



The Conversion of Saturated Hydrocarbons into Carboxylic Acids using $\text{Fe}(\text{CO})_5$ - H_2O_2 Oxidation.

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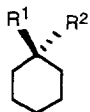
Abstract: Saturated hydrocarbons are transformed into their corresponding homologous carboxylic acids by treatment with iron pentacarbonyl and hydrogen peroxide in pyridine-acetic acid. A mechanism for this reaction is proposed. Attention is also directed to a new and convenient procedure for the determination of carbon monoxide. Copyright © 1996 Elsevier Science Ltd

Gif oxidation systems, based on H_2O_2 or on superoxide, convert saturated hydrocarbons regioselectively and chemoselectively into ketones.^{1,2} For a limited conversion (20-30%) the yield is high. Recently two manifolds have been recognized:³ the Fe^{III} - Fe^{V} manifold, in which much of the earlier work was carried out, and the Fe^{II} - Fe^{IV} manifold. For both manifolds, the selectivity pattern and the kinetic isotope effect (K.I.E.) were identical. However, in the Fe^{III} - Fe^{V} manifold radical chemistry was exceptional. In the Fe^{II} - Fe^{IV} manifold carbon radicals were formed after the initial attack of the activated iron species on a secondary position of the saturated hydrocarbon. Hydroxyl radicals, at least in the solvent pyridine or pyridine-acetic acid, were not involved in this chemistry.⁴ From our earlier work we postulated the initial formation of an Fe^{IV} or Fe^{V} -carbon bond. All the Gif type chemistry that we have carried out could be interpreted as Fe^{II} or Fe^{III} based with activation by H_2O_2 . In fact it sufficed to titrate for Fe^{II} versus Fe^{III} to understand in which manifold one was working. The reactions in the Fe^{II} - Fe^{IV} manifold were significantly faster than those in the Fe^{III} - Fe^{V} analogue.

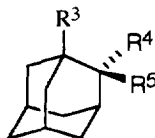
Recently⁵ we reported that saturated hydrocarbons could be selectively carboxylated at secondary positions using carbon monoxide- H_2O_2 in the presence of $(\text{MeO})_3\text{P}$ and Fe^{III} trispicolinate. The function of $(\text{MeO})_3\text{P}$ in the presence of H_2O_2 was to reduce the Fe^{III} to Fe^{II} . The Fe^{II} was then activated by reaction with the H_2O_2 to furnish, by reaction with the hydrocarbon, the Fe^{IV} -carbon bond which by insertion of CO and hydrolysis afforded the carboxylic acid. In the presence of methanol the methyl ester was formed.

Although this work with carbon monoxide gave superior results to those we had published before, it seemed to us that the use of $\text{Fe}(\text{CO})_5$ and H_2O_2 would be more convenient experimentally even though it was without precedent.

Iron pentacarbonyl (2 mmol) was used as a source of the carbonyl group for the formation of carboxylic acids. Starting from the saturated hydrocarbon (20 mmol) the hydrogen peroxide was added (5x2 mmol each 15 min) in pyridine-acetic acid (30-3ml). Under these conditions, up to 2.4 mmol of cyclohexane carboxylic acid was obtained from cyclohexane as well as some coupling products with pyridine (**Table 1**). The titration⁶ for Fe^{II} showed the presence of Fe^{II} and Fe^{III} in the system and we were able to detect and quantify some $\text{Fe}(\text{CO})_5$ at the end of the reaction (500 MHz NMR).⁷



- 1 $\text{R}^1=\text{CO}_2\text{H}$, $\text{R}^2=\text{H}$
- 2 $\text{R}^1, \text{R}^2=\text{O}$
- 3 $\text{R}^1=\text{OH}$, $\text{R}^2=\text{H}$
- 4 $\text{R}^1=2\text{-Pyridyl}$, $\text{R}^2=\text{H}$
- 5 $\text{R}^1=4\text{-Pyridyl}$, $\text{R}^2=\text{H}$
- 6 $\text{R}^1=\text{X}$, $\text{R}^2=\text{H}$



- 7 $\text{R}^5=\text{CO}_2\text{H}$, $\text{R}^3=\text{R}^4=\text{H}$
- 8 $\text{R}^3=\text{CO}_2\text{H}$, $\text{R}^4=\text{R}^5=\text{H}$
- 9 $\text{R}^5=\text{OH}$, $\text{R}^3=\text{R}^4=\text{H}$
- 10 $\text{R}^3=\text{OH}$, $\text{R}^4=\text{R}^5=\text{H}$
- 11 $\text{R}^4, \text{R}^5=\text{O}$, $\text{R}^3=\text{H}$
- 12 $\text{R}^3=2\text{-Pyridyl}$, $\text{R}^4=\text{R}^5=\text{H}$
- 13 $\text{R}^3=4\text{-Pyridyl}$, $\text{R}^4=\text{R}^5=\text{H}$
- 14 $\text{R}^5=2\text{-Pyridyl}$, $\text{R}^3=\text{R}^4=\text{H}$
- 15 $\text{R}^5=4\text{-Pyridyl}$, $\text{R}^3=\text{R}^4=\text{H}$

Table 1

| <u>1</u> | <u>2</u> | <u>4</u> | <u>5</u> | Fe ^{II} | Fe ^{III} | Fe(CO) ₅ |
|----------|----------|----------|----------|------------------|-------------------|---------------------|
| 2.37 | traces | 0.24 | 0.22 | 0.33 | 1.30 | 0.38 |

Cyclohexane 20 mmol, Fe(CO)₅ 2 mmol, H₂O₂ 5x2 mmol each 15 min, Pyridine 30 ml, Acetic acid 3 ml, under argon at 0°C and then up to RT. All the results are in mmol.

A kinetic study using the same conditions as in **Table 1**, showed that the formation of cyclohexane carboxylic acid was relatively fast ($t_{1/2}$ ~30 min). Coupling products to pyridine indicative of radical chemistry, were also formed. Ketone production began only when the other reactions had ceased, just as we observed before in the change from the Fe^{II}-Fe^{IV} to the Fe^{III}-Fe^V manifold.^{3,5} The presence of a carboxylic acid was necessary, as is characteristic of Gif chemistry.³ The best results were obtained in the usual 10:1 pyridine:acetic acid mixture with a 1:10 ratio of Fe(CO)₅ to hydrocarbon.

As in the previous system⁵ (Fe^{III} trispicolinate/(MeO)₃P/H₂O₂/CO), the adamantane selectivity gave predominant carboxylation in the secondary position, C²/C³=0.6 (**Table 2**). A mass balance of 97% was obtained. It is worth noting the stability of the different carboxylic acids formed under the reaction conditions: blank experiments starting from 2 mmol of the acid 1 or 8 showed that the reaction was, as expected, irreversible.

Table 2 Adamantane Selectivity

| Substrate | <u>7</u> | <u>8</u> | <u>9</u> | <u>10</u> | <u>11</u> | <u>12</u> | <u>13</u> | <u>14</u> | <u>15</u> |
|------------|----------|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Adamantane | 0.195 | 0.08 | 0.035 | 0.034 | 0.059 | 0.24 | 0.24 | 0.053 | 0.033 |

Adamantane 10 mmol, Fe(CO)₅ 2 mmol, H₂O₂ 5x2 mmol each 15 min, Pyr 30 ml, AcOH 3 ml, under argon 0°C to RT. All the results are in mmol.

The kinetic isotope effect for cyclohexane versus perdeuterocyclohexane was equal to 2.1, which was similar to the typical value of both manifolds. These characteristics showed that this system responded to the main criteria of other Gif systems. The gas formed during the reaction was characterized and quantified in order to better understand the reaction mechanism. The carbon dioxide was quantified by bubbling through 2 traps of barium hydroxide solution. As far as the determination of carbon monoxide was concerned, several methods are described in the literature. The best known consists in passing carbon monoxide through I₂O₅ at high temperature.⁸ Another uses a ruthenium complex⁹ to trap quantitatively CO.

We decided to examine more economic, room temperature procedures for the determination of carbon monoxide. In each case we examined the oxidation of CO to give CO₂ which, as mentioned above, was readily determined by precipitation as BaCO₃. We considered the use of chlorine water, which should react with carbon monoxide to furnish phosgene readily hydrolysed to carbon dioxide. However, this reaction was too slow.

The reaction of carbon monoxide with chlorine was one of the famous chain reactions cited in the nomination of Hinshelwood and Semenov for the Nobel Prize of 1956. Semenov wrote a monumental text¹⁰ where this reaction was initiated by visible light. With this text in mind carbon monoxide was bubbled through a solution of chlorine water with irradiation by a tungsten lamp. The phosgene formed was immediately converted into CO₂ in presence of water, and then swept out to be trapped with barium hydroxide. The appropriate blank experiments were carried out. It seems to us that this method for the quantification of CO is more practical, economic and convenient than those used previously.¹¹

In the $\text{Fe}(\text{CO})_5\text{-H}_2\text{O}_2$ system, only carbon monoxide and carbon dioxide were produced (**Table 3**). There was no indication of a catalase reaction producing oxygen. Formation of CO_2 and CO occurs even in the absence of acetic acid and was proportional to the amount of H_2O_2 added.

Table 3 Formation of carbon monoxide and carbon dioxide in the presence and absence of acetic acid

| Conditions | CO_2 | CO | Total of gas |
|-----------------------|---------------|-------------|--------------|
| Pyr 33 ml | 3.25 mmol | 2.25 mmol | 5.5 mmol |
| Pyr 30 ml + AcOH 3 ml | 2.05 mmol | 2.44 mmol | 4.6 mmol |

Cyclohexane 20 mmol, $\text{Fe}(\text{CO})_5$ 2 mmol, H_2O_2 5x2 mmol each 15 min, under argon at 0°C to RT.

The preliminary studies so far reported suggested that this new reaction took place in the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ manifold. In accordance with our prior experiments³ we added nitrite, chloride, bromide and azide ions to the reaction (**Table 4**). Major coupling products with chloride and with azide were seen. The amounts of chloride and azide relative to carboxylation depended on the concentration of chloride and azide anions as expected.³ The addition of ascorbic acid increased slightly the yield of chloride, suggesting again that the reaction takes place in the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ manifold.³

Table 4: Inhibition of the carboxylation by addition of a salt and formation of alkyl derivatives

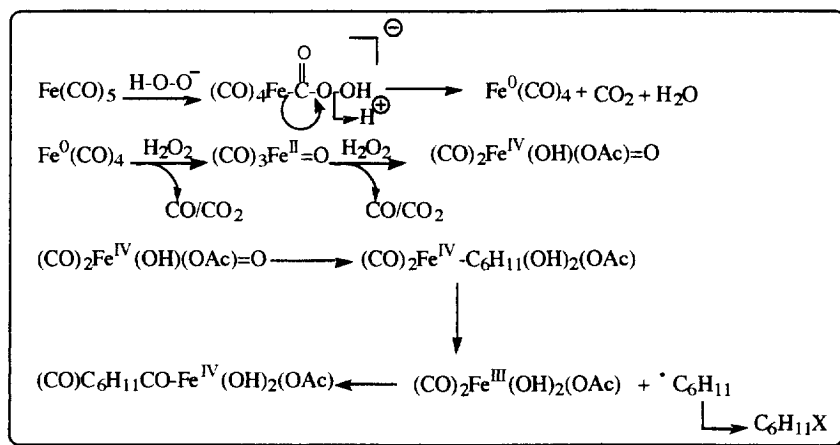
| salt | <u>1</u> | <u>6</u> | <u>2</u> | <u>4</u> | <u>5</u> |
|-----------------|----------|---------------------------------|----------|----------|----------|
| none | 2.09 | n.d. | 0.08 | 0.12 | 0.11 |
| NaNO_2 | 0.40 | 0.10 ($\text{X}=\text{NO}_2$) | n.d. | n.d. | n.d. |
| LiCl | 0.18 | 1.49 ($\text{X}=\text{Cl}$) | n.d. | 0.45 | 0.22 |
| LiBr | 0.75 | 0.21 ($\text{X}=\text{Br}$) | 0.07 | 0.15 | 0.08 |
| NaN_3 | 0.08 | 2.21 ($\text{X}=\text{N}_3$) | 0.81 | 0.11 | 0.05 |

Cyclohexane 20 mmol, $\text{Fe}(\text{CO})_5$ 2 mmol, H_2O_2 5x2 mmol each 15 min, salt 20 mmol, Pyr 30 ml, AcOH 3 ml, under argon, 0°C to RT. All the results are in mmol. n.d.: not detected.

It now possible to propose a mechanism for this interesting new reaction which is in accord with the experimental facts. First, in a blank experiment, it was shown that there was no reaction between carbon radicals produced by photolysis of a Barton PTOC ester¹² and $\text{Fe}(\text{CO})_5$. The latter was recovered quantitatively. So the function of H_2O_2 must be, in part, to remove carbon monoxide coordinated to Fe^0 (**Scheme 1**) to furnish $\text{Fe}^0(\text{CO})_4$. In principle, this might react with a saturated hydrocarbon according to the elegant work of Field.¹³ However, the experimental facts are better explained by the $\text{Fe}^{\text{II}}\text{-Fe}^{\text{IV}}$ manifold. So the $\text{Fe}^0(\text{CO})_4$ species must react further with loss of CO or CO_2 (or both) to furnish $(\text{CO})_3\text{Fe}^{\text{II}}=\text{O}$. A second oxidation with loss of CO/CO_2 would furnish the Fe^{IV} oxenoid species which could be written as $(\text{CO})_2\text{Fe}^{\text{IV}}(=\text{O})_2$. However it is more probable that it is $(\text{CO})_2\text{Fe}^{\text{IV}}(\text{OH})(\text{OAc})=\text{O}$. The usual insertion reaction would give $(\text{CO})_2\text{Fe}^{\text{IV}}\text{-C}_6\text{H}_{11}(\text{OH})_2(\text{OAc})$, the species that fragments into cyclohexyl radical and $(\text{CO})_2\text{Fe}^{\text{III}}(\text{OH})_2(\text{OAc})$. This radical formation explains the coupling with pyridine and the formation of chloride, azide and derivatives.³ However, the cyclohexyl radical could not react with CO under the conditions of our experiments⁵ so the carboxylic acid must come about in a different way. There are several possibilities, but the least complicated would be for the cyclohexyl radical to react with a CO of the species $(\text{CO})_2\text{Fe}^{\text{III}}(\text{OH})_2(\text{OAc})$ to afford the species $(\text{CO})\text{Fe}^{\text{IV}}\text{-CO-C}_6\text{H}_{11}(\text{OH})_2(\text{OAc})$. By hydrolysis this would furnish the carboxylic acid and an Fe^{II} species whilst with methanol, the corresponding methyl ester (0.13 mmol) and the same Fe^{II} species could result.

Thus all the experimental facts can be explained satisfactorily.

Scheme 1: Proposed mechanism



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REFERENCES AND NOTES

- Barton, D. H. R. ; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504-512.
- Barton, D. H. R. ; Hu, B. ; Taylor, D. K. ; Rojas-Wahl, R. V. *Tetrahedron Lett.* **1996**, *37*, 1133-1136.
- Bardin, C. ; Barton, D. H. R. ; Hu, B. ; Rojas-Wahl, R. U. ; Taylor, D. K. *Ibid.* **1994**, *35*, 5805-5808. Barton, D. H. R. ; Chabot, B. ; Delanghe, N. C. ; Hu, B. ; Le Gloahec, V. N. ; Rojas-Wahl, R. U. *Tetrahedron Lett.* **1995**, *36*, 7007-7010.
- Barton, D. H. R. ; Hu, B. ; Taylor, D. K. ; Rojas-Wahl, R. V. *J. Chem. Soc. (Perkin Trans.2)*, **1996**, in press.
- Barton, D. H. R. ; Bévière, S. D. ; Chavasiri, W. ; Doller, D. ; Liu, W.-G. ; Reibenpies, J. H. *New J. Chem.* **1992**, *16*, 1019-1029. Sawyer, D. T. ; Kang, C. ; Llobet, A. ; Redman, C. *J. Am. Chem. Soc.* **1993**, *115*, 5817-5818. Hage, J. P. ; Llobet, A. ; Sawyer, D. T. *Bioorg. Med. Chem. Lett.* **1995**, *3*, 1383-1388.
- Barton, D. H. R. ; Beck, A. H. ; Delanghe, N. C. *Tetrahedron Lett.* **1996**, *37*, 1555-1558.
- Clark, L. *J. Analytical Chemistry* **1962**, *34*, 348-352.
- Quantification of Fe(CO)₅ by 500 MHz NMR. Instrumentation: a Varian Unity 500 equipped with a triple resonance probe (bbp) was run using the following parameters: lock: pyridine-d₅; frequency: 500 MHz; spectral window: 37,558.7 Hz; number of transients: 100,000 (bbp); decoupler mode: nny; decoupler power: 46 db; decoupler mode frequency 9104 Hz; transmitter power: 55 db; pulse width: 5 (bbp); acquisition time: 0.600 s. Internal standard: hexachloroethane 0.0857 mmol, δ=104.2 ppm; Fe(CO)₅ δ_{CO}=210 ppm. In an NMR tube, cyclohexane (0.5 mmol), Fe(CO)₅ (0.05 mmol), ferric acetylacetonate (0.025 mmol) a paramagnetic reagent, pyridine d₅ (0.75 ml), acetic acid (0.075 ml) and the internal standard (0.0857 mmol) were mixed. First a blank experiment without hydrogen peroxide was ran in order to confirm that hexachloroethane was a suitable standard. H₂O₂ (0.25 mmol) was then added. When the reaction was complete 9.46 μmol of Fe(CO)₅ were present; reported to the usual scale (cyclohexane (20) mmol, Fe(CO)₅ (2 mmol), pyridine (30 ml), AcOH (3 ml), H₂O₂ (10 mmol)) it gave 0.38 mmol of iron pentacarbonyl remaining.
- Alaise, V. A. ; Hall, R. T. ; Staats, F. C. and Becker, W. W. *Analytical Chemistry* **1947**, *19*, 347-351.
- Morvillo, A. ; Forti, L. ; Bressan, M. *New J. Chem.* **1995**, *19*, 951-957.
- Semenoff, N. *Chemical Kinetics and Chain Reactions*; Fowler R. H. , Kapitzka, P., Eds; Clarendon Press: Oxford; **1935**, Chap.V, 127-139.
- Quantification of carbon monoxide. In a 250 ml three neck-flask evacuated with a water pump, a cold water solution of chlorine (20 ml. approximately 5 eq corresponding to the expected gases), was added. When the first portion of H₂O₂ was added, the connection between the two flasks was opened, and the tungsten lamp was switched on. This static system was allowed to react for 3.5 h before being connected to a trap of Ba(OH)₂. The gases formed were bubbled, at a low flow rate, through these traps for 3.5 h. The precipitate obtained was filtered and dried in an oven before weighing.
- Barton, D. H. R. in collaboration with Parekh, S. I. *Half a Century of Free Radical Chemistry*; Radicati di Brozolo, L.A., Scaola Normale Superiore Pisa, Eds; Cambridge University Press: 1993.
- Field, L. D. ; Baker, M. V. *J. Am. Chem. Soc.* **1986**, *108*, 7433-7434; Field, L. D. ; Baker, M. V. *J. Am. Chem. Soc.* **1987**, *109*, 2825-2826; Whittlesey, M. K. ; Mawby, R. J. ; Osman, R. ; Perutz, R. N. ; Field, L. D. ; Wilkinson, M. P. ; George, M. W. *J. Am. Chem. Soc.* **1993**, *115*, 8627-8637.

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