Pergamon

*Tetrahedron Letters*, Vol. 37, No. 6, pp. 819-822, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02330-5

# Hypersensitive Radical Probe Studies of Gif Oxidations

**Martin Newcomb*, Pavel A. Simakov, Seung-Un Park**[1]
Department of Chemistry, Wayne State University, Detroit, Michigan, 48202, U.S.A.

***Abstract***: Hypersensitive probes were employed in mechanistic studies of Gif oxidations. The results indicate that, unlike the case in enzyme catalyzed hydroxylation reactions, diffusively free radicals are formed in Gif oxidations of these substrates.

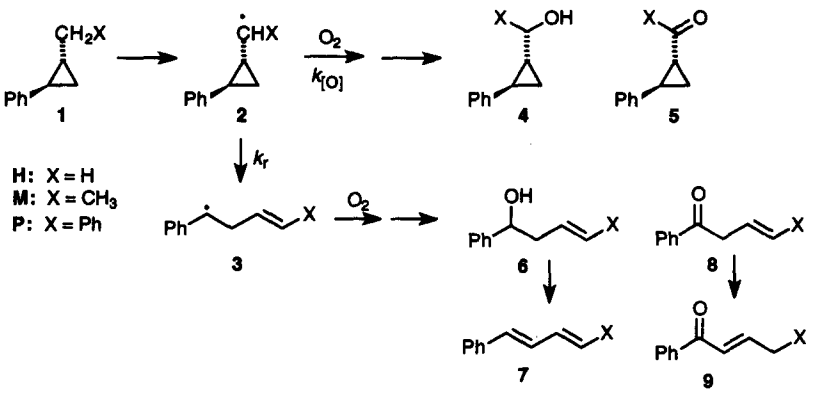
Cytochrome P-450 and soluble methane monooxygenase (MMO) enzymes, which contain iron atoms in quite different environments in their active sites, employ molecular oxygen in ambient temperature hydroxylations of unactivated C–H bonds. Were they available, analogous chemical catalysts for such reactions would be of considerable economic importance, and much of the research directed at this goal has focused on iron species as mimics of the biological catalysts. One promising class of iron catalysts is the Gif family developed by Barton and co-workers.[2] A number of variants of Gif oxidations have been explored, but most involve an iron salt as catalyst for reactions run in pyridine and acetic acid; addition of picolinic acid as a ligand provides enhanced reactivity. Molecular oxygen with a reducing agent, hydrogen peroxide or *tert*-butyl hydroperoxide usually serve as the oxidants in the various Gif reactions.

The mechanisms of Gif-type oxidations are obviously complex with production of a number of products. Alkyl hydroperoxides, incorporating oxygen from $O_2$, are intermediates leading to ketones and alcohols.[3] Mechanisms of Gif oxidations have been formulated in terms of either formation of an iron-oxo species akin to that thought to be involved in P-450 and MMO oxidations[4] or Fenton-type chemistry in which the iron serves to catalyze decomposition of the peroxy compound.[3b,5] In the former mechanism, oxygen insertion into a C–H bond could occur possibly via an iron-carbon intermediate; in the latter, hydroxyl or alkoxyl radicals would abstract hydrogen from hydrocarbon to give alkyl radicals that react with molecular oxygen or cross terminate with peroxyl radicals. One mechanistic approach that has not been exploited extensively in Gif oxidations is the application of mechanistic probes for radical intermediates.[6] In this letter, we report the applications of hypersensitive cyclopropane mechanistic probes in studies of Gif oxidations employing a set of probes that includes one which has been well characterized in enzyme catalyzed hydroxylations. The results indicate that the mechanisms of Gif and enzyme catalyzed oxidations of the cyclopropane probe substrates differ significantly with extensive or exclusive production of diffusively free substrate radicals occurring under Gif oxidation conditions.

The concept of the probe study is illustrated in the Scheme. If probe **1** is converted to radical **2**, then rearrangement of **2** to radical **3** will compete with molecular oxygen trapping of **2** which ultimately produces oxygenated products **4** and **5**. Rearranged radical **3** will ultimately give oxidation products **6** (which could dehydrate to **7**) and **8** (which can rearrange to **9**). Radicals **2** from two of the probes employed (**1H** and **1M**) rearrange so rapidly that bimolecular trapping cannot compete with ring opening, and even an insertion reaction sequence could result in a minor amount of ring opened products. Radical **2P** rearranges about three orders of magnitude less rapidly than radical **2H**. If oxidation occurs via insertion, no ring opened product is expected from probe **1P**, but ring opening should compete with trapping if radicals are formed.

Authentic samples of the possible oxygenation products, excepting **6M** and **6P**, were prepared. A series of control reactions showed that products **4** and **5** in each series and alcohol **6H** were stable to the reaction conditions. Alcohol **6M** was expected to be stable on the basis of the results with **6H**, but alcohol **6P** was expected to dehydrate to **7P**. β,γ-Unsaturated ketones **8H**, **8M** and **8P** were found to isomerize to α,β-unsaturated ketones **9**. Products from addition of the substrate moiety to pyridine are observed in Gif-type reactions, but we made no

**Scheme**




attempt to identify or quantitate such addition products. Alkyl chlorides are also reported to be formed in reactions with $FeCl_3$, but no substantive yields of chloride products were found in GC-mass spectral analysis of the reactions conducted here. In oxidations with $H_2O_2$, phenolic products were obtained from each of the probes, but these were not produced in reactions employing *t*-BuOOH;[7] we note that this behavior requires that the oxidants produced in the two systems were different.

Gif oxidations of the probes were performed with both $H_2O_2$ and *t*-BuOOH. Reactions were conducted for 24 hours in order to mimic the conditions commonly employed in Gif reactions, but analysis of representative runs during the course of the reactions indicated that the product composition did not change after a few hours. Following the reactions, products were extracted from the pyridine-acetic acid solvent, and the crude product mixtures were analyzed by GC-mass spectrometry. The results are in the Table. Low conversions were obtained, but these are similar to those desired in enzyme mechanistic studies in which one attempts to avoid over-oxidation.

The results with probe **1H** can be used to address the question of whether or not Gif oxidations are mechanistically related to enzyme catalyzed hydroxylations. Oxidation of **1H** by a cytochrome P-450 isozyme[8] gives the product ratio shown in the Table. Recent results indicate that the "radical" moiety in P-450 oxidations is not a true intermediate but a part of the reactive ensemble (or transition state) with a life-time of less than 100 femtoseconds, and that most of the rearranged products from P-450 oxidations of cyclopropane probes result from cationic species formed during the course of the oxidation reaction.[9] Hydroxylations of **1H** by two MMO enzyme systems gave no and very little rearranged product **6H**,[10] and these results, in conjunction with the small amount of inversion observed in MMO hydroxylation of chiral ethane,[11] indicate that a very short-lived substrate radical moiety is involved also in MMO oxidations. The production of rearranged products **6H** and **9H** and absence of cyclopropyl products **4H** and **5H** in Gif oxidations of **1H** clearly suggest that these reactions are mechanistically distinct from the enzyme catalyzed hydroxylations. This conclusion is supported by the results with probe **1M** where, again, no cyclopropyl products were found, although studies of enzyme hydroxylations of **1M** are not available for direct comparison.

The probe results are consistent with production of diffusively free radicals **2** in the Gif oxidations. Radical intermediates can be trapped by reaction with molecular oxygen or by cross termination with peroxyl radicals. For probes **1H** and **1M**, a kinetic analysis shows that radical intermediates **2** cannot be trapped appreciably before rearranging. Radical reactions with oxygen occur with rate constants of about $5 \times 10^9$ $M^{-1}$ $s^{-1}$ (alkyl) or $2 \times 10^9$ $M^{-1}$ $s^{-1}$ (benzyl).[12] The concentration of oxygen in the Gif reactions is not known because the vigorous iron catalyzed decomposition of the hydroperoxides almost certainly results in supersaturated solutions early in the reaction, but one might assume that molecular oxygen will reach hundredths of molar concentrations.

**Table.** Products from Oxidations of Hypersensitive Probes.[a]

| Probe | conditions[b] | 4 | 5 | 6 | 8 + 9 | phenols[c] | % Yield |
|---|---|---|---|---|---|---|---|
| **1H** | $GoAgg^{III}$ | 0 | 0 | 1 | 1.7 | 25 | 4.5 |
| | $GoAgg^{V}$ | 0 | 0 | 0 | 1 | 0 | 0.05 |
| | $GoAgg^{V}$ (55)[d] | 0 | 0 | 0 | 1 | 0 | 0.08 |
| | P-450[e] | 4 | 0 | 1 | 0 | 3[f] | |
| | MMO[g] | 1 | 0 | 0 | 0 | 1[f] | |
| **1M** | $GoAgg^{III}$ | 0 | 0 | 0 | 1 | 2.7 | 7 |
| **1P** | $GoAgg^{III}$ | 0 | 2.0 | 1[h] | 0 | 20 | 10 |
| | $GoAgg^{V}$ | 1.3 | 9.6 | 1[h] | 1.2 | 0 | 10 |

[a]Averages of two to five runs for all Gif-type oxidations. Reactions run for 24 h at 20-22 °C unless noted. Normalized ratios of products are given. The final column lists the approximate % yield of oxygenated products. [b]$GoAgg^{III}$ reactions employed $FeCl_3(H_2O)_6$, pyridine, acetic acid, picolinic acid and $H_2O_2$. $GoAgg^{V}$ reactions employed $Fe(NO_3)_3(H_2O)_9$, pyridine, acetic acid, picolinic acid and *t*-BuOOH. See ref 2b. [c]Mixtures of phenols were formed in Go-$Agg^{III}$ oxidations; see note 7. [d]Reaction run at 55 °C. [e]Average results for cytochrome P-450 hydroxylations; see ref. 8. [f]Only the *p*-phenol was produced in enzyme hydroxylations. [g]Results from hydroxylation by the MMO system from *M. capsulatus* (Bath); hydroxylation by the MMO system from *M. trichosporium* OB3b also gave small amounts of **6H** (4-5% relative to **4H**); see ref 10. [h]Product **7P** from dehydration of **6P**.

Alkyl and peroxyl radicals probably cross terminate with spin statistically corrected diffusional rate constants of $5 \times 10^9$ $s^{-1}$, and the peroxyl radicals might also reach hundredths molar concentrations. In all, pseudo-first order rate constants for alkyl radical trapping should be expected to be in the $10^7$ to $10^8$ $s^{-1}$ range. Radical **2H** rearranges to **3H** with a ring opening rate constant of $3 \times 10^{11}$ $s^{-1}$,[13] three to four orders of magnitude faster than the estimated rate constant for trapping. The rate constant for rearrangement of **2M** is not known, but, from the small kinetic difference between ring opening of the cyclopropylcarbinyl radical and its 1-methyl substituted analog,[14] it is expected to be quite similar to that of **2H**.

Radical **2P**, in which the incipient stabilization of the ring opened product by phenyl substitution on the ring is counterbalanced by the phenyl group on the radical center, rearranges with a rate constant of about $1 \times 10^8$ $s^{-1}$ at 20 °C,[15] or similar in magnitude to the expected rate constants for radical trapping reactions. Therefore, the production of both unrearranged (**5P** and **6P**) and rearranged products (**7P** and **9P**) is expected if diffusively free radical **2P** was produced. Our results for **1P** probably should be applied quantitatively only with care, but they suggest that the oxygen and peroxyl radical concentrations were greater in $GoAgg^{V}$ reactions than in $GoAgg^{III}$ reactions during the periods in which most product formation occurred.

Whereas the probe results implicate formation of diffusively free radicals in Gif oxidations, the origin of the radicals cannot be addressed directly from these studies. Hydrogen atom abstraction from the probes by hydroxyl and *t*-butoxyl radicals is an obvious possible source of radicals **2**, but an alternative exists. Formation of an iron-carbon bonded intermediate followed by homolysis has been postulated previously as an origin of radicals in adamantane oxidations.[4b] One might rationalize the probe results similarly, although this would require the *ad hoc* premise that a cyclopropane ring induces iron-carbon bond homolysis for the primary and secondary cyclopropylcarbinyl systems which do not occur in "normal" secondary systems. There is evidence that the cyclopropylcarbinyl radical is stabilized by conjugation of the radical center with the ring, but the total stability thus imparted appears to be similar to that of a typical secondary alkyl radical.[16] Of course, it would be unreasonable to suggest that iron-carbon bond homolysis is induced in the primary and secondary cyclopropyl systems but does not occur for the benzylic system.

In summary, although the conception of Gif oxidations was based on the catalytic hydroxylations of hydrocarbons by the iron-containing P-450 and MMO enzymes, the hypersensitive probe results clearly indicate

that the mechanisms of Gif and enzyme catalyzed oxidations differ significantly for the substrates studied here; in the enzyme hydroxylation reactions, a "radical" is one component of a transition state, whereas diffusively free radials are produced in Gif oxidations of these compounds. The origins of the radicals in the Gif oxidations are not resolved by the probe results, but the absence of unrearranged oxidation products from **1H** and **1M**, the former for which enzyme catalyzed insertion is demonstrated,[9,10] argues in favor of radical production by hydrogen abstraction from these substrates as described by Perkins,[3b] Minisci[5] and Snelgrove *et al.*[17]

**Acknowledgment.** This work was supported by grants from Hoechst Celanese Corporation and the National Science Foundation (CHE-9117929). We thank Dr. K. U. Ingold for a useful exchange of information.

## References and Notes

1. Department of Chemistry, Konkuk University, Seoul, Korea
2. (a) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504-512. (b) Barton, D. H. R.; Chavasiri, W. *Tetrahedron* **1994**, *50*, 19-30.
3. (a) Barton, D. H. R.; Csuhai, E.; Doller, D.; Balavoine, G. *J. Chem. Soc., Chem. Commun.* **1990**, 1787-1789. (b) Knight, C.; Perkins, M. J. *J. Chem. Soc., Chem. Commun.* **1991**, 925-927. (c) Barton, D. H. R.; Beviere, S. D.; Chavasiri, W.; Doller, D.; Hu, B. *Tetrahedron Lett.* **1992**, *33*, 5473-5476. (d) Barton, D. H. R.; Beck, A. H.; Taylor, D. K. *Tetrahedron* **1995**, *51*, 5245-5254.
4. (a) Barton, D. H. R.; Hill, D. R. *Tetrahedron Lett.* **1994**, *35*, 1431-1434. (b) Bardin, C.; Barton, D. H. R.; Hu, B.; Rojaswahl, R.; Taylor, D. K. *Tetrahedron Lett.* **1994**, *35*, 5805-5808.
5. Minisci, F.; Fontana, F. *Tetrahedron Lett.* **1994**, *35*, 1427-1430. Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quici, S. *J. Am. Chem. Soc.* **1995**, *117*, 226-232.
6. Gif oxidation of 3-carene, a potential mechanistic probe substrate, has been reported; see Lee, K.-W.; Kim, S.-B.; Kim, S.-B.; Barton, D. H. R.; Doller, D. *Bull. Korean Chem. Soc.* **1991**, *12*, 459-460.
7. Similar behavior was observed in oxidations of toluene. Specifically, Gif oxidations with $H_2O_2$ produced all three cresol isomers in addition to benzyl alcohol and benzaldehyde, whereas oxidations with *t*-BuOOH gave no cresols. An authentic sample of the *p*-phenol formed from probe **1H** was available for GC-mass spectral identification. The structures of the *o*- and *m*-phenols from **1H** were deduced from their mass spectra (essentially identical to that of the *p*-phenol) and GC retention times. On the basis of the observed behavior in GC analysis of cresol isomers on a Carbowax column, the *o*-phenol eluted with a considerably shorter retention time than the other two. The structures of phenolic products from probe **1M** were deduced from their mass spectral fragmentation patterns. For probe **1P**, phenolic products were obtained as deduced by mass spectrometry, but no attempt was made to assign the structures.
8. Atkinson, J. K.; Ingold, K. U. *Biochemistry* **1993**, *32*, 9209-9214. Atkinson, J. K.; Hollenberg, P. F.; Ingold, K. U.; Johnson, C. C.; Le Tadic, M.-H.; Newcomb, M.; Putt, D. A. *Biochemistry* **1994**, *33*, 10630-10637.
9. (a) Newcomb, M.; Le Tadic, M. H.; Putt, D. A.; Hollenberg, P. F. *J. Am. Chem. Soc.* **1995**, *117*, 3312-3313. (b) Newcomb, M.; Le Tadic-Biadatti, M.-H.; Chestney, D. L.; Roberts, E. S.; Hollenberg, P. F., *J. Am. Chem. Soc.*, in press.
10. Liu, K. E.; Johnson, C. C.; Newcomb, M.; Lippard, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 939-947.
11. Priestley, N. D.; Floss, H. G.; Froland, W. A.; Lipscomb, J. D.; Williams, P. G.; Morimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 7561-7562.
12. Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095-5099.
13. Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915-10921. Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915-10921.
14. Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687-5698.
15. Hollis, R.; Hughes, L.; Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1992**, *57*, 4284-4287.
16. Walton, J. C. *Mag. Res. Chem.* **1987**, *25*, 998-1000.
17. Snelgrove, D. W.; MacFaul, P. A.; Ingold, K. U.; Wayner, D. D. M., accompanying Letter in this issue.

(*Received in USA* 6 *November* 1995; *revised* 25 *November* 1995; *accepted* 3 *December* 1995)