Radical and Non-Radical Mechanisms for Alkane Oxidations by Hydrogen Peroxide−Trifluoroacetic Acid

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The oxidation of cyclohexane by the H_2O_2−trifluoroacetic acid system is revisited. Consistent with a previous report (Deno, N.; Messer, L. A. *Chem. Comm.* **1976**, 1051), cyclohexanol forms initially but then esterifies to cyclohexyl trifluoroacetate. Small amounts of *trans*-1,2-cyclohexadiyl bis(trifluoroacetate) also form. Although these products form irrespective of the presence or absence of O_2, dual mechanisms are shown to operate. In the absence of O_2, the dominant mechanism is a radical chain reaction that is propagated by $CF_3^\bullet$ abstracting H from C_6H_{12} and S_H2 displacement of $C_6H_{11}^\bullet$ on CF_3CO_2OH. The intermediacy of $C_6H_{11}^\bullet$ and $CF_3^\bullet$ is inferred from production of CHF_3 and CO_2 along with cyclohexyl trifluoroacetate, or CDF_3 when cyclohexane-d_{12} is used. In the presence of O_2, fluoroform and CO_2 are suppressed, the reaction rate slows, and the rate law approaches second order (first order in peracid and in C_6H_{12}). Trapping of cyclohexyl radicals by quinoxaline is inefficient except at elevated (∼75 °C) temperatures. Fluoroform and CO_2, telltale evidence for the chain pathway, were not produced when quinoxaline was present in room temperature reactions. These observations suggest that a parallel, nonfree radical, oxenoid insertion mechanism dominates when O_2 is present. A pathway is discussed in which a biradicaloid-zwiterionic transition state is attained by hydrogen transfer from alkane to peroxide oxygen with synchronous O−O bond scission.

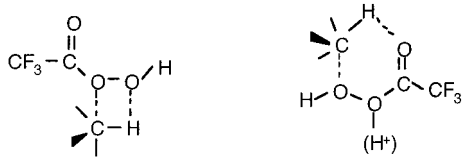
Introduction

Mixtures of H_2O_2 and trifluoroacetic acid readily oxidize alkanes to alkyl trifluoroacetates. The reaction has been studied by Ullrich and Frommer,[1] and by Deno.[2] Trifluoroperoxyacetic acid (TFPA) is presumed to be the agent that oxidizes the alkanes. The equilibrium (eq 1) is rapidly established and shifted to the right under usual conditions (large excess of TFA) for alkane oxidation.[3]

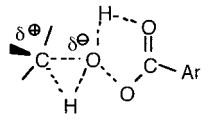
$$CF_3CO_2H + H_2O_2 \rightleftarrows CF_3CO_3H + H_2O \qquad (1)$$

Alkane reactivity depends strongly on the type and number of C−H bonds present with relative reactivity increasing sharply along the series 1° < 2° < 3°. Alkanes with only primary and secondary C−H bonds convert cleanly to esters, apparently with intermediate formation of the precursor alcohols that readily esterify in trifluoroacetic acid. Formation of an ester in large part protects the product from further oxidation to ketones and acids. This was clearly shown by Deno et al.,[2] who observed that positions 4 through 7 of 1-octanol were most reactive. Therefore, the minor side product, 1,2-*trans*-cyclohexadiyl bis(trifluoroacetate) is explained by epoxidation of olefin formed by solvolysis of alcohol/ester or another oxidation path. The products of tertiary alkanes, which are most prone to solvolytic reactions, give complex products.

Alkane oxidation by TFPA is thought to occur by a concerted mechanism. Frommer and Ullrich[1] suggested a 4-center transition state (I), but with discovery of alcohol as the initial product, Deno[2] suggested the 6-center transition state (II). The main evidence for the reaction being concerted is a report by Smith and Sleath that *cis*- and *trans*-decahydronaphthalenes are each converted with 98% retention of configuration.[4]



I **II**



III

Related to this chemistry is the work with aroyl peroxyacids of Schneider and Müller[5] and more recently

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(1) Frommer, U.; Ullrich, V. *Z. Naturforsch.* **1971**, *26b*, 322.

(2) Deno, N. C.; Jedziniak, E. J.; Messer, L. A.; Meyer, M. D.; Stroud, S. G.; Tomezsko, E. S. *Tetrahedron* **1977**, *33*, 2503−8.

(3) Swern, D. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. I, Chapter VII, p 493.

(4) (a) Smith, J. R. L.; Sleath, P. R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1165−1169. (b) For description of experimental method, see: Davison, A. J.; Norman, R. O. C.; *J. Chem. Soc.* **1964**, 5404.

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Minisci and co-workers.[6] Schneider and Müller[5] observed that peroxybenzoic acids with chloro or nitro substituents oxidize tertiary alkanes with high regio- and stereoselectivity. Reactions performed in chloroform gave "reasonable" yields of tertiary alcohol and retention of configuration. Accordingly, they suggested an oxenoid insertion mechanism with transition state III. Minisci and co-workers[6] have challenged the mechanism, offering a radical chain mechanism instead.

$$ArCO_2^{\bullet} + ArCO_2OH \rightarrow ArCO_2H + ArCO_2O^{\bullet} \quad (2)$$

$$ArCO_2O^{\bullet} + RH \rightarrow ArCO_2OH + R^{\bullet} \quad (3)$$

$$ArCO_2OH + R^{\bullet} \rightarrow ArCO_2^{\bullet} + ROH \quad (4)$$

To explain Schneider's and Müller's report[5] of retention of configuration, Minisci suggests that oxidation of the alkyl radical by peracid (eq 4) is a fast cage reaction analogous to the oxygen rebound mechanism for cytochrome P450 oxidations.[7]

In this paper, we report observations showing dual mechanisms operate in the H_2O_2−TFA system. We specifically investigated the role of O_2 in the reactions, analyzed for gaseous products, i.e., CO_2 and CHF_3, and ran reactions in the presence of quinoxaline, which in its protonated form traps alkyl radicals efficiently.[8] For convenience, we used cyclohexane as the prototypical secondary alkane. We find that a free radical chain mechanism clearly operates in the absence of O_2. The mechanism is different than that proposed by Minisci[6] for aroyl peracids. Furthermore, although alkane-derived products do not depend on the presence or absence of O_2, we observed that O_2 retards the rate of oxidation and stops production of CHF_3 and CO_2. Therefore, other mechanisms must operate under these conditions. Possibly it is one of the concerted oxenoid insertion mechanisms suggested above, although we favor and expand on a pathway suggested long ago by Hamilton[9] that well accommodates the dual nature of this reaction.

Results

Consistent with previous reports,[2] we observed that reactions of cyclohexane with H_2O_2−TFA give mainly cyclohexyl trifluoroacetate and small amounts of *trans*-1,2-cyclohexadiyl bis(trifluoroacetate). Experiments were performed to determine specifically the role of free radical intermediates in the absence of catalysts. Of particular interest to us in this work was whether CO_2 and CHF_3 were byproducts of the oxidation. Therefore, yields of CO_2 and CHF_3 were measured. Since these products could occur by reactions that are independent of alkane oxidation,[10] some experiments were performed using cyclohexane-d_{12}. Since radical reactions may be affected by O_2, both the products and reaction kinetics were measured in the presence and absence of O_2. Reactions were also performed with added quinoxaline, an efficient radical trapping agent.[8] Yields of products are calculated based on H_2O_2 used since in all our experiments it was the limiting reagent. These yields are uniformly less than 100%.

Table 1. Oxidation of Cyclohexane in H_2O_2−TFA; Effects of O_2

	% yield[a]			
O_2 (atm)	monoester	diester	CO_2	CHF_3
1	28	10	2	~0.1
0	32	10	34	28
0[b]	46	3	77	44[c]

[a] Based on H_2O_2, 0.18 M; $[H_2O_2]/[C_6H_{12}] = 0.2$; each, entry is an average of two experiments. [b] Cyclohexane-d_{12}, one experiment. [c] $CDF_3/CHF_3 = 21$.

Effects of Oxygen on Products. Table 1 lists results for reactions run at 25 °C for 24 h in the presence and absence of an atmosphere of O_2.[11] The results of Table 1 show an unusual dependence on O_2. Yields of cyclohexyl trifluoroacetate (monoester) and *trans*-1,2-cyclohexadiyl bis(trifluoroacetate) (diester) are relatively unaffected by O_2. However, yields of byproducts, CO_2 and CHF_3 are significantly affected. The yields of CHF_3 and CO_2 in the presence of O_2 are small. Whereas, the yields in the absence of O_2 are significant, being comparable to the combined yields of monoester and diester. The CHF_3 was identified by ^{1}H NMR analyses of the reaction solutions (e.g., see Figure 1) and by GC−MS analyses of the gases above the reaction solutions. No C_2F_6 was detected in the reactions. The yields reported in Table 1 for CO_2 include dissolved CO_2, whereas yields of CHF_3 represent only what was measured in the gas phase. From the solution NMR results, comparable amounts of CHF_3 were in solution. Thus, the yields of CO_2, CHF_3, and total cyclohexane products show an approximate 1:1:1 stoichiometry.

The production of CHF_3 with CO_2 suggests that $CF_3^{\bullet}$ radicals are intermediately formed, at least when O_2 is excluded from the reactions. To determine if CHF_3 results from attack on cyclohexane, an experiment was performed using cylcohexane-d_{12} (entry 3, Table 1). The fluoroform in this reaction was found to contain 96% D. The cyclohexyl trifluoroacetate and 1,2-*trans*-diester incorporated little hydrogen, i.e., they were the d_{11} and d_{10} compounds, respectively.

NMR Analyses of Cyclohexane−H_2O_2−TFA System. Spectra of cyclohexane−H_2O_2−TFA reactions were recorded at intervals after the reagents were mixed (see Figure 1) to obtain product and kinetic information. We observed that alcohol formed initially and then disappeared. Small amounts (<5%) of diester were observed at long times. Absence of additional resonances between δ 2−4 showed little of the cyclohaxane is oxidized to ketones or acids. Fluoroform was observed when oxygen was absent. Methine ^{1}H-resonances for alcohol, ester, and fluoroform NMR resonances were integrated to obtain concentration vs time data, in Figure 2.

(5) Schneider, H.-J.; Müller, W. *J. Org. Chem.* **1985**, *50*, 4609−4615.
(6) Bravo, A.; Bjorsvik, H.-R.; Fontana, F.; Minisci, F.; Serri, A. *J. Org. Chem.* **1996**, *61*, 9409−9416.
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(9) (a) Hamilton, G. A.; Giacin, J. R.; Hellman, T. M.; Snook, M. E.; Weller, J. W. *Ann. N.Y. Acad. Sci.* **1973**, *212*, 4−12. (b) Hamilton, G. A. Chemical Models and Mechanisms for Oxygenases. In *Molecular Mechanisms of Oxygen Activation*; Hayaishi, O., Ed.; Academic Press: New York, 1974; pp 427−430.
(10) Liotta, R.; Hoff, W. S. *J. Org. Chem.* **1980**, *45*, 2887−2890.
(11) Additional reactions were run under more varied conditions but are not shown here. Yields were variable and in some cases higher than those for conditions reported in Table 1. The monoester always dominated over the diester.

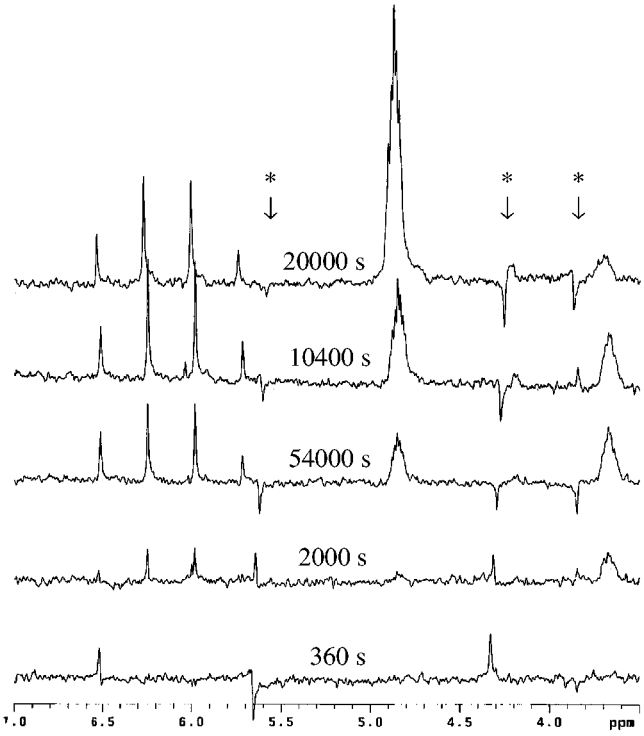


Figure 1. Time dependence of ^{1}H NMR spectra of cyclohexane reacting with H_2O_2−TFA in absence of O_2: cyclohexanol methine, multiplet, $\delta = 3.65$; cyclohexyl trifluoroacetate methine, multiplet, $\delta = 4.85$ ppm; CHF_3, quartet $\delta = 6.15$ ppm. Anomolous peaks (*) are modulation resonances associated with the intense solvent (TFA) peak.

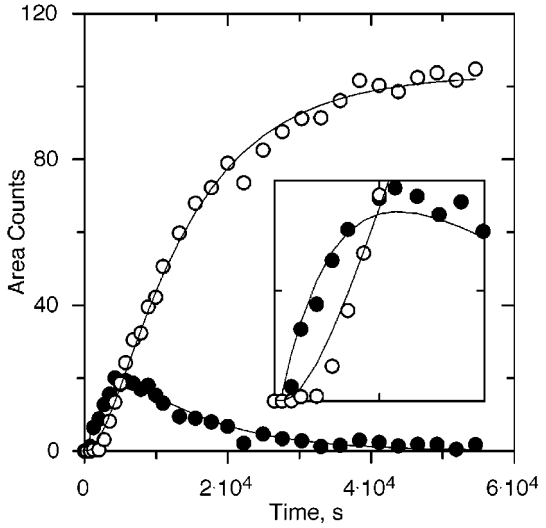


Figure 2. Plot showing concentrations (NMR peak areas) of cyclohexyl trifluoroacetate (○) and cyclohexanol (●) versus time during oxidation of cyclohexane by H_2O_2−TFA in absence of O_2 (first entry in Table 2). Inset: blowup of early time data. Solid lines are fits to kinetic model for eqs 5−7.

The kinetic data (Figure 2) show that the ester grows in with time, but delayed relative to the appearance of alcohol and fluoroform. This behavior suggests a sequential process, $C_6H_{12} \rightarrow C_6H_{11}OH \rightarrow C_6H_{11}OCOCF_3$. However, we observed that the final yields of ester depended on the concentration of cyclohexane, even though it was present in large excess (see Table 2). We suppose side reactions occur that consume TFPA (i.e., production of diester, as well as other reactions[10] that do not involve cyclohexane). Accordingly, the data were fit to the integrated rate equations for parallel and series pseudo-first-order reactions:

Table 2. Observed First-Order Rate Constants for Oxidation of Cyclohexane in H_2O_2−TFA System

cyclohexane (M)	O_2 (atm)	ester yield[a] (%)	$k_5 + k_7$ ($\times 10^5$) (s^{-1})	k_6 ($\times 10^4$) (s^{-1})	k_5 ($\times 10^5$) (s^{-1})	k_7 ($\times 10^5$) (s^{-1})
0.84	0	60[b]	8.6	3.2	5.1	3.5
0.42	0	38[c]	16	3.6	6.1	9.9
0.84	1	50	5.8	3.2	2.9	2.9
0.084	1	37	2.3	2.9	0.86	1.9

[a] Yield based on H_2O_2 concentration, 6.7×10^{-3} M. [b] Maximum yield of CHF_3 in solution was 14%; final yield was 12%. [c] Maximum yield of CHF_3 in solution was 18%; final yield was 13%.

$$C_6H_{12} + TFPA \rightarrow C_6H_{11}OH \quad (5)$$

$$C_6H_{11}OH + TFA \rightarrow C_6H_{11}OCOCF_3 \quad (6)$$

$$TFPA \rightarrow X \quad (7)$$

Table 2 lists psuedo-first-order rate constants and product yields extracted from these experiments. The rate constants show complex dependencies on cyclohexane and O_2. Note that for reactions run in the absence of O_2, the observed pseudo-first-order rate constant for eq 5 is roughly independent of cyclohexane, whereas the rate constant for eq 7 is inversely dependent on cyclohexane. Reactions run in the presence of O_2 show different trends. The observed combined rate of eqs 5 and 7 vary proportionally with cyclohexane and the rates are slower. Since a radical chain path would be inhibited, with O_2 scavenging both $CF_3^\bullet$ and cyclohexyl radicals, slower reaction rates are expected. Consistent with this view, reactions run under an atmosphere of O_2 produced little fluoroform in either solution or gas phases (see Table 1).

From the data in Table 2, we derived the complex overall rate laws for O_2-free (eq 8) and 1 atm O_2 (eq 9) reactions:[12]

$$d[TFPA]/dt = \{5.6 \times 10^{-5}\ s^{-1} + 3.2 \times 10^{-5}\ M^{-1}\ s^{-1}[C_6H_{12}]^{-1/2}\}[TFPA] \quad (8)$$

$$d[TFPA]/dt = \{3.3 \times 10^{-3}\ s^{-1}[C_6H_{12}]^{3/4} + 3.0 \times 10^{-5}\ M^{-1}\ s^{-1}[C_6H_{12}]^{1/4}\}[TFPA] \quad (9)$$

The first terms of these rate laws represent the process that produces alcohol (eq 5). Both rate constant and cyclohexane reaction order show a dependence on O_2, the dependence on cyclohexane being zero order in the absence of O_2 and ~3/4 order in 1 atm of O_2. The second terms in eqs 8 and 9 correspond to the side reaction, eq 7. The terms also show dependencies on cyclohexane and O_2. The reaction order of cyclohexane is −0.5 in the absence of O_2 and ~0.25 in 1 atm of O_2.

Quinoxaline Trapping Experiments. Protonated quinoxaline ($pK_a = 1.5$) has been used to scavenge alkyl radicals in radical chain reactions.[8a] The resulting product is cyclohexylquinoxaline. Both 2- and 6-substituted

(12) For cyclohexane/TFPA ≫1, eqs 5−7 predict for disappearance of TFPA: $R = -k_5[TFPA] - k_7[TFPA]$. Equations 8 and 9 were obtained by assuming $k_{obs} = k[cyclohexane]^n$ for each k_5 and k_7 in Table 2 and solving for the respective oxygen-free and oxygen-rich rate constants and cyclohexane reaction orders.

Table 3. Cyclohexylation of Quinoxaline by the H_2O_2–TFA System

			% yield[a]		
quinoxaline	PO_2 (atm)	T (°C)	cyclohexyl quinoxaline	monoester	diester
0.1	1	25	3	33	5
0	1	25	na[b]	49	7
0.1	0	25	0.04	34	4
0	0	25	na[b]	51	3
0.1	0.2	70	36	17	2
0	0.2	70	na[b]	70	8

[a] Based on H_2O_2, 0.18 M in 25 °C runs and 0.05 M in 70 °C runs, $[C_6H_{12}] = 0.9$ M. [b] Not applicable.

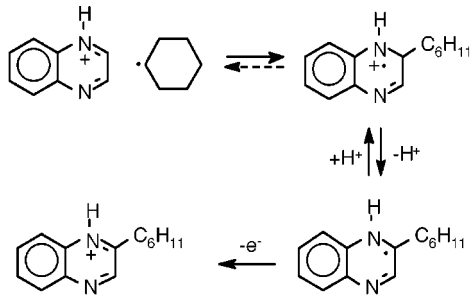
isomers may form, but the 2-isomer dominates at high acidity.[8a] Table 3 lists yields of cyclohexylquinoxaline, cyclohexyl trifluoroacetate, and diester obtained from oxidations of cyclohexane in the presence of quinoxaline. Results of control reactions run under similar conditions in the absence of quinoxaline are also listed. Reactions at 25 °C with quinoxaline yielded relatively little cyclohexylquinoxalines in the absence or presence of O_2. Unlike experiments in Table 1, little CO_2 and CDF_3 were produced in reactions of cyclohexane-d_{12} at 25 °C when O_2 was absent. In contrast to 25 °C results, reactions at 70 °C yielded significant cyclohexylquinoxaline and yields of mono- and diesters were reduced relative to reactions performed without added quinoxaline.

Control Experiments and the Effect of Cl^-. Several control experiments were performed to elucidate the heterolytic/solvolytic chemistry of the products and intermediates in TFA. Cyclohexanone in TFA did not convert to mixed ester-alcohol or diester products when heated for 4 h at 70 °C. Cyclohexene in TFA containing 10 wt % H_2O converts to cyclohexyl trifluoroacetate at room temperature with a rate constant of 1.3×10^{-4} s^{-1}. Reaction of cyclohexane with H_2O_2 in TFA run at 70 °C with added NH_4Cl produced approximately 10% cyclohexyl chloride, 20% cyclohexyl trifluoroacetate, and 10% 1,2-*trans*-diester based on H_2O_2. Less than 1% of cyclohexyl chloride is formed when cyclohexanol is reacted with 0.1 M NH_4Cl in trifluoroacetic acid for 4 h at 70 °C. With 0.1 M NH_4Cl present, ~30% of cyclohexene is converted to cyclohexyl chloride. Less than 20% of cyclohexyl chloride solvolyzes in TFA, even upon heating to 70 °C for 4 h.

Discussion

Radical Chain Mechanism. Although previous reports have ruled out free radical mechanisms in the H_2O_2–TFA system, we find clear evidence that a radical chain mechanism operates, at least under conditions of low O_2 partial pressure. Homolysis of TFPA and involvement of $CF_3^\bullet$ is indicated by the production of CO_2 and fluoroform-*d* in high yields when cyclohexane-d_{12} was oxidized in the absence of O_2. It is not clear why trapping of cyclohexyl radicals was inefficient at 25 °C. However, since little CO_2 and fluoroform were produced in reactions at 25 °C that contained quinoxaline, the results may be rationalized by considering the steps necessary for forming cyclohexylquinoxaline. These steps (Scheme 1) include radical addition, deprotonation, and oxidation by peracid. The addition of cyclohexyl radical is expected to be rapid. Therefore, if the deprotonation step is slow at 25 °C, then the radical chain reaction would be inhibited by cyclohexylquinoxaline.

Scheme 1



The following propagation steps are consistent with much of the data.

$$CF_3^\bullet + C_6H_{12} \rightarrow C_6H_{11}^\bullet + CHF_3 \qquad (10)$$

$$C_6H_{11}^\bullet + HOO_2CCF_3 \rightarrow C_6H_{11}OH + CF_3CO_2^\bullet \qquad (11)$$

$$CF_3CO_2^\bullet \rightarrow CF_3^\bullet + CO_2 \qquad (12)$$

This radical chain differs from the one that operates in oxidations by *m*-chloroperoxybenzoic acid.[6] There, arylacylperoxy radicals, formed by reaction of acyloxy radical with peracid, abstract H from alkanes. However, $H^\bullet$ abstraction by $CF_3CO_2^\bullet$ is not important in the TFA–H_2O_2 system because decarboxylation is too fast ($k \approx 5 \times 10^{-9}$ s^{-1}).[13] Perfluoroalkyl radicals are electrophilic and intrinsically much more reactive that alkyl radicals in H-abstraction reactions. Dolbier and co-workers[14] have shown that the reactivity of *n*-perfluorobutyl radicals is more like that of the *tert*-butoxy radical than the alkyl radical. Reaction of $CF_3^\bullet$ with cyclohexane is exothermic by −8 kcal/mol.[15] Therefore, an efficient chain reaction is plausible.

Equation 11 is an S_H2 reaction. While we are not aware that such a reaction has been documented for TFPA, analogous reactions are known for other peroxides, and Minisci[6] has suggested the analogous reaction occurs in the *m*-chloroperoxybenzoic acid system. In the case of peresters, an ^{18}O labeling study even shows that the alkyl radical attacks the peroxidic oxygen.[16,17]

A zero-order dependence on cyclohexane of TFPA disappearance to ester may be expected in the absence of O_2 where chain termination reactions may be dominated by self-termination of cyclohexyl radicals:[18]

$$2C_6H_{11}^\bullet \rightarrow C_6H_{10} + C_6H_{12} + C_{12}H_{22} \qquad (13)$$

However, these steps alone may not explain the overall reaction kinetics. Additional steps for consuming TFPA

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(14) Shtarev, A. B., Tian, F., Dolbier, W. R., Jr., Smart, B. E. *J. Am. Chem. Soc.* **1999**, *121*, 7335–7341.

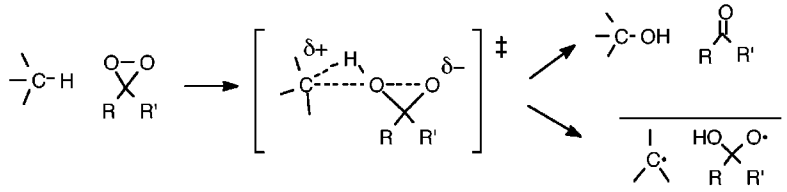
(15) (a) Estimated using standard heats of formation (in kcal/mol): CHF_3, −166.6; *i*-C_3H_7, −21.6; $CF_3^\bullet$, −112.4; C_3H_8, −25.0. (b) See *NIST Standard Reference Database Number 69*; February 2000 Release.

(16) Koenig, T. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, pp 116–120.

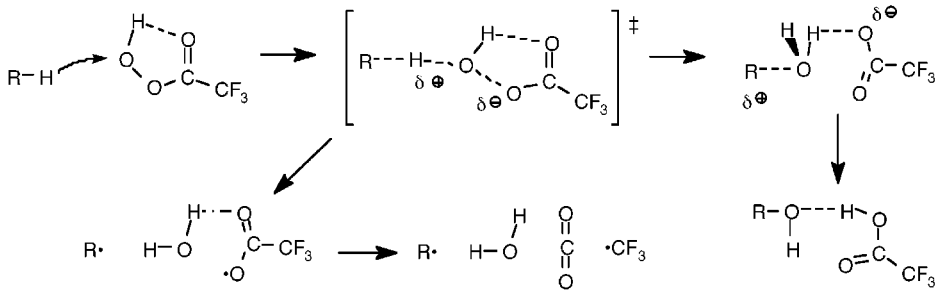
(17) Denney, D. B.; Feig, G. *J. Am. Chem. Soc.* **1959**, *81*, 5322.

(18) (a) Howard, J. A. In *Organic Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. 2, Chapter 12, p 32. (b) Walling, C. *Free Radicals in Solution*; John Wiley and Sons: New York, 1957; pp 243, 244, 418–421.

Scheme 2



Scheme 3



must be included. The chain reaction might operate even in the presence of modest concentrations of O_2, provided propagation steps are rapid enough.

When O_2 is present, little CO_2 and negligible CHF_3 were produced. Probably, $CF_3^{\bullet}$ radicals are scavenged by O_2 to form $CF_3O_2^{\bullet}$ radical. The further involvement of a chain reaction is speculative. Little information exists about the reactivity of $CF_3OO^{\bullet}$ radical for H abstraction from alkanes. A dilemma that any radical mechanism must overcome is explaining how cyclohexanol and then ester are produced without making CO_2 and cyclohexanone or caprolactone. For example, Minisci and coworkers[6] report that oxidation of cyclohexane by *m*-peroxybenzoic acid in dichloromethane (65 °C, air atmosphere) produces cyclohexanol, cyclohexanone, and caprolactone in ratios of 1:1:2, respectively. Therefore, we do not rule out that both radical-chain and nonchain mechanisms operate in such a way that O_2 inhibits the radical chain pathway allowing nonradical pathways to dominate.

Nonradical Mechanisms. The effects we observe for O_2 and quinoxaline and reports of retention of stereochemistry at *tertiary* centers[4,5,19] make a strong case for an alternative pathway not involving diffusive intermediates. We favor a mechanism based on an explanation given by Hamilton[9] nearly 30 years ago. He described a general mechanism for reaction of alkanes with oxenoid agents, including TFPA, in which the reactions occur by transfer of hydrogen from alkane to oxenoid reagent to give a TS and/or intermediates that are a resonance hybrid of radical and ionic structures. The resulting products and their stereochemistry depend on the electronic character and relative stability of the TS/intermediates.

$$R{-}H + O{=}X \rightarrow [R^{\bullet}\ H{-}O{-}X^{\bullet} \leftrightarrow R^{+}\ H{-}O{-}X^{-}] \rightarrow R{-}O{-}H + X \quad (14)$$

Such a mechanism has recently been adopted for dioxiranes, another class of oxenoid reagent that, like peracids, react with alkanes and show evidence for both radical and concerted mechanisms.[20,21] Theoretical calculations[22] predict a TS, achieved by hydrogen transfer, that is a polarized biradicaloid intermediate rather than a radical pair. After the TS, the reaction path divides into two channels, one leading to O-insertion products (alcohol and ketone) and the other separating into alkyl and α-hydroxyalkoxyl radicals (see Scheme 2).[22a]

Hamilton did not elaborate a mechanism for peroxy acids. Therefore, we suggest the mechanism in Scheme 3, which is analogous to the dioxirane mechanism.[22a,b] The alkane H is transferred synchronous with peroxide O−O bond scission leading to a transition state with alkyl and acyloxy groups separated by an incipient water molecule. The electron donating and electron withdrawing properties of the respective groups favor zwitterionic character in the TS and its subsequent collapse to "concerted" products. Carbon−oxygen bond formation may only require a rotation of the water molecule such that front attack on the alkyl group occurs with retention of configuration. If the alkyl group separates from the TS complex, then radical character may develop in the respective groups. Radicals that escape the solvent cage initiate chain reactions 10−12, unless inhibitors are present. The probability of radical escape need not be high since the chain reaction multiplies the event.

An upper limit for the activation barrier is roughly estimated assuming homolytic intermediates. The enthalpy for reaction of propane with TFPA to form 2-propyl

(19) Both examples involve reactions in which dichloromethane, not TFA, is the solvent. Also, while Schneider and Müller[5] performed peroxybenzoic acid reactions at reflux temperatures, Smith and Sleath[4] ran TFPA reactions at 0 °C.

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radical, trifluoroacetoxy radical, and water, each in the gas phase, is $\Delta H° = 29$ kcal/mol (eq 15).[23,24]

$$CH_3CH_2CH_3 + RCO_2OH \rightarrow RCO_2^{\bullet} + H_2O + CH_3CH{\cdot}CH_3 \quad (15)$$

However, the energy to produce the radicals in a solvent cage may be smaller as a result of hydrogen bonding of water to the acyloxy radical. Although alkoxy radicals are thought not to form hydrogen bonds,[25] hydrogen bonding of acyloxy radicals is, to our knowledge, an unexplored topic. The strength of the intramolecular hydrogen bond in peroxyformic and peroxyacetic acids was estimated by Swern to be 6−7 kcal/mol.[26] More recently, Bach et al. have calculated ~5 kcal/mol for the strength of the hydrogen bond in peroxyacetic acid.[27] A similarly strong hydrogen bond of the incipient water to acyloxy radical or to solvent (e.g., TFA) would cause the homolytic reaction to occur with an energy of ~24 kcal/mol. The transition state in Scheme 3 may be earlier on the reaction coordinate and be lower in energy than a water-separated radical pair, depending on the zwitterionic character and resulting solvation effects.

Another consideration is that C−C bond cleavage may occur at some point along the reaction coordinate to form $CF_3^{\bullet}$, CO_2, H_2O, and $R^{\bullet}$. Having it occur after the TS, or along a parallel path, seems more consistent since efficient conversion of $R^{\bullet}$ to ROH is difficult to envision, except for the chain reaction (eqs 10−12). Although an energetically less favorable trajectory, the potential for initiating radical chain reactions amplifies its importance.

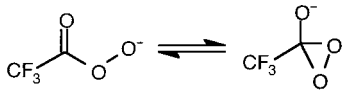
An alternate path transfers hydrogen to the peracid carbonyl with concerted cleavage of the peroxide O−O bond:

$$R{-}H + O{=}C(O_2H)CF_3 \rightarrow [{}^{\bullet}C_6H_{11}\ HOC(=O)CF_3\ OH^{\bullet}] \rightarrow C_6H_{11}OH + HOC(=O)CF_3 \quad (16)$$

The energetics of this path seem prohibitive. We estimate the enthalpy is ~42 kcal/mol[28] to produce cyclohexyl, hydroxyl, and trifluoroacetic acid from cyclohexane and TFPA. As implied by structure II, there would have to be strong electrostatic or covalent bonding interactions between hydroxyl and cyclohexyl groups for this path to be competitive.

Yet another possibility stems from Mimoun's proposal[29] that peracids may isomerize to hydroxydioxiranes. By analogy to dioxiranes, they should be capable of oxenoid insertion. Although hydroxydioxiranes are relatively unknown, recent studies by Porter et al.[30] allow us to consider this possibility in some detail. Their work supports Mimoun's proposal but limits the importance of hydroxydioxiranes to base-promoted reactions. They observed scrambling of ^{18}O-peroxide label is facile in peroxybenzoate anion but not in peroxybenzoic acid. Ab initio structure-electronic calculations were consistent with the observation. The calculations predict relatively high energies for isomerization of several peroxy acids (eq 17), including TPFA, whereas the energies for isomerization of their conjugate anions (eq 18) are significantly lower.

$\Delta G° = 16$ kcal/mol[31] (17)



$\Delta G° \sim 0$ kcal/mol[30,31] (18)

The large free energy for eq 17 makes it improbable that hydroxytrifluoromethyldioxirane is involved in our systems. That eq 18 is an isergonic reaction suggests that the conjugate anion may form under conditions that promote ionization of TFPA. In water, TFPA has a $pK_a = 3.7$ that corresponds to $\Delta G_a° \approx 5$ kcal/mol such that the anion may readily equilibrate with the peroxy acid. In TFA, a low dielectric solvent ($\epsilon = 8.55$),[33] $\Delta G_a°$ will be larger. Therefore, involvement of the anion of hydroxytrifluoromethyldioxirane is probably negligible in our system and in systems[4,5] using dichloromethane ($\epsilon = 9.0$)[33] as solvent.

Finally, we comment on the mechanism for the minor product, *trans*-1,2-diester. This product is attributed to epoxidation of cyclohexene. Although some cyclohexene may come from solvolysis of cyclohexanol/cyclohexyl trifluoroacetate,[2] reactions that we ran with Cl^- added to scavenge carbocations show that other pathways may contribute cyclohexene. We observed 10% cyclohexyl chloride when 0.1 M NH_4Cl was added. Presumably it formed by ionic reaction of cyclohexene:

$$c\text{-}C_6H_{10} + H^+ \rightleftarrows c\text{-}C_6H_{11}{}^+ \xrightarrow{Cl^-} c\text{-}C_6H_{11}Cl \quad (19)$$

In control experiments, little cyclohexyl chloride was produced during solvolysis of cyclohexanol in trifluoroacetic acid with 0.1 M NH_4Cl, but significant cyclohexyl chloride was formed when cyclohexene was reacted in trifluoroacetic acid with 0.1 M NH_4Cl. Therefore, solvolysis of cyclohexanol or cyclohexyl trifluoroacetate during the reaction of TFPA with cyclohexane do not adequately

(23) Estimated from BDEs of propane (99 kcal/mol for 2° C−H),[24] CF_3CO_2−OH (49 kcal/mol),[27] and water (119 kcal/mol).[24]

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(28) Sum of 49 (CF_3CO_2−OH → $CF_3CO_2^{\bullet}$ + •OH),[27] 99 [$(CH_3)_2CH$−H → H• + $(CH_3)_2CH^{\bullet}$),[24] and −106 kcal/mol ($CF_3CO_2^{\bullet}$ + •H → CF_3CO_2−H). This last values is derived from thermochemical cycle using proton and electron affinities of $CF_3CO_2^{\bullet}$ and ionization potential of H•.[15b]

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explain the 1,2-*trans*-diester. Cyclohexene might also derive from reactions such as eqs 20 and 21.

$$C_6H_{12} + HO_3CCF_3 \rightarrow [C_6H_{11}^{+}\ H_2O\ {}^{-}O_2CCF_3] \rightarrow C_6H_{10} + H_3O^{+} + {}^{-}O_2CCF_3 \quad (20)$$

$$C_6H_{11}^{\bullet} + HO_3CCF_3 \rightarrow C_6H_{10} + H_2O + {}^{\bullet}O_2CCF_3 \quad (21)$$

Conclusion

We have obtained new results regarding the mechanism of alkane oxidations in the H_2O_2−TFA system. Previous reports suggested the mechanism does not involve free radicals. However, we find that under certain conditions the reaction clearly does. Reactions performed in the absence of O_2, or in air at 70 °C, seem best explained by a radical-chain mechanism. Under these conditions, (a) CO_2 and CHF_3 were produced in yields that roughly correspond with the yields of cyclohexyl trifluoroacetate; (b) CDF_3 was produced when cyclohexane-d_{12} was used; and (c) with added quinoxaline (70 °C), cyclohexylquinoxalines were major products. Furthermore, the kinetics of the reaction are complex and inconsistent with the process envisioned by Deno (bimolecular involving transition structure II).[2] Yet, we find that, in the presence of O_2 at 25 °C, similar evidence for a free radical mechanism is lacking. Little CO_2 and negligible CHF_3 are formed. Yields of cyclohexylquinoxaline are negligible. The kinetics of the oxidation, as evidenced by the first term in eq 9, approach second order-first order each in cyclohexane and TFPA. We conclude a parallel mechanism not involving free radicals must operate. On the basis of literature precedent, a biradicaloid zwitterionic transition state is proposed for this latter process. It is attained by cyclohexane transferring hydrogen to PTFA peroxidic oxygen. Consistent with reports of retention of configuration in related systems, this transition state may readily collapse to alcohol with retention of configuration. Separation of the TS to free radicals or ions may also be possible, thereby accounting for products by radical chain reactions and for byproducts such as cyclohexene. Our discussion and selection of literature precedents have been influenced by structure-electronic calculations currently in progress at our laboratory. A thorough account of these calculations will be reported later.

Experiment Section

Generally, experiments were performed in TFA solutions that contained the alkane and other reagents as described here and in the tables and figures given below. A typical reaction mixture contained 200 μL of cyclohexane (1.85 mmol) and 39.0 μL of 30% hydrogen peroxide (0.36 mmol) in 2.00 mL of TFA. For anaerobic reactions, the reagents were added to a 5-mL ampule and degassed using three freeze−pump−thaw cycles, and then the ampule was flame-sealed. For reactions under O_2, reagents were added to an 8-mL screw-top glass vial, the solution and headspace were purged with oxygen, and the vial was closed with a Teflon-lined cap or mini-inert valve gas sampling cap if gas samples were to be taken. Headspace gas samples were taken with a gas-sampling syringe. For reactions in sealed ampules, the ampule was placed in 250-mL round-bottom flask, closed with a stopcock adapter, and then shaken to cause the ampule seal to break and release its contents. The adapter outlet was fitted with a serum cap so that gas samples could be removed through the opened stopcock with a gastight syringe. Solutions were prepared for analysis by adding 300 μL samples to a test tube containing approximately 0.7 g of anhydrous $NaCO_3$ and 3 mL of dichloromethane containing decane as an internal standard. After release of CO_2, the dichloromethane layer was dried with magnesium sulfate and analyzed by GC−MS (HP 5890 gas chromatograph equipped with HP 5971 mass-selective detector and 30 m × 0.25 mm i.d. capillary column (HP-5MS) with 0.25 μm film thickness of cross-linked 5% phenyl methyl silicone. Headspace gas analyses were performed on the same instrument using the single-ion detection mode. ^{1}H NMR spectra were recorded at 300 MHz using a Varian VXR-300s spectrometer operating at 7.01 T with a standard 5 mm multinuclear broad band probe. ^{1}H NMR spectra in TFA were run unlocked but were referenced to cyclohexane (δ = 1.2 ppm). Spectral and chromatographic properties of reaction products were matched with data obtained from authentic samples of cyclohexanol and 1,2-cyclohexanediol in TFA. Cyclohexylquinoxaline was assigned on the baiss of its literature mass spectrum.[8b]

Reaction Kinetics. Anaerobic experiments were run in 5 mm o.d. pressure/vacuum valve NMR tubes (Wilmad Glass, Buena, NJ). The TFA (0.5 mL) was degassed inside of the NMR tube by three freeze−pump−thaw cycles. The tube was warmed to room temperature and back-filled with nitrogen. Then, hydrogen peroxide was added to the NMR tube through a septum using a gastight syringe. The stock hydrogen peroxide solution had been subjected to a nitrogen purge for 10 min prior to the transfer. The mixture was allowed to equilibrate for 30 min, after which time degassed cylcohexane was injected using a gastight microliter syringe. The tube was shaken vigorously to mix the contents and then immediately placed inside the thermostated (25 °C) NMR probe.

Henry's Law Constant for CO_2 in TFA. Henry's law constant for CO_2 in the reaction mixtures was measured as follows. To a reaction that had run its course in a sealed vessel, 10-μL aliquots of a 1 M Na_2CO_3 solution were added, and the concentration of CO_2 gas in the headspace was measured by GC−MS. The gas phase concentration increased linearly with the number of additions. The slope of the line equated to a Henry's law constant of 9 atm M^{-1}. This number was used to convert the yield of CO_2 in a reactor headspace to total yield (gas + solution).

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