Pergamon

Tetrahedron Letters, Vol. 35, No. 32, pp. 5805-5808, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01199-0

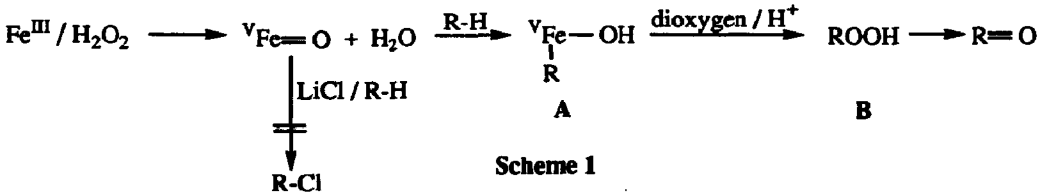
The Fe^{II}-Fe^{IV} and Fe^{III}-Fe^{V} Manifolds in an Expanded World of Gif Chemistry

Christophe Bardin, Derek H. R. Barton,* Bin Hu, Roy Rojas-Wahl and Dennis K. Taylor.

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

Abstract: The species responsible for hydrocarbon activation and formation of alkyl chlorides in the Fe^{II} and Fe^{III}-H_2O_2 and *tert*-butyl hydroperoxide systems are identified. The importance of the Fe^{II}-Fe^{IV} manifold in providing a mechanism which permits the selective functionalization of saturated hydrocarbons by ionic trapping with chloride, azide, and other anions is made manifest. Comparison is made with the Fe^{III}-Fe^{V} manifold where ionic trapping is never seen.

Gif chemistry[1] permits the selective functionalization of saturated hydrocarbons at secondary positions to give ketones. The proposed mechanism for this reaction is shown (Scheme 1) and involves the formation of an iron-carbon σ-bond (A) and an alkyl hydroperoxide (B). As in all Gif type systems so far studied the activation of the Fe^{III} is peroxide dependent but the hydroperoxide comes from molecular oxygen.



Scheme 1

In the Fe^{III}-H_2O_2 system chlorides and bromides can be formed by CCl_4 and $BrCCl_3$ respectively but are never seen by a reaction with chloride or bromide anions.[2] Formation of chloride is possible however if PPh_3 is added to the Fe^{III}-H_2O_2 system containing chloride ion.[3] In contrast, chlorides are readily and efficiently formed[4,5] by Fe^{III}-*tert*-butyl hydroperoxide (TBHP) oxidation of saturated hydrocarbons at 60°C (half-live ≈ 110 minutes) when chloride ion is present. Likewise azides, thiocyanates, cyanides and even nitro-compounds (from nitrite anion) are easily prepared.[6]

Recently Minisci and Fontana[7] have suggested that the formation of chlorides in the Fe^{III}-TBHP system involves the reaction of carbon radicals with chloride ion bonded to Fe^{III}. In agreement we have already reported that carbon radicals are present at 60°C.[5] However, on addition of chloride ion, radical formation, as judged by capture by pyridine ceases. As a consequence we did not take into consideration sufficiently the importance of this radical formation.[8] However, further work by Minisci, Fontana, Araneo and Recupero[9] has provided evidence for radical formation and for hydrogen abstraction from the saturated hydrocarbon by *tert*-butoxy radical as the activation process.

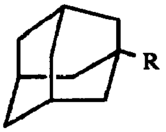
We now report that Fe^{II} is at the origin of chloride formation in all the aforementioned systems, but that hydroxyl radicals are not involved (using H_2O_2) while *tert*-butoxy radicals are responsible for hydrocarbon activation with TBHP in the presence of Fe^{II}.

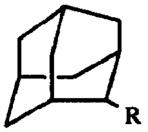
Table 1. Adamantane reactivity / selectivity based on the Fe^{II}-H_2O_2 and Fe^{II}-TBHP systems.[a]

Entry	System[b]	Products (mmol)	Total Yield (mmol)	C^2 / C^3 ratio[c]
1	(A)	**1** (0.06), **2** (0.05), **4** (0.02)	0.13	0.18
2	(A) + LiCl (9mmol)	**1** (0.10), **2** (0.04), **3** (0.05), **6** (0.20)	0.39	1.05
3[d]	(A) + PA (6mmol)	**1** (0.06), **2** (0.04), **4** (0.03)	0.13	0.30
4	(A) + LiCl (9mmol) + PA(6mmol)	**1** (0.08), **2** (0.03), **3** (0.01), **6** (0.17)	0.29	1.42
5	(B)	**1** (0.57), **2** (0.18), **4** (0.15), **5** (0.04)	0.94	0.25
6	(B) + LiCl (9mmol)	**1** (0.42), **2** (0.13), **3** (0.22), **4** (0.01), **5** (0.01), **6** (0.36)	1.15	0.49
7[d]	(B) + PA (6mmol)	**1** (0.43), **2** (0.11), **4** (0.11), **5** (0.02)	0.67	0.24
8	(B) + LiCl (9mmol) + PA (6mmol)	**1** (0.43), **2** (0.15), **3** (0.05), **4** (0.02), **5** (0.01), **6** (0.32)	0.98	0.55
9	(C)	**1** (1.14), **2** (0.62), **4** (0.38), **5** (0.11)	2.25	0.28

[a] All products were identified by GC (comparison with authentic samples), GCMS and NMR. [b] Conditions; (A) $Fe(ClO_4)_2.6H_2O$, 3 mmol); Adamantane, 10 mmol; H_2O_2 (30%), 3 mmol; pyridine / AcOH, (10:1), 33 mL; 25°C under argon for 3 hrs. (B) As in (A) except TBHP (3 mmol) was employed instead of H_2O_2. (C) Adamantane, 10 mmol; di-*t*-butyl peroxalate, 10 mmol; pyridine, 33 mL; 40°C under argon for 3 hrs: See Text. [c] The C^2 / C^3 ratio is defined as the total secondary products divided by total tertiary products. [d] PA refers to picolinic acid.

1 : R = 2-pyridyl
2 : R = 4-pyridyl
3 : R = Cl



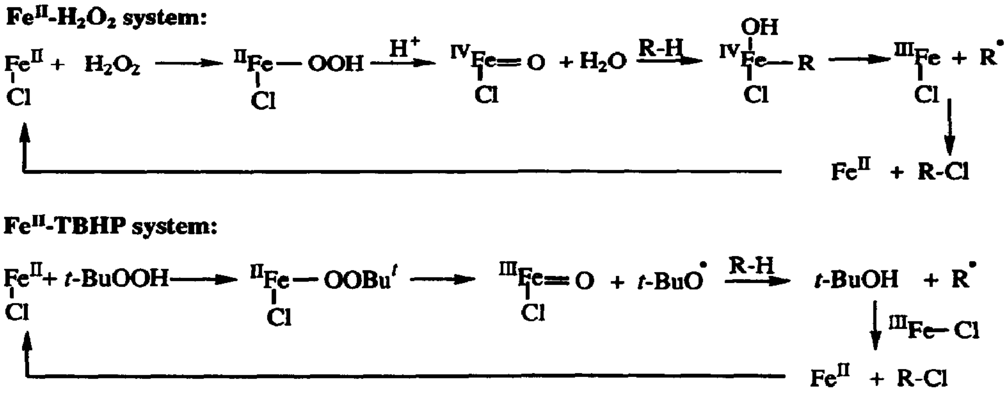


4 : R = 2-pyridyl
5 : R = 4-pyridyl
6 : R = Cl

Table 1 shows the reactivity of adamantane towards the Fe^{II}-H_2O_2 and Fe^{II}-TBHP systems. Addition of chloride ions (Entries 2 and 4) to the Fe^{II}-H_2O_2 system not only increases significantly the amount of reaction but also results in a dramatic increase in the C^2 / C^3 ratio. The activation of adamantane is therefore catalyst dependant and suggests as such that the activation of the hydrocarbon cannot be due to formation of hydroxyl radicals (Fenton chemistry) as the C^2 / C^3 ratio should remain constant. Support for carbon radicals in the Fe^{II} system came from experiments similar to those in Table 1. When $Fe^{II}(ClO_4)_2$ and cyclohexane (40 mmol) were used, 1.07 mmol of chloride was formed. When Tempo (5 mmol) was added chloride formation was suppressed completely in favor of formation of 1.06 mmol of cyclohexyl Tempo adduct. This suggests that the alkyl chloride is not formed via ligand coupling. Furthermore, the product distribution in Table 1 is indicative of carbon radical chemistry. The 3°-adamantyl radical being highly reactive, (pyramidal and "primary-like")[10] reacts preferentially with the solvent (protonated pyridine) while the 2°-adamantyl radical is of greater stability, (planar)[10] and reacts with the Fe^{III}-Cl species to produce Fe^{II} and alkyl chloride. Such coupling is of course known.[11] For Entries 2 and 4 the initial process must be Fe^{IV} oxenoid insertion followed by iron-carbon bond radical fragmentation.

Additional evidence against the activation process being due to formation of hydroxyl radicals came when excess benzene was added to the reaction mixture. No phenol was produced. Likewise functionalization of toluene gave benzyl chloride and benzyl alcohol / acetate and no cresols. Also the formation of highly reactive hydroxyl radicals in traditional Fenton chemistry is reflected in $k_H/k_D = 1.0$.[12] The Fe^{II}-H_2O_2 system described here is very fast ($T_{1/2}$ <<< 30 sec. at -20°C) and has $k_H/k_D = 2.1$[13] The latter is in agreement with an Fe^{IV} oxenoid process, (as in related Gif systems[1]) as a preliminary to radical formation. Recent literature supports this conclusion.[13,14]

The Fe^{II}-TBHP system has completely different characteristics. (a) The reaction is slower ($T_{1/2} \approx 3$ min. at -20°C); (b) $k_H/k_D = 8.0$[13]; (c) the efficiency is higher (Entries 5-8, Table 1) while the C^2 / C^3 ratio is lower (0.24-0.55). Although the formation of alkyl radicals could not be confirmed by trapping with Tempo, (Fe^{II} converts tempo to the parent hydroxylamine on the Fe^{II}-TBHP time scale.), the product distributions shown in Table 1 are again indicative of the intermediacy of 2° and 3°-adamantyl radicals.[10] When *tert*-butoxy radicals were generated at 40°C in pyridine by decomposition of pre-formed di-*t*-butylperoxalate[15] under argon in the presence of adamantane, all the adamantyl radicals were captured by pyridine with a C^2/C^3 selectivity of 0.28 (Entry 9). The same ratio was seen in the presence of oxygen.



Scheme 2

The species responsible for alkane activation in the Fe^{II}-TBHP chlorination system was further identified by evaluating the relative reactivity of primary, secondary and tertiary C-H bonds in this system by employing equal amounts of cyclohexane and 2,3-dimethylbutane at 0°C. After statistical correction the relative reactivities were found to be: 1° (0.03): 2° (1.0) : 3° (2.9) in close agreement with those determined for genuine tert-butoxy radicals, *i.e.*, 1° (0.1): 2° (1.0) : 3° (4.4) at 40°C.[16] Our results along with those outlined by Minisci[7,9] clearly suggest that the activation of hydrocarbons by the Fe^{II}-TBHP system is a result of efficient formation of *tert*-butoxy radicals. The mechanism of hydrocarbon activation and alkyl chloride formation in the Fe^{II}-H_2O_2 and Fe^{II}-TBHP systems is shown in Scheme 2.

The formation of chloride in the Fe^{III}-TBHP system can also be rationalized as resulting from the Fe^{II}-TBHP manifold. Scheme 2. It was previously determined that the C^2 / C^3 adamantane ratio in the Fe^{III} experiments was 0.55[5] along with $k_H/k_D = 8.0$.[17] Again these criteria are identical with the Fe^{II}-TBHP experiments described herein. It is possible that the Fe^{II}-TBHP cycle is initiated by the reduction of Fe^{III} to Fe^{II} at 60°C. This is, however, a minor reaction because of the slow rate of chloride formation.

The difference in chemical behaviour between the Fe^{II} and Fe^{III}-H_2O_2 systems is highlighted by the following experiment. When cyclohexane and $Fe^{II}(ClO_4)_2$ were treated with a 10-fold excess (with respect to

Fe^{II}) of H_2O_2 (3 mmol every 15 minutes at 0°C) in the presence of excess chloride ion in a similar way to the experiments described in Table 1, facile chloride formation was observed only while the system contained Fe^{II} (titration).[18] However as soon as all the Fe^{II} had been oxidised to Fe^{III} (2 additions of H_2O_2), addition of further aliquots of H_2O_2 resulted in the relatively slow formation of ketone with very little additional chloride. The mechanism therefore changed from being radical (Fe^{II}) to one involving the Fe^{III}-Fe^{V} non-radical manifold.

Finally, the addition of thiocyanate or azide ions to the Fe^{II}-H_2O_2 and TBHP systems also produced substantial quantities of monosubstituted derivatives. Comprehensive mechanistic details for all the systems described herein will be published shortly. We consider that the results now reported are a proof that Gif Fe^{III}-H_2O_2 chemistry is not radical chemistry.

Acknowledgements. We thank Quest International and the Welch Foundation for their support of this work. We thank Prof. Minisci for a good supply of manuscripts.

References and notes

1. D. H. R. Barton, D. Doller, *Acc. Chem. Res.*, **1992**, *25*, 504 and references cited therein.
2. D. H. R. Barton, E. Csuhai, D. Doller, *Tetrahedron*, **1992**, *48*, 9195-9206.
3. D. H. R. Barton, S. D. Bévière, *Tetrahedron Lett.*, **1993**, *34*, 5689-5692.
4. D. H. R. Barton, S. D. Bévière, W. Chavasiri, D. Doller, B. Hu, *Tetrahedron Lett.*, **1993**, *34*, 1871-1874.
5. D. H. R. Barton, S. D. Bévière, W. Chavasiri, *Tetrahedron*, **1994**, *50*, 31-46.
6. D. H. R. Barton, W. Chavasiri, *Tetrahedron*, **1994**, *50*, 47-60.
7. F. Minisci, F. Fontana, *Tetrahedron Lett.*, **1993**, *35*, 1427-1430.
8. D. H. R. Barton, D. Hill, *Tetrahedron Lett.*, **1994**, *35*, 1431-1434.
9. F. Minisci, F. Fontana, S. Araneo, F. Recupero, in press: *Tetrahedron Lett.*, 1994, F. Minisci, F. Fontana, S. Araneo, F. Recupero, **1994**, private communication.
10. G. H. Kruppa, J. L. Beauchamp, *J. Am. Chem. Soc.*, **1986**, *108*, 2162-2169; J. C. Walton, *Chem. Soc. Reviews*, **1992**, 105-112; I. Tabuschi, J. Hamuro, R. Oda, *J. Am. Chem. Soc.*, **1967**, *89*, 7127-7129.
11. J. K. Kochi, in *Free Radicals*, J. K. Kochi, ED.; John Wiley and Sons, Inc.: New York, **1973**.
12. D. T. Sawyer, C. Kang, A. Llobet, C. Redman, *J. Am. Chem. Soc.*, **1993**, *115*, 5817-5818 and references cited therein.
13. Determined for equal quantities of cyclohexane and cyclohexane-d_{12} at 0°C.
14. I, Yamazaki, L. H. Piette, *J. Am. Chem. Soc.*, **1991**, *113*, 7588-7593.
15. P. D. Bartlett, E. P. Benzing, R. E. Pincock, *J. Am. Chem. Soc.*, **1960**, *82*, 1762-1768.
16. W. A. Pryor, D. L. Fuller, J. P. Stanley*J. Am. Chem. Soc.*, 1972, *94*, 1632-1638.
17. Unpublished results.
18. L. J. Clark, *Analytical Chemistry*, **1962**, *34*, 348-352.

(*Received in USA* 2 *May* 1994; *revised* 14 *June* 1994; *accepted* 16 *June* 1994)