Pergamon

Tetrahedron Letters, Vol. 36, No. 39, pp. 7007-7010, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01450-0

Further Evidence for the Fe^{II}-Fe^{IV} and Fe^{III}-Fe^{V} Manifolds in the Substitution of Saturated Hydrocarbons.

Derek H. R. Barton*, Beatrice M. Chabot, Nathalie C. Delanghe, Bin Hu,
Valerie N. Le Gloahec and Roy U. Rojas Wahl.

Department of Chemistry, Texas A&M University, College Station TX 77843-3255, USA.

Abstract : *The substitution of saturated hydrocarbons by the anions nitrite, thiocyanate, azide and chloride, using H_2O_2 and TBHP as oxidants has been shown to depend upon the Fe^{II}-Fe^{IV} manifold and to involve radical chemistry. As soon as the Fe^{II} has been oxidised to Fe^{III}, the reactions proceed in the Fe^{III}-Fe^{V} manifold where oxidation, but no anion substitution, is seen.*

Gif type systems operating in the Fe^{III}-Fe^{V} manifold in the presence of chloride ion never produce alkyl chlorides[1,2]. We were surprised, therefore, when the addition of triphenylphosphine to a normal Fe^{III}-H_2O_2 reaction replaced the usual ketonisation process by chlorination[3]. When TBHP (t-butylhydroperoxide) was used as an oxidant at 60°C chloride formation was again observed and other anions such azide, thiocyanate and nitrite reacted to give the appropriate alkyl derivatives[4,5]. The informative experiments of Minisci[6] showed that chloride formation was indicative of carbon radicals reacting with Fe^{III}-Cl to give Fe^{II}+R-Cl. We have established that chloride formation is associated with Fe^{II} reacting with hydrogen peroxide in what we call the Fe^{II}-Fe^{IV} manifold[7]. As usual in pyridine hydroxyl radicals are not involved[8]. If the initial reagent is Fe^{III}, chloride formation, when seen, is associated with reduction in some way of Fe^{III} to Fe^{II} followed by reaction with the oxidant.

Using Fe^{II} and H_2O_2 we were able to demonstrate that chloride formation was a very fast reaction[7] which stopped when all the Fe^{II} had been oxidised to Fe^{III}. At this point the normal ketonisation reaction associated with Fe^{III}+H_2O_2 took over. Since alkyl chloride was not formed during this relatively slow oxidation, although there was an excess of Fe^{III}-Cl present, this was powerful evidence that radicals are not involved[7] in the ketonisation reaction.In the H_2O_2-chloride experiments it was useful to add the oxidant in portions and to confirm the conversion of all Fe^{II} into Fe^{III} by titration.

The same experiment was repeated with TBHP as follows: to a solution of pyridine (30 ml) and acetic acid (3 ml) at room temperature under air was added $Fe^{II}(ClO_4)_2.6H_2O$ (3 mmol), cycloctane (20 mmol), LiCl (15.0 mmol), PA (picolinic acid) (9.0 mmol) and then at every 15 minutes from time zero TBHP (3 mmol) up to 30 mmol total. After 2 additions all the Fe^{II} had been converted to Fe^{III} (titration) and 3.4 mmol of cyclooctyl chloride had been formed. No additional chloride was formed, but ketone (6 mmol) was produced slowly over 3 days. The behaviour of the TBHP-Fe^{II} system is very similar to that of the H_2O_2-Fe^{II} system:

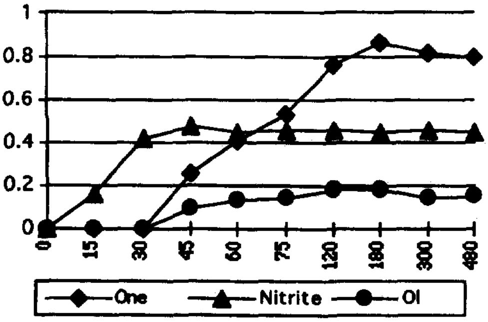
chloride formation proceeds as long as Fe^{II} is present by a radical reaction: this is followed by ketonisation in the second stage.

We have now carried out similar experiments using H_2O_2 and TBHP with $Fe^{II}(ClO_4)_2.6H_2O$ as catalyst in the presence of NaSCN, $NaNO_2$, NaN_3 and LiCl. In all experiments the Fe^{II} is oxidised, after the first additions of the oxidant, to Fe^{III}. At this point the formation of the derivatives ceases and the systems ketonize the hydrocarbons instead.The pyridine coupling products of the hydrocarbons whilst Fe^{II} is present, are characteristic of radical chemistry.

Ascorbic acid reduces Fe^{III} to Fe^{II} (titration[9]). The addition of ascorbic acid either at the beginning of the reaction, or during the reaction, increases the yield of the substituted hydrocarbons with some increase in the amount of pyridine coupling products as expected for increased Fe^{II} formation.

Figs.1 and 2 show typical evolution of the reactions with time using H_2O_2 and TBHP respectively. In Fig.1 the nitro-derivative is formed rapidly and the ketone and alcohol start to appear after the nitrocyclohexane formation is complete. This corresponds to Fe^{II} conversion to Fe^{III}. Similarly in Fig.2 the evolution of cyclohexyl azide with time is followed with similar results.

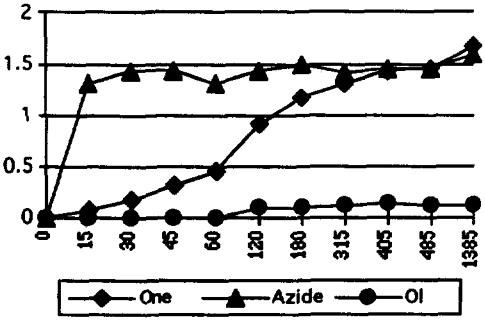
Fig. 1



Fe^{II}- H_2O_2 system.

Fig.1 : Conditions : $NaNO_2$ 15 mmol
$Fe(ClO_4)_2$, 6 H_2O 1 mmol;
PA 3 mmol;C_6H_{12} 20 mmol;
ascorbic acid 1 mmol;
pyridine 30 ml; H_2O_2 5x2 mmol.

Fig. 2



Fe^{II}- TBHP system.

Fig.2 : Conditions : NaN_3 15 mmol;
$Fe(ClO_4)_2$, 6 H_2O 1 mmol;
PA 3 mmol; C_6H_{12} 20 mmol;
ascorbic acid 1 mmol;
pyridine 25 ml; TBHP 5x2 mmol.

In table 1 the results using H_2O_2 as oxidant are summarised. Without the addition of acetic acid or better picolinic acid there is little substitution or oxidation. Picolinic acid has better effect than acetic acid. The addition of ascorbic acid has a beneficial effect on the yield of the substitution products by keeping the iron as Fe^{II} for a longer time (Entries 4, 8 and 12)[10].

Table 1 : Fe^{II} - H_2O_2 system.

Entry	Salts	Conditions	$Fe(ClO_4)_2$, 6 H_2O	RX	1	2	3	4
1	$NaNO_2$	A	2 mmol	nd	0.02	nd	nd	nd
2	$NaNO_2$	A+AcOH(3 ml)	2 mmol	0.20	0.25	nd	0.05	0.03
3	$NaNO_2$	A+PA(6 mmol)	2 mmol	0.24	1.02	0.15	0.10	0.05
4	$NaNO_2$	A+PA(6 mmol)+AscA(1 mmol)	2 mmol	1.15	0.39	0.13	0.29	0.15
5	NaSCN	A	2 mmol	0.20	0.20	0.03	nd	nd
6	NaSCN	A+AcOH(3 ml)	2 mmol	0.10	0.11	nd	nd	nd
7	NaSCN	A+PA(6 mmol)	2 mmol	0.25	0.19	nd	nd	nd
8	NaSCN	A+PA(9mmol)+AscA(1.5mmol)	3 mmol	0.95	0.20	0.05	0.03	0.02
9	NaN_3	A	2 mmol	0.07	0.18	nd	nd	nd
10	NaN_3	A+AcOH(3 ml)	2 mmol	0.76	0.80	0.10	nd	nd
11	NaN_3	A+PA(6 mmol)	2 mmol	2.24	0.86	0.15	0.05	0.02
12	NaN_3	A+PA(6 mmol)+AscA(1 mmol)	2 mmol	4.22	0.56	nd	0.10	0.05
13	LiCl	B+AcOH(3 ml)	3 mmol	1.69	2.68	trace	nd	nd
14	LiCl	C+AcOH(3 ml)	3 mmol	4.22	3.35	trace	nd	nd

1 cyclohexanone; 2 cyclohexanol; 3 ortho-pyridine coupling product; 4 para-pyridine coupling product. All results are in mmol. PA: picolinic acid, AscA: ascorbic acid, nd not detected.
(A) cyclohexane 20 mmol; Pyridine 30 ml; NaX 15 mmol; H_2O_2 5x2 mmol each 15 min. (B) cyclohexane 40 mmol; Pyridine 30 ml, LiCl 15 mmol; H_2O_2 10x3 mmol each 15 min. (C) cyclohexane 40 mmol; Pyridine 30 ml, LiCl 15 mmol; H_2O_2 10x3 mmol each 15 min. $FeCl_2$ 2x3 mmol added after 15 min and 30 min. Entry (4) : AscA 2 mmol from the beginning; entry (8) : AscA 1.5 mmol added portionwise in mixture with H_2O_2 each 15 min; entry (12) : AscA 2 mmol added portionwise: 4 x 0.5mmol every 30 min.[11]

In table 2 the results using TBHP as oxidant are presented. Contrary to the results in Table1 the Fe^{II}-TBHP system does not need a carboxylic acid to functionalise hydrocarbons. In fact the addition of acetic acid has a deleterious effect. As in Table 1 the addition of ascorbic acid also leads to an increase in the anionic trapping products.

Table 2 : Fe^{II} - TBHP system.

Entry	Salts	Conditions	$Fe(ClO_4)_2$, 6 H_2O	RX	1	2	3	4
1	$NaNO_2$	D	1 mmol	0.25	1.4	nd	0.16	0.07
2	$NaNO_2$	D+ AcOH(2.5 ml)	1 mmol	0.09	0.25	0.07	0.04	0.02
3	$NaNO_2$	D+AscA(1 mmol)	1 mmol	0.44	1.2	nd	0.45	0.31
4	$NaNO_2$	D+AscA(1 mmol)+PA(3 mmol)	1 mmol	1.2	1.15	nd	1.15	0.57
5	NaSCN	D	3 mmol	4.0	0.9	nd	nd	nd
6	NaSCN	D+AcOH(2.5 ml)	3 mmol	0.5	0.08	nd	nd	nd
7	NaSCN	D+PA(9 mmol)	3 mmol	0.34	0.17	0.06	0.02	trace
8	NaSCN	D+AscA(1 mmol)	3 mmol	3.9	0.4	nd	trace	trace
9	NaSCN	D+PA(3 mmol)+AscA(1 mmol)	1 mmol	0.24	0.16	nd	0.08	trace
10	NaN_3	D	1 mmol	0.6	0.67	0.11	trace	trace
11	NaN_3	D+PA(3 mmol)+AscA(1 mmol)	1 mmol	1.6	1.45	0.08	0.85	0.43
12	LiCl	E+AcOH(3 ml)	3 mmol	2.25	3.61	0.13	nd	nd

1 cyclohexanone; 2 cyclohexanol; 3 ortho-pyridine coupling product; 4 para-pyridine coupling product. All results are in mmol. PA: picolinic acid, AscA: ascorbic acid, nd not detected.
(D) Cyclohexane 20 mmol ; Pyridine 25 ml; NaX 15 mmol; TBHP 5x2 mmol added each 15 min.
(E) Cyclooctane 20 mmol; Pyridine 30ml; LiCl 15 mmol; TBHP 10x3 mmol. Entry (4)+(8)+(9): AscA added portionwise : 0.5 mmol each 15 min; entry (3)+(11) : AscA added from the beginning.

Finally, we are able to distinguish between the well publicized Fe^{II} - superoxide chemistry (Gif^{III}, Gif^{IV})[1,12] and the Fe^{II} - Fe^{IV} manifold with two simple experiments: Addition of 5 mmol LiCl to a typical Gif^{IV} system with 20 mmol cyclooctane does not give any cyclooctylchloride at all, but affords as usual ketone (Fe^{II} - superoxide = Fe^{III} - O_2^{2-}, Fe^{III} - Fe^{V} manifold). However, addition of H_2O_2 to the very same system yields cyclooctylchloride (1.97 mmol) as the major product besides cyclooctanone (1.03 mmol). This is a clear proof, that in the Gif^{III} and Gif^{IV} system no Fe^{IV} is generated, but an Fe^{V} species.

References and Notes.

1. Barton, D.H.R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504-512.
2. Barton, D.H.R.; Csuhai and D. Doller *Tetrahedron* **1992**, *48*, 9195-9206.
3. Barton,D.H.R.; Beviere, S.D. *Tetrahedron Lett.* **1993**, *34*, 5689-5692.
4. Barton,D.H.R.; Beviere,S.D.; Chavasiri,W.; Doller D.; Hu B. *Tetrahedron Lett.* **1993**, *34*, 1871-1874.
5. Barton, D.H.R.; Beviere, S.D.; Chavasiri, W. *Tetrahedron* **1994**, *50*, 31-46.
   Barton,D.H.R.; Chavasiri,W. *Tetrahedron* **1994**, *50*, 47-60
6. Minisci,F.; Fontana,F.; Araneo,S.; Recupero, F. *Tetrahedron Lett.* **1994**, *35*, 3759-3762.
7. Bardin,C.; Barton,D.H.R.; Hu,B.; Rojas Wahl, R.U.; Taylor,D.K. *Tetrahedron Lett.* **1994**, *35*, 5805-5808.
8. For similar conclusions see Sawyer,D.T.; Hage, J. P. ; Sobkowiak, *J. Am. Chem. Soc.* **1995**, *117*, 106; and references there cited.
9. Clark, L. J, *Anal. Chem.* **1962**, *34*, 348-352.
10. Cf. Udenfriend, S.; Clark, C. T; Axelrod, J. ; Brodie, B.B. *J. Biol. Chem.* **1954**, *208*, 731.
    Ito, S.; Ueno, K ; Mitarai, A; Sasaki, K.*J. Chem. Soc., Perkin Trans. 2*, **1993**, 255.
11. All yields (in mmol) were determined by G.-C. using a Hewlett Packard 5890 series II instrument equipped with flame ionization detectors, with N2 as a carrier gas. The columns used for chromatography were DB-WAX (30 m) or DB-5 (30 m) capillary columns from J&W Scientific (0.32 mm i. d. , 25 µm film thickness). In the case of cyclohexane no products were formed except those indicated. For parallel experiments with cyclooctane (unpublished) good mass balances were observed. A typical experiment was as follows: 20 mmol cyclooctane, 3 mmol $FeCl_2$ 4 H_2O, 15 mmol NaX, 9 mmol picolinic acid, 10x3 mmol H_2O_2, 30 ml pyridine. The mass balance obtained was 95%.
12. Barton, D. H. R.; Boivin, J.; Gastiger, M.; Morzycki, J.; Hay-Motherwell, R. S.; Motherwell, W. B.; Ozbalik, N.; Schwarzentruber, K. M.; *J. Chem. Soc., Perkin Trans. I*, **1986**, 947 and references therein.

(*Received in USA* 14 *June* 1995; *revised* 19 *July* 1995; *accepted* 28 *July* 1995)