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On the Distinction Between Radical Chemistry and Gif Chemistry

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Abstract: Normalized data for cyclooctane and for cyclododecane are compared with cyclohexane as unity. In radical chemistry cyclooctane is 2-3 times more reactive per hydrogen, whereas in Gif chemistry cyclohexane is more reactive than cyclooctane or cyclododecane. Thus by simple competitive experiments a distinction between radical chemistry and Gif chemistry can be made.

In a recent review article[1] Prof. M.J. Perkins commented on the role that radicals might play in Gif chemistry. In a further article one of us pointed out that radical chemistry could not explain the majority of the facts, so far as Fe^{III}-H_2O_2 and Fe^{II}-superoxide chemistry were concerned.[2] In contrast, all the phenomena associated with tert-butylhydroperoxide (TBHP) have been shown to be explained by the reactions of *tert*-butoxy- and *tert*-butylperoxy radicals.[3,4] In view of the article by Perkins[1] we have decided to work on procedures which will enable a decision between radical and non-radical (Gif) chemistry.

As we have already pointed out[5] there is a difference in reactivity between cyclohexane and cyclooctane after normalization (per hydrogen) in radical chemistry and in Gif chemistry. For a radical mechanism the reactivity per hydrogen is 2-3 times greater for cyclooctane than for cyclohexane. For cyclododecane the difference with respect to cyclohexane is smaller and cyclohexane is slightly more reactive.

The literature data and new results, not hitherto published, are summarised in Table 1. The new data confirm that cyclooctane in Gif chemistry is somewhat less reactive than cyclohexane. The same applies to cyclododecane. In any case a comparison of cyclooctane and cyclohexane shows a clear difference between radical and Gif chemistry.

Prof. B. Giese (University of Basel) has kindly suggested that cyclooctane has a compressed conformation compared to cyclohexane and that the difference in radical reactivity could be due to relief of conformational strain when the cyclooctyl radical is formed.[6] The prefered conformation of cyclododecane is more relaxed[7] and so a major effect is not to be expected. In our Gif theory the activation process is an insertion of an Fe^{V} species into a C-H bond. It is, therefore, mechanistically different from hydrogen atom abstraction. We have recognized two manifolds in Gif chemistry.[8] The first is Fe^{III}-Fe^{V} as illustrated in

Scheme 1.

$$\mathrm{Fe^{III}\text{-}OOH} \longrightarrow \mathrm{Fe^{V}{=}O} \xrightarrow{\mathrm{CH_2R_2}} \mathrm{Fe^{V}\text{-}CHR_2} \longrightarrow \text{Products}$$

Scheme 1

Table 1. Summary of Relative Reaction Rates with respect to Cyclohexane Normalized per Number of Hydrogens.

	Conditions	**Cyclooctane**	**Cyclododecane**
Radical	Fe^{III} + TBHP + PA (ketone only)	2.82[9]	0.85[9]
Radical	Fe^{III} + TBHP + PA (ketone + alcohol)	2.55[9]	0.87[9]
Radical	Fe^{III}(1) + TBHP(5) + PA(3)	3.06[a]	0.94[a]
Radical	Fe^{III} + TBHP +Cl^-	2.08[10]	0.93[10]
Radical	Fe^{III} + TBHP + N_3^-	2.17[11]	0.63[11]
Radical	Fe^{III} + TBHP + SCN^-	1.49[11]	0.81[11]
Radical	Fe^{III}(1) + TBHP(5)	1.79[a]	0.99[a]
Radical	Radical Bromination with $BrCCl_3$	3.3[12]	1.9[12]
Radical	Radical $(CH_3)_3O\bullet$	2.3[13]	-
Non-Radical	Fe^{III} + H_2O_2	0.76[14]	0.43[14]
Non-Radical	Fe^{III}(1) + H_2O_2(4) + Ac.Ac.(52)	0.75[a]	0.64[a]
Non-Radical	Fe^{III}(1) + H_2O_2 + PA + $BrCCl_3$	1.08[12]	0.63[12]
Non-Radical	Fe^{III}(1) + H_2O_2(4) + PA(4)	0.82[a]	0.66[a]
Non-Radical	Fe^{III}(1) + H_2O_2(5) + PA(3)	0.72[a]	0.75[a]
Non-Radical	Fe^{III}(1) + H_2O_2(5) + PA(3) in CH_3CN-Py	0.50[a]	0.59[a]
Non-Radical	Fe^{II}(3) + H_2O_2(3) + PA(6) in CH_3CN-Py	0.90[a]	1.05[a]
Non-Radical	Fe^{II}(1) + H_2O_2(1) + PA(3)	0.96[a]	0.86[a]
Non-Radical	Fe^{II}(1) + O_2 / Zn(20) + Ac.Ac.(52)	0.83[a]	0.73[a]
Non-Radical	Fe^{II}(1)+ H_2S / O_2 + PA(3)	0.88[a]	0.53[a]

Fe^{II}: $FeCl_2,4H_2O$; Fe^{III}: $FeCl_3,6H_2O$; PA: Picolinic Acid; Ac.Ac.: Acetic Acid; Py: Pyridine.

[a] This article. See reference 15.

Although it is probable that two iron atoms are involved in the active site[8] we use only one to simplify the discussion. Radicals are rarely seen in this manifold. Exceptions are seen when the iron-carbon bond is weakened by structural features such as the tertiary position in adamantane and the hypersensitive radical probes of Newcomb.[16] By now there are thousands of experiments in the Fe^{III}-Fe^{V} manifold where carbon radicals have not been detected even though the solvent used, pyridine, is an excellent trap for radicals.

The second manifold is Fe^{II}-Fe^{IV} as shown in Scheme 2.

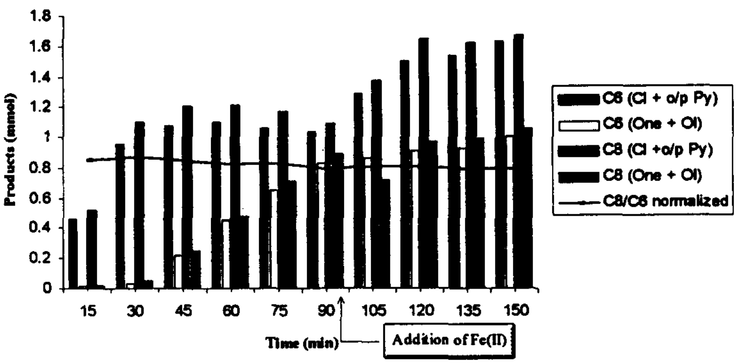
$$\mathrm{Fe^{II}\text{-}OOH} \longrightarrow \mathrm{Fe^{IV}{=}O} \xrightarrow{\mathrm{CH_2R_2}} \mathrm{Fe^{IV}\text{-}CHR_2} \longrightarrow \mathrm{Fe^{III}} + {}^{\bullet}\mathrm{CHR_2}$$

Scheme 2

Again this Scheme is simplified. It is the Fe^{II}-Fe^{IV} manifold that regularly produces carbon radicals which are captured by pyridine in the absence of oxygen. Of course one must justify why an iron-carbon bond is needed in the Fe^{II}-Fe^{IV} manifold at all. Both manifolds have the same KIE (cyclohexane versus cycohexane d_{12}) of about 2. So the activation process must be similar. Recently we have shown that iodide ion is a good trap for the iron-carbon bond in both manifolds.[17] If the radical chemistry in the Fe^{II}-Fe^{IV} manifold really comes from a radical attack (for example from hydroxyl radical) on the hydrocarbon then cyclooctane should be more reactive than cyclohexane. If, however, there is prior activation of the hydrocarbon by an iron-carbon bond formation, then the relative reactivity should be more or less the same as in the Fe^{III}-Fe^{V} manifold.

The results of this competition are shown in the Diagram. The reaction starts with Fe^{II} activation in the presence of chloride ion. Hence the radicals formed make cycloalkyl chlorides as well as ketones and alcohols and some pyridine coupling. As the Fe^{II} is oxidized to Fe^{III} the chloride formation ceases, but starts again as soon as a second portion of Fe^{II} is added. The ratio of cyclooctane derived products relative to cyclohexane derivatives normalized per hydrogen is shown by the horizontal line. It is clear that the reactivity of the two hydrocarbons is slightly in favor of cyclohexane across the whole range of the experiment. This is good support for the proposal for iron-carbon bond formation in both of the manifolds.

Competition cyclohexane / cyclooctane in the 2 manifolds



Reaction conditions: $Fe(ClO_4)_2$, $6H_2O$ (3.00 mmol + same amount after 100 mn); PA (9 mmol); LiCl (15 mmol); Pyridine (30 mL); Cyclohexane (20 mmol); Cyclooctane (20 mmol); H_2O_2 (25 mmol) was added every 15 mn at RT (10x2.5).
Fe^{II} titrations (%) vs time (mn): 61 (15'); 11 (30'); 0 (75'); 3 (150'); 7 (280').

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15. Reactions were carried out in pyridine (30 mL) or in a mixture of acetonitrile / pyridine (23 / 7 mL). Cyclohexane (10 mmol) was compared either to cyclooctane (10 mmol) or cyclododecane (10 mmol). Reactions starting with Fe^{III} were performed under air. Argon atmosphere was used in Fe^{II} experiments except when oxygen was the oxidant (For details on the H_2S / O_2 conditions, see: Barton, D.H.R.; Li, T.; MacKinnon, J. *Chem. Commun.* **1997**, 557-558.). The results were obtained after complete consumption of the oxidant (H_2O_2) or after 24h (TBHP).

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