

SELECTIVE OXIDATION OF ALKANES PROMOTED BY COPPER IONS

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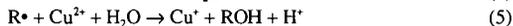
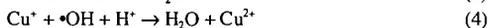
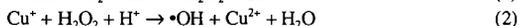
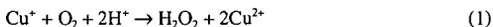
ABSTRACT

A system that uses the Cu(I)/Cu(II) couple and O₂ oxidizes alkanes, including methane, to alkyl ester in trifluoroacetic acid (TFA). Formation of an ester in large part protects the alkyl group from further oxidation, and the esters may then be hydrolyzed to the corresponding alcohol. We show that the system can be adapted to operate electrocatalytically with oxidation of alkane occurring in the cathodic compartment of an electrolysis cell due to the activation of O₂ by electrogenerated Cu(I) ions. The mechanism of the oxidation appears to involve alkyl radicals. Trapping by Cu(II) ions converts the alkyl radicals to the ester product. Alkyl radicals with 2 or more carbons may first convert to olefins which subsequently add TFA to give ester products. The results are compared with oxidation of alkanes in Cu(II)-H₂O₂-TFA.

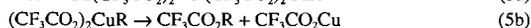
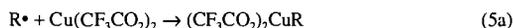
INTRODUCTION

Processes for directly and selectively oxidizing methane to methanol and alkanes to higher alcohols, instead of ketones and acids, could have enormous economic and environmental impacts. A major problem to be overcome is the high reactivity of alcohols toward oxidizing agents, relative to alkanes. Catalytica Advanced Technologies recently reported a significant conceptual advance: methane could be oxidized selectively to methyl sulfate using mercury or platinum catalysts in sulfuric acid.¹ This approach has been extended to other alkanes and ester-forming acids by other groups. Sen has reported extensively on the use of Pd(II) catalysis in TFA.² Also, Vargafik et al. observed Co(II)/Co(III) to be an effective oxidant in TFA.³ Simultaneously, Camaioni and Lilga developed a system based on the Cu(I)/Cu(II) couple and O₂.⁴ In all of these systems, formation of an ester in large part protects the alkyl group from further oxidation, and the esters may then be hydrolyzed to the corresponding alcohol.

The mechanisms of these oxidations are uncertain. The systems developed by Catalytica and by Sen are thought to involve non-radical electrophilic pathways in which metal ion oxidants directly activate the alkane C-H bond. In developing our Cu(I)/Cu(II)-O₂ oxidation system, we assumed free radical mechanisms operate analogous to Fenton-type reactions that operate in aqueous systems (Equations 1-5).

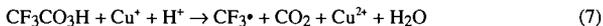


Rates of attack on functionalized substrates by strongly electrophilic radicals such as $\bullet\text{OH}$ and $\text{SO}_4^{\bullet-}$ show a pronounced dependence on the electronic character of the adjacent functional groups (see Table 1). Therefore, a viable system might involve electrophilic radicals abstracting H from alkanes to form organic radicals that subsequently convert to esters on oxidation by transition metal ions. The Cu(I)/Cu(II) couple is well suited for such a system in that O₂ rapidly oxidizes Cu(I) to Cu(II) and generates active oxidizing intermediates (Equation 1) and Cu(II) ions react non-selectively with alkyl radicals to form organocopper(III) intermediates that undergo reductive elimination to give esters or loss of a β -hydrogen to give an alkene (Equations 5a-c). Since TFA adds rapidly to alkenes (Equation 5d), esters are produced in either case.



In this paper, we present a study of alkane oxidation by the Cu(I)/Cu(II)-O₂-TFA system and by the complementary Cu(II)-H₂O₂-TFA system. The latter system was examined because H₂O₂

may be an intermediate in the former system. H_2O_2 reacts with TFA to make trifluoroperacetic acid (TFPA). TFPA oxidizes alkanes at room temperature without need for metal catalysis⁵ and the reactions are reported to occur without generation of alkyl radicals. Primary and methane C-Hs are relatively unreactive. However, Sen observed that addition of Pd(II) accelerated the rate and improved the yield methyl trifluoroacetate from methane.⁶ With respect to our system, reduction of TFPA by Cu(I) may result in decarboxylation (Equations 6 and 7) and initiation of free radical redox reactions.



PROCEDURES

Generally, experiments were performed in TFA solutions that contained the alkanes and other reagents as described below and in the Tables and Figures.

Oxidations promoted by reacting Cu(I) with O_2

In preliminary experiments, oxidations were promoted by reactive dissolution of Cu_2O and Cu metal in TFA solutions containing Cu(II) ions and alkane in contact with air or O_2 gas. Experiments were also performed by adding deoxygenated solutions of Cu(I) trifluoroacetate to solutions of alkane that were stirred under an O_2 atmosphere. See Table 2 for specific conditions and methods. To make the reactions catalytic in Cu ions, oxidations were run in an electrochemical cell that allowed for the generation of known amounts of Cu(I) at known rates without changing the total concentration of copper in the solution. Initial experiments simply used an open beaker with two platinum electrodes and a potentiostat operating in constant current mode. In subsequent experiments, we used a gas-tight, Teflon and glass cell (ca. 100 mL volume). Ports in the top of the cell admitted the electrodes and gas recirculation connections and allowed for gas/liquid sampling. The working electrode was a platinum mesh cylinder. The auxiliary electrode was a platinum mesh flag centered within the working electrode and separated from the working solution by a porous Vycor frit. The solution in the auxiliary electrode chamber was typically 1 M H_2SO_4 . A saturated calomel reference electrode was positioned next to the working electrode via a salt bridge with porous Vycor frit. The salt bridge contained 5 M KOC_2F_3 . Typically, the cell was operated at a potential of -0.1 V vs. SCE and a current of 50 mA. The cell was connected to a gas recirculation system that consisted of a MasterFlex pump with Teflon pump head and Teflon tubing and 5-L gas ballast that served to minimize changes in gas concentrations during experiments. Initial gas compositions were set with calibrated rotometers and verified by gas chromatography.

Oxidations using H_2O_2 -TFA

Solution experiments were conducted in 5 mL ampoules or in 8 mL screw-top sample vials with Teflon lined caps. Reaction mixtures were made by adding 200 μL of cyclohexane and 39.0 μL of 30% hydrogen peroxide to 2.00 mL of TFA or 2.00 mL of a TFA/Cu(II) stock solution. Anaerobic samples were degassed using three freeze-pump-thaw cycles, and the ampoules flame-sealed. For aerobic samples the head space was purged with oxygen after all components were added. Gas samples were taken using a Hamilton SampleLock™ syringe with a gas sampling needle. Gas analyses were performed by GC-MS and quantified by using an internal argon standard. 300 μL aliquots of each reaction solution were neutralized and the organic components extracted by adding the sample to a test tube containing approximately 0.7 g anhydrous sodium carbonate, 3 mL of dichloromethane and 10.00 μL of a decane in dichloromethane solution that served as an internal standard. After neutralizing the TFA, the dichloromethane layer was dried with magnesium sulfate and analyzed by gas chromatography.

Analyses

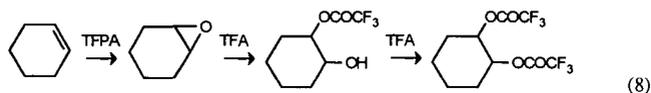
Gas chromatography was performed using an HP 5890 gas chromatograph with a 30-m HP-5MS capillary column (crosslinked 5% phenyl methyl silicone, 0.25 μm film thickness, 0.25 mm column i.d.). Chromatograms were recorded using an HP 5971 mass-selective detector. Gaseous components were quantified by using the mass-selective detector to extract ions unique to each component. All instrument responses were in the linear region of the respective calibration curves, and calibrations were verified periodically. ^1H NMR spectra were recorded at 300 MHz using a Varian VXR-300 spectrometer operating at 7.01 T with a standard 5 mm multinuclear broad band probe. ^1H NMR spectra in TFA were run unlocked, but were referenced

to cyclohexane and matched with spectra of mixtures prepared from authentic samples of cyclohexanol and 1,2-cyclohexanediol in TFA.

RESULTS

Several scoping experiments were performed to learn the potential of Cu promoted oxidations in TFA. Table 2 shows results for oxidations of methane and cyclohexane that were obtained under a variety of conditions. The results show that oxidations could be promoted by addition of Cu(I) solutions, Cu(I) oxides, or Cu(0) metal to solutions of Cu(II) and O₂. Consistent with a report by Vargaftik et al.,^{2a} no conversion was observed with O₂ and just Cu(II). In these experiments, the alkane was present in excess and Cu(I) was the limiting reagent. Therefore, the yields are calculated assuming a stoichiometry of 1 mole of product per 2 moles of Cu(I) ions. Addition of Cu(I) ions as solutions or solid Cu(I) oxides or Cu(0) metal causes the Cu(II) concentrations to increase and eventually precipitate. This situation can be circumvented by performing the oxidations in an electrolytic cell. The oxidations then become catalytic in Cu(I)/Cu(II) ions. The last entry in Table 2 shows a result obtained in a single compartment electrolytic cell. Here, Cu(II) is reduced to Cu(I) at the cathode and presumably water, present in solution, was oxidized at the anode. The 46% yield of cyclohexyl trifluoroacetate is based on the number of electrons discharged through the cell assuming that 2 electrons are required to produce 1 molecule of ester.

In addition to cyclohexyl trifluoroacetate, we observed lesser amounts of secondary oxidation products. Cyclohexanone was present in minor quantities, typically <2% of cyclohexyl trifluoroacetate. Of the possible disubstituted products, the mono and diester of *trans*-1,2-cyclohexanediol were dominant. The high regioselectivity for these secondary products probably is due to oxidation of cyclohexene. Epoxidation by TFPA is facile and subsequent reactions with TFA will give the monoester and diesters (Equation 8).



Electrocatalytic Oxidation of Cyclohexane in the Cu(II)-O₂-TFA System

We performed additional experiments in a divided electrolytic cell so that the cathodically-driven process could be studied, independent of processes occurring at the anode. The cell was closed from the atmosphere so that the gas composition could be controlled and analyzed as the oxidation proceeded. We were particularly interested in learning whether CO₂ was a byproduct. Its production would suggest a mechanism in which TFA is oxidized to CF₃• radicals. In which case, CF₃• or CF₃O₂• may attack alkane C-H bonds (e.g., Equations 9-11).

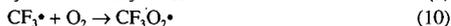


Figure 1 shows results obtained for cyclohexane oxidation that occurred in the cathodic compartment of the electrolytic cell. Moles of cyclohexyl trifluoroacetate and CO₂ are plotted against the moles of electrons discharged through the cell. CO₂ is a minor product relative to cyclohexyl trifluoroacetate. Therefore, Equations 9, 10 and 11 may contribute in a small way to the oxidation. Perhaps, having 10% water in the system and in situ generation of H₂O₂ favors reaction of Cu(I) with H₂O₂ rather than with CF₃CO₂H. The yield of cyclohexyl trifluoroacetate was found to be strongly dependent on the initial amount of O₂ in contact with the Cu(II) solution. Figure 2 shows the yields of monoester and diester for 3 cases: ~50 mL of air in the cathode compartment, cathode compartment recirculated with a 5-L volume of air, and cathode compartment recirculated with 5 L of O₂. The best yields were obtained with the smallest amount of O₂.

The Cu(II)-H₂O₂-TFA System

Reactions were run under aerobic and anaerobic conditions with and without Cu(II) ions present. Table 3 lists results for reactions run at 25 °C for 24 h. The first and second entries show results obtained with Cu(II) catalysis. The esters of cyclohexanol and *trans*-1,2-cyclohexanediol were the dominant cyclohexane products, and in contrast to the Cu(I)-O₂

system, yields of the diester exceeded yields of monoester. Anaerobic conditions and Cu(II) ions gave the highest yields and largest ratios of diester:monoester. Reactions run without Cu(II) ions gave predominantly monoester and showed little dependence on the presence or absence of O₂ (Table 3). Deno observed even greater preference for monoester using excess H₂O₂ (last entry of Table 3).⁵ NMR spectroscopy (¹H and ¹⁹F) of reaction mixtures showed that Cu(II) ions accelerated the oxidations. The NMR spectra also showed CF₃H was produced in significant quantities when reaction solutions were initially degassed. Gas chromatographic-mass spectral analyses of the gases above the reactions confirmed the identity of CF₃H and provided a measure of the amounts of CF₃H and CO₂ that were produced. The yields of CO₂ reported in Table 3 include dissolved CO₂, whereas yields of CF₃H in Table 3 represent only what was in the gas phase. Considering the solution NMR results, comparable amounts of CF₃H were in solution. The results show that yields of CF₃H were strongly dependent on O₂. Reactions that were run in the presence of O₂ generated little CF₃H, although yields of CO₂ were relatively unaffected when Cu(II) ions were present. Analysis of the results from Cu(II)-catalyzed reactions (Table 3) shows that reaction solutions that were initially degassed gave approximately 1 molecule of CO₂ per molecule of cyclohexane that converted. When O₂ was present initially, the stoichiometry was >1 (compare first and second entries of Table 3 and note that % yield of diester based on H₂O₂ is twice the % yield based on converted cyclohexane). When Cu(II) ions were absent and O₂ was present, the yield of CO₂ was very small. Finally, cyclohexane-d₁₂ was oxidized under anaerobic conditions to determine the fraction of CF₃H produced by Equation 9. In the absence of O₂, the ratio CF₃D/CF₃H was 20/1, both in the presence or absence of Cu(II) ions, showing that CF₃• radicals mainly had abstracted H from cyclohexane.

CONCLUSIONS

These experiments show that Cu ions are effective in promoting selective oxidation of alkanes to alkyl trifluoroacetate esters. Furthermore, it is possible to initiate oxidation in the cathodic compartment of an electrolysis cell making the oxidations catalytic in Cu and enabling continuous operation. The reactions appear to be Fenton-type systems in which oxidations of Cu(I) ion by O₂ and peroxide generate oxidizing species that abstract H to give organic radicals that react with Cu(II) converting to products and propagating a redox chain reaction (e.g., Equations 2-5). In the following discussion we reconcile observations and, in the end, comment on the mechanism of the uncatalyzed H₂O₂ system.

Distribution of Monoester and Diester from Cyclohexane

The distributions of mono and disubstituted products differ markedly for the Cu(I)-O₂-TFA and Cu(II)-H₂O₂-TFA systems. The former favors monoester and the latter favors diester. The former generates H₂O₂ in situ while the latter starts out with H₂O₂. These variations may be accommodated by a free radical redox chain reaction that involves Equations 1-3, 6, 7, 9-11, then 5a, and 5c followed by 5d and 8. Given that Equations 6 and 8 are facile, the different product distributions arise from how introduction of H₂O₂ affects the competing reactions. Presumably, in situ generation of H₂O₂ favors low steady-state concentrations of H₂O₂, such that Equation 6 is slow compared to Equation 2 and Equation 5d (with R(-H) = cyclohexene) is fast compared to Equation 8. Therefore, Equations 6-11 are not important in Cu(I)-O₂ oxidations. However, when starting with H₂O₂ as we do in the Cu(II)-H₂O₂-TFA system, TFA forms (Equation 6) in sufficient amounts such that Equation 8 competes effectively with Equation 5d.

Factors Affecting Yields

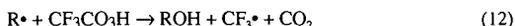
The yields of products have been calculated based on reducing equivalents used in the Cu(I)-O₂ system or H₂O₂ used in the Cu(II)-H₂O₂ system. These yields were generally less than 100% due to reactions that consume reagent without generating alkyl radicals. Equation 4 is an example of such a reaction. Liotta and Hoff observed that solutions of 30% H₂O₂/water in TFA decompose with generation of CF₃H.⁷ Apparently, the decomposition involves radical reactions that serve to initiate alkane oxidations when Cu(II) ions are present or O₂ is absent.

Effects of O₂

O₂ affects the reaction systems in various ways. First of all, it is required when peroxide is not a reagent. Even so, its effect in the electrocatalyzed system is curious in that yields of monoester vary inversely with the amount of available oxygen, i.e., the system is more efficient when starved for oxygen. Other products do not appear with increasing O₂. Therefore, we assume that reduction to water occurs. If so, then it may be that higher concentrations of O₂ allow direct reduction at the cathode and/or greater fractions of Equations 1 and 2 to occur near

the electrode surface where the $\bullet\text{OH}$ is reduced to water much faster than it is scavenged by alkane.

When peroxide is a reagent, the effects of O_2 are complex and not fully understood. In the absence of O_2 , CF_3H and CO_2 were produced in amounts that were comparable to the alkyl esters, and when cyclohexane- d_{12} was used, $\text{CF}_3\text{D}/\text{CF}_3\text{H}$ ratios of >20 were obtained. These observations are consistent with a radical chain decomposition in which propagation steps include: attack on RH by $\text{CF}_3\bullet$; and oxidation of $\text{R}\bullet$ by Cu(II) if present and by $\text{CF}_3\text{CO}_3\text{H}$ if Cu(II) is absent (Equation 12).⁸



When O_2 and Cu(II) ions are present, less CO_2 and little CF_3H were produced. Probably $\text{CF}_3\bullet$ radicals are scavenged by O_2 leaving the less reactive $\text{CF}_3\text{O}_2\bullet$ radical to propagate the reaction (Equation 11). The mechanism in the presence of O_2 and absence of Cu(II) is most uncertain. A dilemma that any radical mechanism must overcome is explaining how cyclohexanol⁸ and then ester are produced without making cyclohexanone and CO_2 . Perhaps, O_2 serves to inhibit the radical chain pathway and allow heterolytic pathways to operate.^{5,8}

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8. Deno reported cyclohexanol is initially produced (see Ref. 5). Using ^1H NMR, we too observed it to form and esterify in successive steps.

Table 1. Rate Constants^(a) for H-Abstraction from CH₃-X by HO• and SO₄^{-•}

X	HO•	SO ₄ ^{-•}
	<i>k</i> /10 ⁸ M ⁻¹ s ⁻¹	<i>k</i> /10 ⁶ M ⁻¹ s ⁻¹
-OH	9.6	10
-CH ₃ ^(b)	7	2.2
-OCOMe ^(c)	2.2	
-H	0.9	<0.8
-OSO ₃ ⁻	0.5	
-CO ₂ H	0.17	0.014

^(a)From Notre Dame Radiation Laboratory Radiation Chemistry Data Center (<http://www.rcdc.nd.edu/>). ^(b)Total rate constant divided by 2. ^(c)Attack on the acetoxy methyl group is neglected; see value for acetic acid.

Table 2. Yields of Alkyl Ester from Cu(I) Promoted Oxidation in Trifluoroacetic Acid^(a)

Alkane	% ^(b)	Method
Methane	5	Dissolution of Cu ₂ O under 1 atm. of 80/10/10 CH ₄ /O ₂ /N ₂
	9	Addition of CF ₃ CO ₂ Cu solution to 13 atm. 26/1 CH ₄ /O ₂
Cyclohexane ^(c)	17	Addition of CF ₃ CO ₂ Cu to solution stirred in air
	19	Dissolution of solid Cu ₂ O in air
	30	Comproportionation of Cu(0) and Cu(II) in air
	46	Electrolysis of Cu(II) solution in air

^(a)Solutions contained 10 vol% H₂O. ^(b)Based on Cu(I) added assuming 2 moles Cu(I) consumed per mole of ester formed. ^(c)Cyclohexane ~1 M.

Table 3. Oxidation of Cyclohexane in H₂O₂-TFA: Effects of Cu(II) and O₂

Cu(II) M	P _{O₂} Atm	% Yield ^(a)			
		Monoester	Diester	CO ₂	CF ₃ H
0.05	1	7	18	34	0.1
0.05	0	9	52	38	15
0	1	28	10	2	-0.1
0	0	32	10	34	20
0 ^(b)	0.2	66	5	nd ^(c)	nd

^(a)See note (a) in Table 3. ^(b)Deno, et al.,⁵ no Cu ions and [H₂O₂]/[C₆H₁₂] = 1.15.

^(c)not determined.

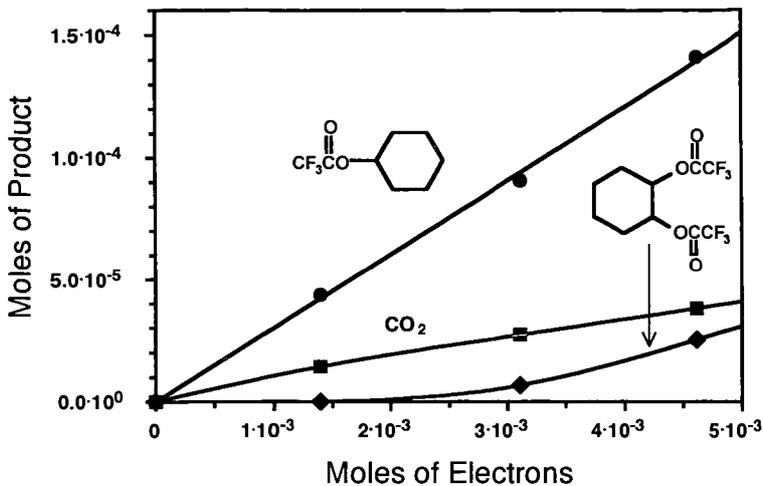


Figure 1. Cu(I)/Cu(II) promoted oxidation of cyclohexane to esters of cyclohexanol (●) and *trans*-1,2-cyclohexanediol (◆) and TFA to CO₂ (■) in the cathodic compartment of a closed, divided electrolysis cell. Conditions: 0.09 M cyclohexane, 0.08 M Cu(II), 10wt% H₂O/TFA, 2.2×10⁻³ moles O₂, E_{applied} = -0.1V vs. SCE.

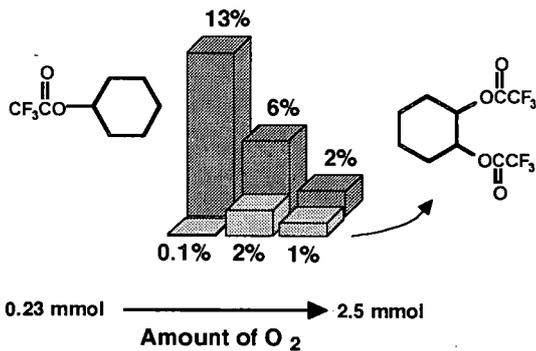


Figure 2. Effect of O₂ contacted with solution on ester yields (% moles product per mole e⁻ discharged). Conditions: 0.09 M cyclohexane, 0.08 M Cu(II), 10wt% H₂O/TFA, 6×10⁻³ moles e⁻ discharged at E_{applied} = -0.1V vs. SCE.