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The Role of Alkoxyl Radicals in Gif ($GoAgg^V$) Chemistry.[1]

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Abstract: The oxidation of cyclooctane using *tert*-alkyl hydroperoxides under $GoAgg^V$ conditions has been examined using selected alkyl hydroperoxides as mechanistic probes. The results indicate that the products are formed by alkoxyl radical-induced reactions, there being no need to invoke any chemistry involving high valent iron-oxo species.

Enzyme mimetic chemistry has long been a very popular research area. The cytochrome P-450's[4] and methane monooxygenases (MMO's)[5] have attracted particular attention because they can functionalize alkanes. High valent iron-oxo species are generally believed to be the active intermediates that cleave the alkanes' unactivated C-H bonds. Barton et al[6] have conjectured that the numerous "Gif" chemical systems actually mimic the behavior and mode of action of P-450 and / or MMO enzymes. Most of the Gif systems use an iron salt as a catalyst, hydrogen peroxide or *tert*-butyl hydroperoxide (TBHP) as the primary oxidant,[7] and a pyridine / acetic acid mixture as the solvent. The substrate is commonly a cyclic alkane and the reactivity of the catalyst is frequently enhanced by the addition of picolinic acid.

In Gif systems which use an Fe^{III} salt as the catalyst together with TBHP, Barton has proposed[8] that a high valent iron-oxo species (formally $Fe^V{=}O$) is formed which can insert into an unactivated C-H bond to give an alkyl-Fe^V complex (e.g. $c\text{-}C_6H_{11}\text{-}Fe^V\text{-}OH$). This complex (together with dioxygen, if available) is the supposed precursor of the observed organic reaction products (mainly ketones from cycloalkanes, alcohols from *tert*-CH bonds and hydroperoxides in the presence of O_2). Of course, all these products could also be accounted for in terms of "normal" free radical chemistry initiated by the formation of the *tert*-butoxyl radical, see reactions 1-10. Indeed, Minisci et al[9] have shown that *tert*-butoxyl radicals are present under certain Gif conditions by their trapping with electron-rich alkenes.[10] Herein, we report results obtained with cyclooctane in a specific Gif system, $GoAgg^V$.[8b] We have employed the "usual" TBHP and three other *tert*-alkyl hydroperoxides each of which serves as a mechanistic probe. These are "probes" because if the hydroperoxide, ROOH, yields the corresponding alkoxyl radical, RO•, this radical will show a characteristic reaction product "signature".

$$Fe^{III} + ROOH \longrightarrow Fe^{IV}{=}O + H^+ + RO\bullet \tag{1}$$
$$Fe^{IV}{=}O + ROOH \longrightarrow Fe^{III} + OH^- + ROO\bullet \tag{2}$$
$$RO\bullet + ROOH \longrightarrow ROH + ROO\bullet \tag{3}$$
$$ROO\bullet + ROO\bullet \longrightarrow RO\bullet + O_2 + RO\bullet \tag{4}$$
$$RO\bullet + c\text{-}C_8H_{16} \longrightarrow ROH + c\text{-}C_8H_{15}\bullet \tag{5}$$
$$c\text{-}C_8H_{15}\bullet + O_2 \longrightarrow c\text{-}C_8H_{15}OO\bullet \tag{6}$$
$$c\text{-}C_8H_{15}OO\bullet + ROOH \longrightarrow c\text{-}C_8H_{15}OOH + ROO\bullet \tag{7}$$
$$c\text{-}C_8H_{15}OO\bullet + c\text{-}C_8H_{15}OO\bullet \longrightarrow c\text{-}C_8H_{15}OH + c\text{-}C_8H_{14}O + O_2 \tag{8}$$
$$c\text{-}C_8H_{15}\bullet + ROO\bullet \longrightarrow c\text{-}C_8H_{15}OOR \tag{9}$$
$$c\text{-}C_8H_{15}OO\bullet + ROO\bullet \longrightarrow \left\{\begin{array}{l} ROH + c\text{-}C_8H_{14}O + O_2 \\ \text{and } c\text{-}C_8H_{15}OOR + O_2 \end{array}\right. \tag{10}$$

Oxidation of cyclooctane (0.142M) with TBHP (0.284M) using $GoAgg^V$ conditions (0.0142M $Fe^{III}(NO_3)_3$ in pyridine, acetic acid (10:1, v/v) and 0.0426 M picolinic acid at room temperature) under air gave cyclooctanone, cyclooctanol, cyclooctyl *tert*-butyl peroxide and 2-cyclooctylpyridine.[11] The results of duplicate experiments are given in Table 1, with product yields expressed in equivalents relative to the Fe^{III} catalyst. Duplicate experiments were also carried out under an argon atmosphere after prior deoxygenation of the reactants (see also Table 1). Of course, these conditions are not strictly "anaerobic" because dioxygen is formed continuously via reaction 4. Naturally, under these "anaerobic" conditions the yield of ketone is reduced (by ca. 40%). However, the yields of mixed peroxide (reaction 9) and 2-cyclooctylpyridine are increased. These aerobic results (apart from the mixed peroxide) are consistent with earlier work on cyclooctane and cyclohexane in the $GoAgg^V$ system (see Table 1).[8b] "Anaerobic" results have also been reported for the oxidation of cyclooctane by a $GoAgg^{IV}$ system, i.e. without the addition of picolinic acid, which indicated that the mixed peroxide was formed but the yields of ketone and alcohol were not given.[8b]

Table 1. The Reaction of Cycloalkanes with *tert*-Butyl Hydroperoxide under $GoAgg^V$ Conditions.

Cycloalkane	Conditions	*c*-$C_8H_{14}O$	*c*-$C_8H_{15}OH$	*c*-$C_8H_{15}OOBu^t$	2-*c*-C_8H_{15}-C_5H_4N
Cyclooctane	Aerobic	3.78	0.02	0.09	Trace
Cyclooctane	Aerobic	3.53	0.05	0.13	[a]
Cyclooctane[b]	Aerobic	3.72	0.16	[c]	[c]
Cyclohexane[d]	Aerobic	5.10[e]	0.56[f]	[c,g]	[c]
Cyclooctane	Anaerobic	2.12	0.04	0.31	0.013
Cyclooctane	Anaerobic	2.17	0.07	0.42	0.013

[a] Not detected. [b] Yields of cyclooctane-derived products (in mmol) from a competitive oxidation of cyclooctane and cyclohexane, duration of experiment unspecified (ref. 8b). [c] Not reported. [d] Yields (in mmol) for the oxidation of cyclohexane, duration of experiment unspecified (ref. 8b). [e] c-$C_6H_{10}O$. [f] c-$C_6H_{11}OH$. [g] c-$C_6H_{11}OOBu^t$.

We have previously employed 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH) as a mechanistic probe to explore the real chemistry lying behind another purported example of alkane oxidation via a high valent iron-oxo species.[12] The alkoxyl radical derived from this hydroperoxide undergoes extremely rapid β-scission.

$$PhCH_2CMe_2O\bullet \longrightarrow PhCH_2\bullet + Me_2CO \qquad (11)$$

Replacement of the "usual" TBHP in a $GoAgg^V$ system by MPPH gave mainly products derived from the benzyl radical formed in reaction 11, viz. benzaldehyde, benzyl alcohol, bibenzyl and the mixed peroxide formed by the cross-coupling of $PhCH_2^\bullet$ and $PhCH_2CMe_2OO^\bullet$ radicals (see Table 2). A very small amount of cyclooctanone was produced under aerobic conditions but not under "anaerobic" conditions. We suggest that under aerobic conditions further oxidation of the main product, benzaldehyde, yields the highly reactive benzoylperoxyl radical[13] and that it is this radical which abstracts a hydrogen atom from the cyclooctane.

$$PhCHO \xrightarrow[O_2]{ROO\bullet} PhC(O)OO\bullet \xrightarrow{c\text{-}C_8H_{16}} PhC(O)OOH + c\text{-}C_8H_{15}\bullet \xrightarrow{O_2} c\text{-}C_8H_{14}O \qquad (12)$$

Table 2. The Reaction of Cyclooctane with MPPH under $GoAgg^V$ Conditions.

Conditions	*c*-$C_8H_{14}O$	PhCHO	$PhCH_2OH$	$(PhCH_2)_2$	$PhCH_2OO$-CMe_2CH_2Ph
Aerobic	0.19	10.4	0.04	0.07	0.06
Aerobic	0.27	10.5	0.02	0.05	0.06
Anaerobic	[a]	1.7	0.46	0.56	2.96
Anaerobic	[a]	1.7	0.66	0.72	3.56

[a] Not detected.

The alkoxyl radical derived from *o*-methyl cumene hydroperoxide (*o*-MCH) is about 100 times longer lived than the alkoxyl radical derived from MPPH.[14] Nevertheless, when *o*-MCH is employed in place of TBHP in the $GoAgg^V$ system only minor amounts of cyclooctanone were produced (see Table 3). The main products are those derived from unimolecular decay reactions of the *o*-methylcumyloxyl radicals, viz. β-scission (reaction 13) and intramolecular hydrogen abstraction (reaction 14).

$$(13)\quad o\text{-}CH_3C_6H_4COMe + Me^{\bullet} \xleftarrow{\beta} o\text{-}CH_3C_6H_4CMe_2O^{\bullet} \xrightarrow{\text{intra}} o\text{-}\dot{C}H_2C_6H_4CMe_2OH\quad (14)$$

Table 3. The Reaction of Cyclooctane with *o*-Methyl Cumene Hydroperoxide under GoAgg^{V} Conditions.

Conditions	c-$C_8H_{14}O$	*o*-Me-C_6H_4COMe	*o*-OCH-$C_6H_4CMe_2OH$	*o*-$HOCH_2$-$C_6H_4CMe_2OH$	*o*-$MeC_6H_4CMe_2OO$-$CH_2C_6H_4CMe_2OH$
Aerobic	0.09	0.02	1.98	0.86	0.75
Aerobic	0.11	0.10	0.81	0.76	0.97
Anaerobic	0.10	0.13	0.64	0.95	1.07
Anaerobic	0.09	0.12	0.58	0.90	1.11

With cumene hydroperoxide (CH) the GoAgg^{V} reaction yields cyclooctane derived products reminiscent of the TBHP reaction, however acetophenone (formed by the β-scission of "free" cumyloxyl radicals, reaction 15), is also a major product, particularly under "anaerobic" conditions (see Table 4).

$$C_6H_5CMe_2O^{\bullet} \longrightarrow C_6H_5COMe + Me^{\bullet} \qquad (15)$$

Table 4. The Reaction of Cyclooctane with Cumene Hydroperoxide under GoAgg^{V} Conditions.

Conditions	c-$C_8H_{14}O$	c-$C_8H_{15}OH$	PhC(O)Me	c-$C_8H_{15}OOCMe_2Ph$	2-c-C_8H_{15}-C_5H_4N[a]
Aerobic	3.36	0.20	5.24	1.00	[b]
Aerobic	3.42	0.19	6.78	1.01	[b]
Anaerobic	1.61	0.11	5.89	0.59	0.048
Anaerobic	1.40	0.12	7.27	0.79	0.016

[a] $CH_3C_5H_4N$ was not resolved from C_5H_5N. [b] Not detected.

The tertiary alkyl hydroperoxides we have employed were chosen because they yield *tert*-alkoxyl radicals having vastly different rate constants for unimolecular β-scission (plus intramolecular H-atom abstraction for the *o*-MCH-derived radical). The lifetimes[15] of the alkoxyl radicals are: $PhCH_2CMe_2O^{\bullet}$ ~ 5 ns;[14] *o*-$MeC_6H_4CMe_2O^{\bullet}$ ~ 400 ns in CH_3CN;[14] $C_6H_5CMe_2O^{\bullet}$ ~ 1.6 μs in CH_3CN,[16] ~ 0.5 μs in CH_3COOH;[16] and $Me_3CO^{\bullet}$[17] ~ 12 μs in CH_3CN, ~ 3.6 μs in CH_3COOH. The pseudo-first-order rate constant for H-atom abstraction from cyclooctane by an alkoxyl radical is[12] $k_5[C_8H_{16}] = 2.7 \times 10^6\ M^{-1}\ s^{-1} \times 0.142\ M = 3.8 \times 10^5\ s^{-1}$, corresponding to a lifetime of 2.6 μs. Thus, with the two short-lived alkoxyls, $PhCH_2CMe_2O^{\bullet}$ and *o*-$MeC_6H_4CMe_2O^{\bullet}$, the principal products are those derived from their unimolecular reactions, whereas the relatively long-lived $Me_3CO^{\bullet}$ radical yields products derived mainly via H-atom abstraction from the cycloalkane. With CH under "anaerobic" conditions acetophenone constitutes ca. 74% of the products which is roughly the yield expected on the basis of the lifetimes given above, i.e., on the basis of the competition between reactions 15 and 5. In a similar vein, cyclooctane has been reported to be 2.8 times as reactive as cyclohexane with TBHP under GoAgg^{V} conditions at room temperature.[8b] This is the expected reactivity ratio for alkoxyl radical chemistry since $k_5 = 2.7 \times 10^6\ M^{-1}\ s^{-1}$ at 25 °C[12] and $k(RO^{\bullet} + c\text{-}C_6H_{12}) = 1.2 \times 10^6\ M^{-1}\ s^{-1}$ at 30 °C.[16]

The conclusion is inescapable. GoAgg^{V} chemistry is most succinctly explained in terms of classical free radical chemistry with initiation via alkoxyl radicals formed in reaction 1. Our results are congruent with those of Minisci et al[9,19] and Newcomb et al[20] and our conclusions are the same: GoAgg^{V} chemistry (and possibly a lot more of Gif chemistry) involves *free-radicals* and an Fe^{III} / Fe^{IV} couple, not a "*radical-free*" Fe^{III} / Fe^{V} couple.

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