Concerning the Mechanism of 'Gif' Oxidations of Cycloalkanes

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The oxygen atom of cyclodecanone, formed by oxidation of cyclodecane using $FeCl_3$–H_2O_2 in pyridine–acetic acid, is largely derived from molecular oxygen: taken in conjunction with results of radical-trapping experiments, this supports a free-radical mechanism for the hydrocarbon activation.

Several variants of the 'Gif' oxidation systems have now been reported, in which unactivated methylene groups may be transformed into ketone carbonyl.[1] Thus the 'GoAgg II' system of H_2O_2–$FeCl_3$ in pyridine–HOAc will convert cyclohexane into cyclohexanone. Mechanistic analogy has been tentatively drawn with an iron-based methane oxygenase.[2] The alternative of simple free-radical activation of the cyclohexane has hitherto been discounted.[1,2] However, the recent demonstration that cyclohexyl hydroperoxide is an intermediate in the GoAgg II oxidation of cyclohexane[3] prompted us to re-examine the evidence against a radical mechanism.

Iron(III)–H_2O_2 systems are widely recognised as sources of hydroxyl radicals.[4] Presumably, by analogy, ROOH could produce RO$^•$. Both hydroxyl and alkoxyl radicals are capable of abstracting hydrogen from a saturated hydrocarbon. Hydroxyl radicals are very reactive and rather unselective, whilst secondary alkoxyl radicals show a selectivity for secondary *versus* tertiary hydrogen of *ca.* 1 : 4.[6] A value (per hydrogen) of 1 : 3, reported for Gif oxidation of adamantane at room temperature, does not seem inconsistent with hydroxyl radical attack on the hydrocarbon, augmented by alkoxyl attack.† Similarly, a mixture of hydroxyl- and alkoxyl-radical attack on cyclohexane might reasonably be expected to

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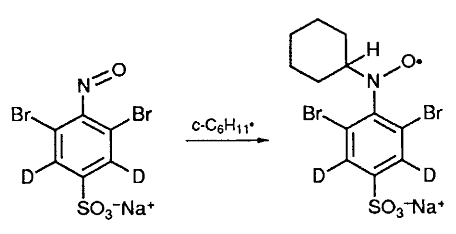
† The tertiary/secondary selectivity (per hydrogen) in radical attack on adamantane is likely to be slightly perturbed from values for acyclic systems. For attack by chlorine atoms, which are generally intermediate inselectivity between hydroxyl and alkoxyl, the ratio has been reported to lie between 2 and 6, depending on solvent (I. Tabushi, J. Hamuro and R. Oda, *J. Am. Chem. Soc.*, 1967, **89**, 7127).



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give the relatively small deuterium kinetic isotope effect which has been observed ($k_H/k_D = 2.5$).[7,‡,§]

With these considerations in mind, we have undertaken some preliminary experiments to test the plausibility of a radical mechanism for GoAgg II oxidations. Because we experienced difficulty in reproducibly recovering cyclohexanone from oxidations of cyclohexane (following the general conditions outlined in ref. 3), our experiments employed the conversion of cyclodecane into cyclodecanone. Yields, measured by gas chromatography, were consistently slightly lower (*ca.* 15%) than those reported by Barton and colleagues for cyclohexanone (*cf.* ref. 3), but were generally reproducible. The radical hypothesis assumes that the processes shown in Scheme 1 are operating.

A simple feature of this scheme, which may be addressed experimentally, is the participation of molecular oxygen. Previously proposed mechanisms for GoAgg oxidation have assumed that the oxygen incorporated into the product is derived from the hydrogen peroxide *via* complexation with the iron,[1–3] but little effort has been made to exclude molecular oxygen from the reactions. Although molecular oxygen is in fact a product of the Fe^{III}–H_2O_2 reaction,[4] we initially examined oxidation of cyclodecane using solutions which had been deoxygenated prior to addition of hydrogen peroxide and which were then maintained under an atmosphere of nitrogen. Only a marginal reduction in cyclodecanone yield was apparent when the results were compared with those of experiments in air. However, when a gentle nitrogen purge was maintained throughout the reaction in order to sweep out molecular oxygen formed *in situ*, the yield of cyclodecanone was virtually eliminated (<2%).

$$\mathrm{HO^{\bullet} + R_2CH_2 \xrightarrow{\qquad\qquad} R_2CH^{\bullet}}$$
$$\mathrm{R_2CH^{\bullet} + O_2 \xrightarrow{\qquad\qquad} R_2CHOO^{\bullet}}$$
$$\mathrm{R_2CHOO^{\bullet} \xrightarrow{\text{H-donor }(H_2O_2?)} R_2CHOOH}$$
$$\mathrm{2R_2CHOO^{\bullet} \xrightarrow{\qquad\qquad} R_2CO + R_2CHOH + O_2}$$
$$\mathrm{R_2CHOOH \xrightarrow{\text{Fe cat.}} R_2CHO^{\bullet}}$$
$$\mathrm{R_2CHO^{\bullet} + R_2CH_2 \xrightarrow{\qquad\qquad} R_2CHOH + R_2CH^{\bullet}}$$
$$\mathrm{R_2CHOH \xrightarrow{[Ox]} R_2CO}$$

Scheme 1

For a more definitive demonstration that the oxygen in the product is derived from molecular oxygen, the cyclodecane oxidation was repeated with vigorous stirring under an atmosphere of $^{18}O_2$. Examination of the reaction mixture (after aqueous washing) by gas chromatography with coupled FTIR detection showed that the cyclodecanone product had two carbonyl stretching bands, at 1719 and 1687 cm^{-1}, of similar intensities, indicating incorporation of *ca.* 50% ^{18}O into the product. This level of incorporation of ^{18}O was corroborated by the presence of molecular ion peaks of comparable intensity at m/z 154 and 156 in the mass spectrum. The conditions chosen for this experiment employed roughly equivalent quantities of $^{18}O_2$ and $H_2{}^{16}O_2$. This correspondence is, however, likely to be coincidental, with the result reflecting parallel dissolution of $^{18}O_2$ gas and *in situ* generation of $^{16}O_2$ from the unlabelled hydrogen peroxide. We are unaware of any precedent for reduction of molecular oxygen under these conditions, although in the early Gif reactions molecular oxygen and a powerful reducing agent were used instead of H_2O_2.

In addition to testing the incorporation of molecular oxygen, we have obtained evidence for the participation of both hydroxyl and cyclohexyl radicals in oxidations of cyclohexane using GoAgg II. Hydoxyl radical participation was demonstrated by *p*-hydroxylation (*inter alia*) of phenylalanine incorporated into the reaction system;[8] cyclohexyl radicals (from cyclohexane oxidation) were detected by spin trapping using deuteriated 3,5-dibromo-4-nitrosobenzenesulphonic acid sodium salt[9] to give the spin adduct **1** (a_N = 14.1 G, a_H = 8.0 G). The same spin adduct was detected when $FeCl_3$ and H_2O_2 were replaced by di-*tert*-butyl peroxyoxalate (as a source of butoxyl radicals). Whilst the trapping results indicate that both hydroxyl and cyclohexyl radicals are generated in these GoAgg II experiments, it is the oxygen incorporation result which suggests a *preponderant* free-radical pathway for the reaction.

Finally, whilst recognising that Scheme 1 is short on detail, it is clear that one expected product from cyclohexane would be cyclohexanol. We subjected a small quantity of cyclohexanol to the reaction conditions and found that it was efficiently oxidised to cyclohexanone.

In summary, we believe that these preliminary results, taken in conjunction with a reappraisal of published reactivity data, suggest that a radical mechanism for oxidation of *e.g.* cyclohexane by H_2O_2–$FeCl_3$ in pyridine–acetic acid, in which both hydroxyl and alkoxyl radicals are hydrogen abstractors, may play a more important role in these reactions than hitherto recognised.

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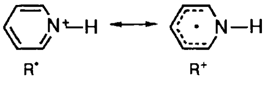
‡ k_H/k_D for hydrogen abstraction from cyclohexane by $HO^{\bullet}$ is only slightly greater than unity (E. S. Rudakov, L. K. Volkova and V. P. Tret'yakov, *React. Kinet. Catal. Lett.*, 1981, **16**, 333). We have been unable to find a literature value of k_H/k_D for hydrogen abstraction from cyclohexane by alkoxyl radicals, but since the reaction will be approximately thermoneutral, with a roughly symmetrical transition state, the figure is likely to be greater than the (room temp.) value of *ca.* 5 reported for abstraction from the weaker benzylic CH bonds of toluene (G. F. Larson and R. D Gilliom, *J. Am. Chem. Soc.*, 1975, **97**, 3444).

§ A further reported objection to the radical path for oxidation of unactivated methylene groups is that *tert*-adamantyl radicals, which are acknowledged to be formed in the oxidation of adamantane, alkylate the pyridine solvent, whilst reaction at the secondary position gives instead adamantanone.[1] However, the ready alkylation of protonated pyridine is believed to pass through a transition state with alkyl cation character (*e.g.* G. P. Gardini, F. Minisci and G. Palla, *Chim. Ind.* (*Milan*), 1971, **53**, 263). Clearly this reactivity pattern should be facilitated for tertiary R groups, so that tertiary radical attack on protonated pyridine (the concentration of which will be critical) may be very much faster than attack by primary or secondary alkyl radicals. Thus, dissolved molecular oxygen might compete successfully for all but the tertiary radicals. Some indirect support for this hypothesis can be adduced from relative reactivity data reported by Minisci *et al.* (F. Minisci, R. Mondelli, G. P. Gardini and O. Porta, *Tetrahedron*, 1972, **28**, 2403). In this context, it is also pertinent to recall that the tertiary adamanyl cation, although bridgehead, is significantly more stable than its secondary isomer (G. A. Olah, G. Liang and G. D. Mateescu, *J. Org. Chem.*, 1974, **39**, 3750). These considerations would accommodate the reported dependence of the tertiary : secondary oxygenation ratio on oxygen pressure.[1]



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