquinone

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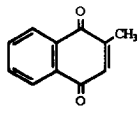
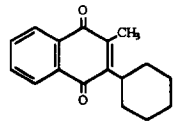
Abstract: The reaction between cyclohexane and 2-methyl-1,4-naphthoquinone **1** using hydrogen peroxide in the Fe^{II}-Fe^{IV} manifold gave the adduct **2** in good yield. The same reaction was carried out with the Fe^{III}-H_2O_2 system and gave also some 3-alkyl-2-methyl-1,4-naphthoquinone. The presence of Fe^{II} during the reaction showed that the Fe^{II}-Fe^{IV} manifold was again dominant.

The selective functionalization of saturated hydrocarbons remains a problem of industrial and mechanistic interest. What we call Gif chemistry[1] takes place at room temperature and nearly neutral conditions to furnish selectively ketones from saturated hydrocarbons. In early studies in what we call the Fe^{III}-Fe^{V} manifold, there was little evidence for carbon radicals. Recently, however, we have recognized that there is a second manifold based on Fe^{II}-Fe^{IV} where radical chemistry is predominant. The radical chemistry that takes place in the Fe^{II}-Fe^{IV} manifold is much faster than that seen in the Fe^{III}-Fe^{V} non-radical manifold.[2] A simple titration for Fe^{II}, when hydrogen peroxide oxidation is used, is sufficient to decide whether the chemistry will be radical or non-radical.[3] However, Fe^{II} with hydrogen peroxide does not produce hydroxyl radicals in pyridine[4] and the selective activation of the hydrocarbon is produced by an Fe^{IV} species.[2]

The simple reduction of Fe^{III} to Fe^{II} is sufficient to change the chemistry observed. For example, in the Fe^{III}-Fe^{V} manifold the formation of alkyl chloride is never seen, even when a large excess of chloride ion is present. The addition of triphenylphosphine plus hydrogen peroxide reduces the Fe^{III} to Fe^{II} and one enters the Fe^{II}-Fe^{IV} manifold. Alkyl chloride formation replaces ketonisation. This is due to the reaction of carbon radicals attacking the Cl-Fe^{III} bond.[5]

Quinones are well known for their reactivity towards carbon radicals.[6] We decided therefore to examine the reactivity of 2-methyl-1,4-naphthoquinone in the Fe^{II}-Fe^{IV} and Fe^{III}-Fe^{V} manifolds expecting to find radical chemistry in the first, but not in the second.

Table 1 shows the reactivity of 2-methyl-1,4-naphthoquinone **1** towards the Fe^{II}-H_2O_2 system. Using H_2O_2, the major product formed was 3-cyclohexyl-2-methyl-1,4-naphthoquinone **2** (entry 1). The authentic sample was prepared by photolysis of the cyclohexyl Barton PTOC ester[7] in CH_2Cl_2.

1 2

This result was expected: the 2-methyl-1,4-naphthoquinone, a well known radical trap,[6] was attacked by the cyclohexyl radical which was formed by the Fe^{II}-Fe^{IV} manifold.[2] This reaction must be very fast because the formation of chloride, which is also a fast reaction, was not observed (entry 4). The addition of acetic acid did not have much influence (entry 2), but the presence of a carboxylic acid like picolinic acid, was necessary to obtain the quinone adduct **2** (entry 3). The entry 7 shows that the utilization of acetic acid instead of picolinic acid was less efficient. In all these reactions, almost no oxidation products were formed and we still observed an important amount of Fe^{II}.[3] When the reaction was carried out without hydrocarbon (entries 5 and 6), no products were formed and the mass balance in quinone was 95% in both cases. Some 3-hydroxy-2-methyl-1,4-naphthoquinone was detected by GCMS in the presence of oxidant (entry 5). This compound can be formed by hydration of 2-methyl-1,4-naphthoquinone to give the 1,3,4-trihydroxy-2-methyl-naphtalene which is easily oxidized under air. [8]

Table 1: Fe^{II} system.

Entry	Conditions	Products (mmol)				
		R=O	R-Cl	**2**	**1**	Fe^{II}
1	A	n.d.	n.d.	0.75	0.37	0.39
2	A+AcOH 1.5 ml	n.d.	n.d.	0.95	0.46	0.41
3	B	0.13	n.d.	n.d.	2.04	0.28
4	A*	n.d.	traces	0.86	0.94	---
5	C +AcOH 1.5 ml	---	---	---	2.13	---
6	C*+AcOH 1.5 ml	---	---	---	2.38	---
7	D+AcOH 1.5 ml	n.d.	n.d.	0.50	---	---

Except as specified, these reactions were carried out under a slow argon stream with 20 mmol cyclohexane in 15 mL pyridine at 0°C to room temperature for 24 hours. PA refers to picolinic acid, AcOH to acetic acid and n.d to not detected. (A) $Fe^{II}(ClO_4)_2{\cdot}6H_2O$: 0.5 mmol, PA: 1.5 mmol, 2-methyl-1,4-naphthoquinone: 2 mmol, H_2O_2: 2 mmol. * with LiCl: 10 mmol. (B) $Fe^{II}(ClO_4)_2{\cdot}6H_2O$: 0.5 mmol, 2-methyl-1,4-naphthoquinone: 2 mmol, H_2O_2: 2 mmol. (C) $Fe^{II}(ClO_4)_2{\cdot}6H_2O$: 1.5 mmol, 2-methyl-1,4-naphthoquinone: 2.5 mmol, H_2O_2: 1.5 mmol, without cyclohexane, 0.23 mmol of 3-hydroxy-2-methyl-1,4-naphthoquinone was detected by GCMS. * without H_2O_2. (D) $Fe^{II}(ClO_4)_2{\cdot}6H_2O$: 1.5 mmol, 2-methyl-1,4-naphthoquinone: 2,5 mmol, LiCl: 5 mmol, H_2O_2: 1.5 mmol, under argon at -20°C during 3h and under air at room temperature over night.

A result that was not expected was obtained when we used the 2-methyl-1,4-naphthoquinone with the Fe^{III}-H_2O_2 system (**Table 2**): the formation of oxidation products was completely inhibited and 3-cyclohexyl-2-methyl-1,4-naphtoquinone and a small amount of cyclohexyl chloride appeared (entry 1). Adding acetic acid does not influence the reaction (entry 2), but the presence of a suitable carboxylic acid was necessary as in the Fe^{II} -H_2O_2 system (entry 3). Without Fe^{III} and H_2O_2 no reaction occurs (entries 4 and 5). The presence of a

large amount of Fe^{II} at the end of the reaction, which is never found in normal Fe^{III}-H_2O_2 reactions with hydrocarbon, indicated that the Fe^{II}-Fe^{IV} mechanism was involved in the formation of the adduct **2**. The blank experiment made without H_2O_2 shows that only the presence of the quinone is necessary to reduce the Fe^{III} to Fe^{II} (entry 4).

Table 2: Fe^{III} system.

Entry	Conditions	Products (mmol)				
		R=O	R-Cl	**2**	**1**	Fe^{II}
1	A	n.d.	0.11	0.57	1.12	0.21
2	A+AcOH 1.5ml	n.d.	0.09	0.51	1.11	0.30
3	B	0.05	n.d.	n.d.	1.75	0.20
4	C	n.d.	n.d.	n.d.	2.33	0.32
5	D	n.d.	n.d.	n.d.	1.91	---

Except as specified, these reactions were carried out under argon atmosphere with 20 mmol cyclohexane in 15 ml pyridine at 0°C to room temperature for 24 hours. (A) $Fe^{III}(PA)_2Cl_2HPyr_2$: 0.5 mmol, 2-methyl-1,4-naphthoquinone: 2 mmol, H_2O_2: 2 mmol. (B) $Fe^{III}Cl_3.6H_2O$: 0.5 mmol, 2-methyl-1,4-naphthoquinone: 2 mmol, H_2O_2: 2 mmol. (C) $Fe^{III}(PA)_2Cl_2HPyr_2$: 0.5 mmol, 2-methyl-1,4-naphthoquinone: 2.5 mmol, without H_2O_2. (D) without iron salt, 2-methyl-1,4-naphthoquinone: 2 mmol, H_2O_2: 2 mmol.

In the proposed mechanism for this reaction (**Scheme 1**), only a small amount of Fe^{II} produced by hydration of the 2-methyl-1,4-naphthoquinone is necessary. The Fe^{II}-Fe^{IV} manifold produces an alkyl radical which reacts with the quinone to form the radical intermediates **3** and **4**. This intermediate **4** can also reduce Fe^{III} to Fe^{II} and give the quinone adduct.

Table 3: Fe^{III} system using different ligands.

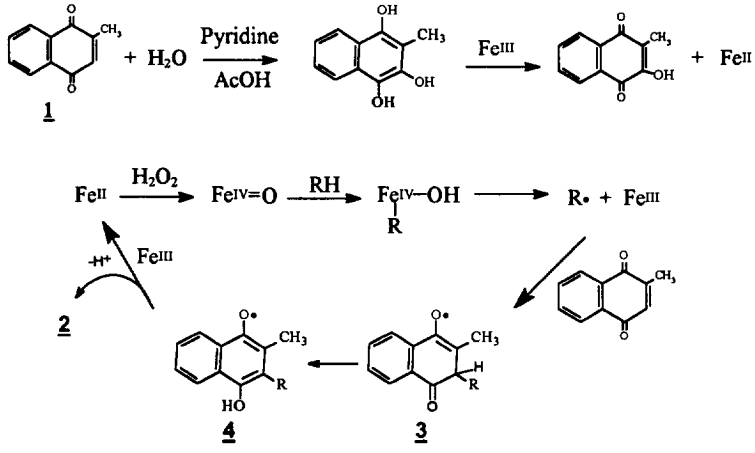
Entry	Conditions	Products (mmol)	
		R=O	**2**
1	A+ $Fe^{III}(ClO_4)_3$	1.68	0.10
2	A+ $Fe^{III}(acac)_3$	0.41	0.34
3	A+ $Fe^{III}Br_3$	0.40	n.d.
4	A+ $Fe^{III}F_3$	1.51	n.d
5	A+ $Fe^{III}(Fod)_3$	0.10	2.21
6	A+ $Fe^{III}Cl_3$	1.52	n.d
7	B+ $Fe^{III}Cl_3$	0.73	0.54
8	A+ $Fe^{III}(PA)_3$	0.85	0.74

Fe^{III} salt: 1 mmol, cyclohexane: 40 mmol, 2-methyl-1,4-naphthoquinone: 5 mmol, H_2O_2: 10 mmol in 30 ml pyridine, 3 ml AcOH. (A) room temperature for 24 hours, under air. (B) under vacuum at -20°c for 5h and closed system at room temperature over night. Fod refers to 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionate.

Using pyridine-acetic acid, the nature of the ligand coordinated to the iron still had a major influence on the formation of the adduct as is shown in **Table 3**. The utilization of halogen ligands under air did not give any quinone adduct (entries 3, 4 and 6) and it was almost the same for the perchlorate (entry 1). The reaction carried out under vacuum, using chloride ligand produced only a small amount of the compound **2**

(entry 7). The chelate ligands seem to be the best choice for this reaction (entries 5, 8), except for the acetyl acetonate (entry 2).

In all the experiments in **Table 3**, an excess of acetic acid was present. This provides the carboxylate ligand environment necessary for Gif chemistry in either manifold.



Scheme 1. Proposed mechanism for the functionalization of saturated hydrocarbons with 2-methyl-1,4-naphthoquinone

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