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# Unusual Phase Transfer Mechanism of the Ruthenium-catalyzed Oxidation of Alcohols with Hydrogen Peroxide

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***Abstract:*** A kinetic investigation of the Ru-catalyzed oxidation of 1-phenyl ethanol to acetophenone using $H_2O_2$ under PT conditions shows that this system differs from classic extraction and interfacial mechanisms often encountered in PTC oxidations. Vesicles formed by the phase transfer agent in the organic phase are proposed as the catalytic reaction sites. Such structures are evidenced by microscopic studies. The effects of substituents, different phase transfer agents, and metal catalysts are studied and discussed in view of this mechanism. © 1999 Elsevier Science Ltd. All rights reserved.

## INTRODUCTION

### *Phase transfer catalysis of uncharged species*

Most phase transfer reactions are based on an interfacial anion exchange process leading to an extraction of various charged nucleophiles as ion pairs into organic media. A less prevalent mechanism occurs *via* the extraction and activation of uncharged protic reagents or metal salts that are transferred into the organic medium as complexes of the phase transfer agent. Phase transfer oxidation reactions with hydrogen peroxide belong to this family of reactions which we have termed as "PTC of Uncharged Species".[1] A typical illustration of this phenomenon is the facile formation of non-stoichiometric hydrates of quaternary ammonium salts (quats) with the general structure $R_4N^+X^-(H_2O)_n$ in presence of minute amounts of water. We have demonstrated this immense dehydration aptitude of quats in phase transfer systems[2] that sometimes results in complete inhibition of the catalytic reactions due to deficiency of water molecules at the interface.[3] The critical role of water in phase transfer systems has been reviewed.[3b]

The affinity of ammonium salts towards water is stronger for large lipophilic cations particularly with harder counter anions such as fluoride or hydroxide (and to a lesser degree chloride). Thus, the unexpectedly high water solubility of $(n\text{-Oct})_4N^+F^-$ led us to propose this compound as a universal reagent for total anion assay in aqueous solutions.[4] The hydrogen bonding of a relatively naked hard anion to water in an apolar medium induces a certain polarity and, consequently, a certain nucleophilicity, upon the latter. Side catalytic hydrolysis reactions were thus observed when fluoride anion was reacted with receptive substrates such as alkyl chlorides[5] or nitrohaloaromatics[6] in the presence of water.

Exercising the same conception we have applied other uncharged protic reagents under PTC conditions. HBr was regioselectively reacted with secondary alcohols;[7] HOCl was engaged in PT oxidations of alcohols,[8] cycloalkanones,[9] aldehydes,[10] and alkylaromatics;[11] alkyl anilines were prepared from anilines and alkyl halides;[12] and acetic acid was esterified with benzyl chloride in the absence of a base.[13] Quite surprisingly even carbon acids such as malonates, chloroform or acetylenes could be activated *via* hydrogen bonding to

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quat fluoride.[14, 15] On the other hand, for the same reasons, presence of protic compounds such as water, carboxylic acids or phenols inhibited the progress of simple nucleophilic exchange PTC reactions such as esterifications of alkyl halides by formate anion due to reduced nucleophilicity.[16, 17] Intramolecular hydrogen bonding of monosodium glutarate accounted for the preferential ion-pair extraction of this acid over other dibasic acids.[18] The remarkable cocatalytic effect of certain diols on PTC reaction under basic conditions was rationalized likewise.[19]

Another mode of action was proposed for extraction of uncharged metal salts by phase transfer catalysts *e. g.* the extraction of rhodium chloride into benzene[20] (eq 1) with Aliquat 336.[8]

$$R_4N^+Cl^-_{(org)} + RhCl_{3(aq)} \rightleftharpoons R_4N^+RhCl_4^-{}_{(org)} \qquad (1)$$

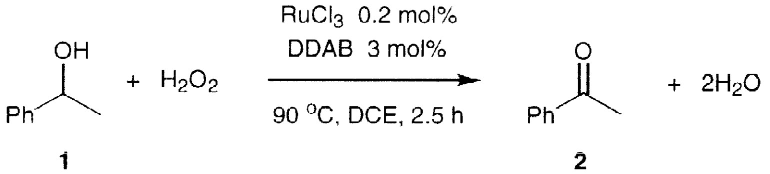
Adducts of this nature were applied in numerous catalytic reactions by several researchers. Our contribution was mainly in rhodium-catalyzed hydrogenation of aromatic systems,[21] cobalt-catalyzed autoxidation of toluenes to benzoic acids[22] and aldehydes,[23] ruthenium-catalyzed hypochlorite oxidation of activated methylbenzenes, and the copper-catalyzed dehydrogenation of hydroxy acids by *t*-butyl hydroperoxide.[24] Recently Weddle *et al* showed that in the catalytic hydrogenation of benzene, the putative $[(C_8H_{17})_3NCH_3]^+[RhCl_4]^-$ ion-pair catalyst is rapidly transformed into a distribution of $Cl^-$ and $[(C_8H_{17})_3NCH_3]^+$ stabilized $Rh^0$ nanoclusters.[25]

*Supramolecular catalysis and hydrogen peroxide/PTC oxidation mechanisms*

Supramolecular catalysis is emerging as one of the plausible options for fulfilling today's demands of high atomic yield and sustainable, "green" chemistry, through imitation of nature's enzymatic systems that combine transition-metal catalysis with molecular recognition.[26] One method to unite these attributes into one catalyst is the use of phase transfer catalysis (PTC).[27] Supramolecular structures formed in transition metal/PTC systems may be envisaged as a midpoint between heterogeneous and homogeneous catalysts.[28] Interestingly, formation of such ordered structures may contradict the classic mechanistic interpretations.

Applications of dilute hydrogen peroxide as an oxygen source are attracting much attention owing to a combination of factors, mainly (i) good availability and low price of the oxidant; (ii) low molecular weight and high percentage of available oxygen; and (iii) environmentally acceptable (water) by-products.[29] The significant enhancement of hydrogen peroxide activity in the presence of transition-metal catalysts, *e. g.* V, Mo, W, Co, Mn, or Fe oxides, is well documented.[30] We have applied hydrogen peroxide under PTC conditions in the oxyhalogenation of arenes[31, 32] and, when combined with $RuCl_3$, in the cleavage of styrene to benzaldehyde,[33] the oxidation of primary alcohols,[34] the transformation of aniline to nitrobenzene,[35] and the side chain oxidation of alkyl arenes.[36] The extraction of hydrogen peroxide in phase transfer system was usually attributed[37] to the formation of non-stoichiometric hydrogen bond adducts of quaternary ammonium salts with $H_2O_2$ with the general structure $R_4NX \cdots H_2O_2$. Such complexes were isolated and characterized by Sokolov.[38] However, exceptions have been noted, *e. g.* the formation of inverse emulsions in catalysis with peroxometalates.[39]

Previously we have shown[34] the facile oxidation of alcohols by hydrogen peroxide catalyzed by $RuCl_3$ and didecyldimethylammoniumbromide (DDAB). In this system (eq 2), 1-phenyl ethanol **1** is quantitatively oxidized to acetophenone **2**.



(2)

Herein we present the results of kinetic and mechanistic studies of the above reaction, including substituent and isotopic effects, and propose that in contrast with the conventional PTC ion-pair mechanisms, the catalytic reaction in the $H_2O_2$/DDAB/$RuCl_3$ system occurs inside vesicles in the organic phase.

## RESULTS AND DISCUSSION

### *Kinetic investigation of the oxidation of 1-phenyl ethanol 1*

In a typical reaction, 30% aqueous $H_2O_2$ was added continuously to a stirred vessel charged with **1** and catalytic amounts of $RuCl_3$ and DDAB in dichloroethane (DCE). The pH measured 3-4 throughout the reaction.[40] Product formation was monitored by GC relative to an internal standard. Acetophenone **2** was the sole product. At the end of the reaction, the catalytic complex could be separated and reused without loss of activity. A typical reaction profile is presented in figure 1. The overall reaction was found to fit a first-order profile, with $k_{obs}=2.46*10^{-4}$ $s^{-1}$ ($r^2=0.991$). As expected, the dependence of the reaction rate on the concentration of **1** was separately found to be first-order, with $k=2.31*10^{-4}$ $s^{-1}$ ($r^2=0.989$), giving the rate equation $v=k[\mathbf{1}]$.

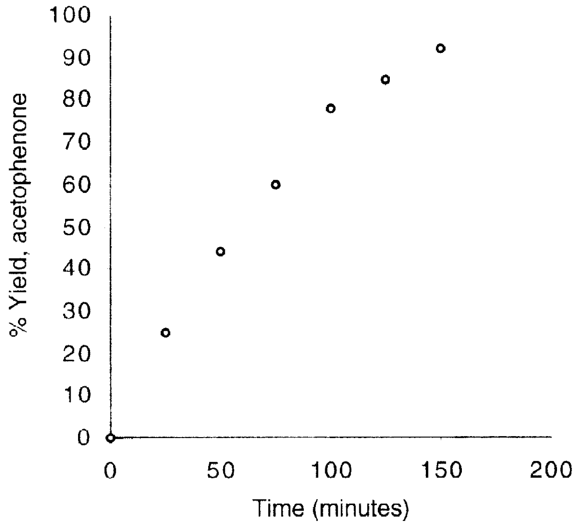


Figure 1. Reaction profile for the oxidation of **1**.
41 mmol **1**, 1.2 mmol DDAB, 0.077 mmol $RuCl_3$, 30% $H_2O_2$ (0.22 ml/min), 10 ml DCE (solvent).

Blank reactions indicated that the oxidation takes place only in the organic phase. However, determination of $[H_2O_2]$ in the organic phase is problematic due to the fact that, in addition to being consumed in the reaction, $H_2O_2$ also undergoes simultaneous unproductive decomposition. In fact, in addition to thermal decomposition at 90 °C, $RuCl_3$, DDAB, and even the alcohol substrate facilitate the catalytic decomposition of $H_2O_2$. These fast decomposition reactions preclude the direct measurement of $[H_2O_2]$ in the organic phase, but it is still possible to calculate the overall amount of $H_2O_2$ in the system at time t ($N_t$) from the equation $N_t = N_f - (N_d + N_r)$, in which $N_f$ is the number of moles of $H_2O_2$ fed into the vessel, $N_d$ is the number of moles of $H_2O_2$ decomposed, and $N_r$ is the number of moles of $H_2O_2$ reacted in the oxidation reaction. As shown in figure 2, $[H_2O_2]$ remains practically constant throughout the reaction.

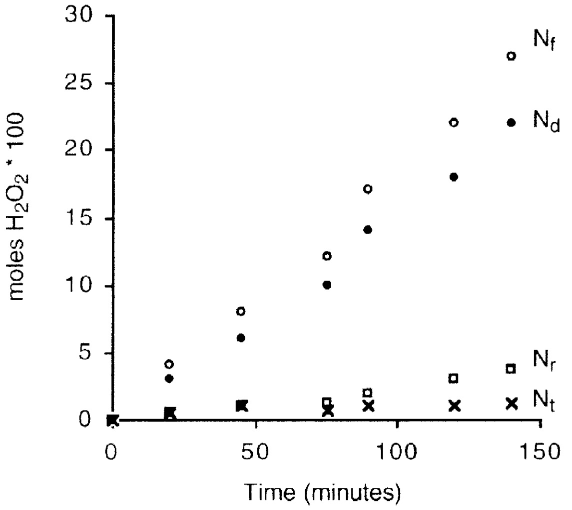


Figure 2. Mass-balance of $H_2O_2$ in the reaction system.
41 mmol **1**, 3 mol% DDAB, 0.2 mol % $RuCl_3$, 30% aq $H_2O_2$ (0.22 ml/min), 10 ml DCE (solvent), 90 °C.

Repeated experiments with different $[H_2O_2]$ in the feed stream afforded the following $N_t$ values: $1.7*10^{-3}$ mol for 15% $H_2O_2$; $3.0*10^{-3}$ mol for 30% $H_2O_2$; and $6.2*10^{-3}$ mol for 50% $H_2O_2$. Accordingly, $H_2O_2$ participates in the rate-determining step, but because $[H_2O_2]$ remains constant, the observed reaction corresponds to pseudo first-order kinetics.

When the deuterated substrate Ph-CDOH-$CH_3$ **1**-*d* was prepared and oxidized, it was found that $k_H/k_D \sim 1$, attesting that the rate-determining step does not involve the cleavage of the benzylic C-H bond. Furthermore, correlation studies performed on *p*-X-$C_6H_4$-CHOH-$CH_3$ (X = MeO, Me, Br, and $NO_2$) resulted in a linear Hammett plot with a low reaction constant ($\rho = 0.5$), implying that the chemical reaction is not the rate-determining step.[41] This was supported by calculation of the Arrhenius energy of activation, which gave $E_a$=14.6 kjmol$^{-1}$ (3.5 kcalmol$^{-1}$; $r^2$=0.993 for four measurements at 50, 65, 75, and 90 °C), a typical value for a diffusion controlled rate-determining step.

Consequently, we thought the rate limiting step could be extraction of $H_2O_2$ into the organic phase, and expected the stirring rate to affect $k_{obs}$. However, the same initial rate ($k_{obs} = 1.5*10^{-3}$ s$^{-1}$) was obtained regardless of the stirring rate (4 experiments at 200, 350, 500 and 800 rpm mechanical stirring).

In summary, the kinetic evidence points to a reaction that occurs in the organic phase, for which the rate determining step is not chemically controlled, and also not dependent on the extraction between the aqueous and organic phases.

Based on these results, the existence of a diffusion barrier *inside the organic phase* was assumed. This assumption was vindicated by direct observation of vesicular structures in the organic phase using Transmission Electron Microscopy (TEM), and analysis of the composition of these structures by Energy Dispersive Analysis of X-rays (EDAX). While the freeze fracture sample of pure **1** is homogeneous, distinct formations, which are roughly circular in shape, can clearly be seen in a similarly prepared sample taken from the reaction mixture (figure 3, the size varies from 10 to 50 nm). As these are the pictures of platinum masks of the fracture, they cannot be used to determine the chemical composition of the vesicles. However, TEM and EDAX measurements performed on dried reaction samples showed circular structures with a similar size distribution (figure 3c).[42] The characteristic K and L lines of ruthenium and bromide were identified by EDAX measurements *only inside* these structures.

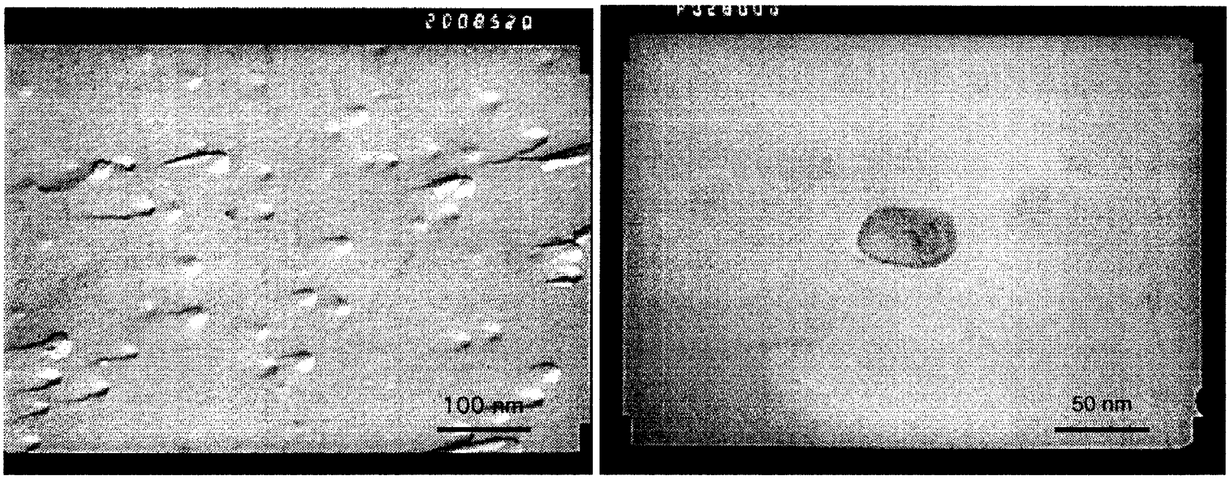


Figure 3. Transmission Electron Microscope (TEM) images of the reaction mixture: (left) platinum mask x 200 000; (right) dried sample x 400 000.

We therefore propose that the DDAB molecules form organized, probably vesicular[43] structures in the organic phase, and that the Ru catalyst resides in the aqueous layer of these vesicles (figure 4). The alcohol substrate and the hydrogen peroxide molecules may reach the reaction site by diffusion. The observed kinetics can be explained in this case by assuming that the chemical reaction is faster than the diffusion of the reactants into the vesicles. This diffusion would depend on the diffusion constants $k_{diff}$ of the reactants, as well as on their concentration, and the overall rate equation would be $v = k_{diff.\,1}[\mathbf{1}]k_{diff.\,H2O2}[H_2O_2]$.[44] As $[H_2O_2]$ remains constant throughout the reaction, the rate equation becomes $v = k_{obs}[\mathbf{1}]$ in which $k_{obs} = k_{diff.\,1}\,k_{diff.\,H2O2}[H_2O_2]$. These rate equations adequately rationalize the reaction's lack of sensitivity towards temperature, stirring rate changes. Also explained is the absence of substituent and kinetic isotope effects.

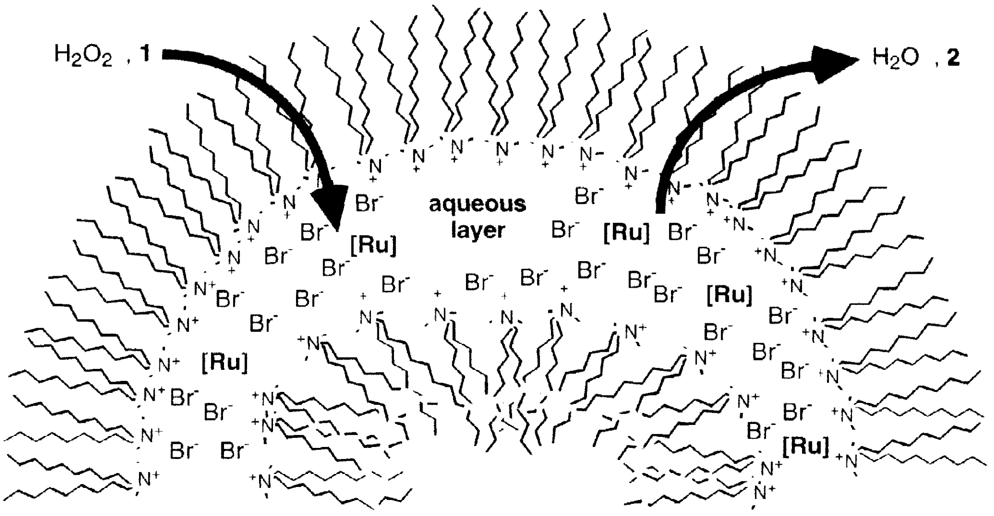


Figure 4. Schematic cross-section of the vesicular structures in the organic phase.

*Effects of the phase transfer catalyst on oxidation rate and ruthenium extraction*

The structure and size of the quaternary ammonium cation are known to be key factors in PTC systems. Lipophilic and asymmetric cations are generally more effective in extracting inorganic catalysts into the organic phase.[45] Accordingly, we have found that $RuCl_3$ extraction increases with ammonium cation lipophilicity, reaching a plateau when cations containing 12 or more carbon atoms are utilized. In the oxidation reaction, water soluble phase transfer agents *e. g.* $Me_4N^+Br^-$ were found to be inactive, while lipophilic ammonium salts with asymmetric cations showed a rate increase compared to symmetric ones. Thus, $k_{obs}$ values were $7.8*10^{-4}$, $1.1*10^{-3}$, $1.1*10^{-3}$, $1.1*10^{-3}$, $1.1*10^{-3}$, $1.3*10^{-3}$, and $1.3*10^{-3}$ $M^{-1}s^{-1}$ when $Pr_4N^+Br^-$, $Bu_4N^+Br^-$, $Hex_4N^+Br^-$, $Oct_4N^+Br^-$, $Non_4N^+Br^-$, $Oct_3MeN^+Cl^-$, and DDAB were employed, respectively (under typical reaction conditions).

When the oxidation was performed in the presence of ammonium salts with different counterions, the order of activity was observed to be $Hex_4N^+Br^-$ > $Hex_4N^+I^-$ > $Hex_4N^+Cl^-$ ($k_{obs}$ = $1.1*10^{-3}$, $1.0*10^{-3}$, and $0.9*10^{-3}$ $M^{-1}s^{-1}$ respectively). Explanation of this phenomena is not straightforward, especially as blank reactions showed that $Br_2$ or $Br^-$ alone did not affect the reactions.[46] Apparently, the formation of vesicular structures in the organic phase requires a counteranion of intermediate size, charge distribution, and hydration number. Following these empirical tests DDAB was selected as the phase transfer agent for this investigation.

*The effects of various catalysts on alcohol oxidation and $H_2O_2$ decomposition*

Various transition metal salts were tested as catalysts (table 1). All of the catalysts tested underwent facile extraction into the organic phase in the presence of 7 equivalents of DDAB. $PdCl_2$ was found to cause the least amount of $H_2O_2$ decomposition, but $RuCl_3$ was found to be the best catalyst for the oxidation reaction despite the fast decomposition of the oxidant.

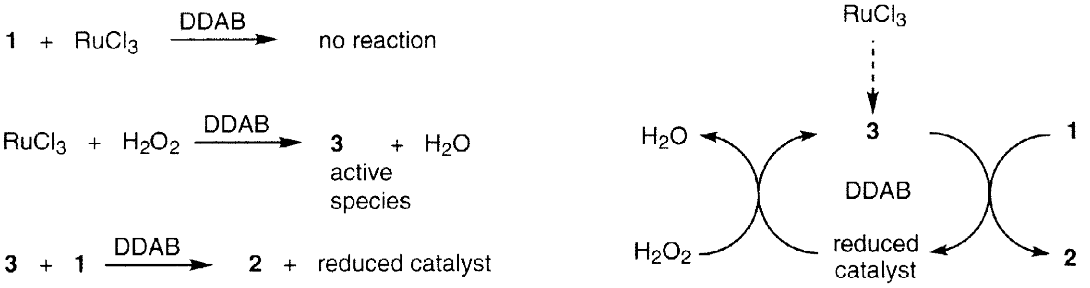
Table 1. Activity of metal salts in the oxidation and $H_2O_2$ decomposition reactions.

| Catalyst | Initial oxidation rate ($M^{-1}min^{-1}*10^{-2}$)[a] | $H_2O_2$ decomposition rate ($mol/min*10^{-2}$)[b] |
|---|---|---|
| $RhCl_3.3H_2O$ | 0.45 | 3.30 |
| $RuCl_3.3H_2O$ | 7.80 | 11.20 |
| $VOCl_2$ | 0.51 | 2.00 |
| $PdCl_2$ | 0.45 | 0.02 |
| $FeCl_3$ | 0.30 | 9.90 |

[a] 41 mmol **1**, 1.2 mmol DDAB, 0.07 mmol metal catalyst, $H_2O_2$ 30% (added continuously at 0.22 ml/min), 90 °C. Product formation was monitored by GC. [b] 10 ml DCE, 1.2 mmol DDAB, 0.07 mmol metal catalyst, 0.7 ml $H_2O_2$ 30% (added in one batch), 25 °C. $H_2O_2$ decomposition was monitored by measuring the amount of $O_2$ liberated.

*The active catalytic species in the oxidation reaction*

Blank reactions performed with a stoichiometric amount of the catalyst precursor $RuCl_3$ but without $H_2O_2$ (1 equivalent of **1**, 1 equivalent of $RuCl_3$, and 15 equivalents of DDAB; 90 °C; 3 h) confirmed that the catalyst precursor itself is inactive (scheme 1). However, when a mixture of 1 equivalent of $RuCl_3$ and 15 equivalents of DDAB was treated with 30% $H_2O_2$, the active species **3** was produced. In this reaction, after all the $H_2O_2$ has either reacted with the catalyst precursor or decomposed, 1 equivalent of **1** was added and a quantitative conversion to **2** was observed. The oxidative efficacy of species **3** was further demonstrated in oxidation of styrene to benzaldehyde (64% yield at 100% conversion), tetralin to tetralone (75% yield at 80% conversion), and aniline to nitrobenzene (60% yield at 80% conversion).



Scheme 1. (left) stoichiometric oxidation; (right) catalytic cycle.

The active catalytic species **3** can therefore be assumed to be an oxygenated Ru moiety with an oxidation number >III. Ru(IV), (V), (VI), (VII), and (VIII) are all known oxidation catalysts,[47] but oxidation states VI-VIII are known to exist in solution only as highly oxygenated ions or molecules,[48] *viz.* $Ru(VIII)O_4$, $[Ru(VII)O_4]^-$, and $[Ru(VI)O_4]^{-2}$, and are reported to be active as oxidants only in basic media.[49,50] Both Ru(IV) and Ru(V) have been shown to catalyze alcohol oxidation.[51-55] In this case, however, IR and UV-vis spectroscopic measurements show that **3** is a Ru(IV) species. UV-vis spectra of the catalyst precursor $RuCl_3$ and of a 15:1 mixture of DDAB:$RuCl_3$ were identical to the literature spectrum of *cis*-$RuCl_3.3H_2O$ ($\lambda_{max}$=396 nm). Addition of $H_2O_2$ resulted in a spectrum similar to that of Ru(IV) ($\lambda_{max}$=290 nm). Similarly, the IR spectrum of **3** showed a typical Ru(IV) peak at 790 $cm^{-1}$ (which did not appear in the spectra of the $RuCl_3$ and DDAB:$RuCl_3$ solutions). This peak disappeared after a stoichiometric amount of **1** was added. Based on the above data, we suggest that **3** is a Ru(IV)=O species.

## CONCLUSION

In contrast with the classic extraction and interfacial PTC mechanisms, the above Ru/$H_2O_2$/DDAB system exhibits an unusual kinetic pattern. This is rationalized on the basis of aggregation of DDAB molecules to form vesicular structures containing the active Ru species. These structures constitute a diffusionary barrier inside the organic phase. Consequently, the complex catalytic transformation appears as a simple pseudo first order reaction. Efficient catalyst recycling renders this oxidation procedure as a "green" alternative to existing oxidation methods.

## EXPERIMENTAL SECTION

*Materials, general methods, and instrumentation.* Unless noted otherwise, chemicals were purchased from Aldrich, Fluka, or Merck, and were used without further purification. **1**-*d* was synthesized according to the literary procedure.[56] Substituted substrates *p*-X-$C_6H_4$-CHOH-$CH_3$ (X = MeO, Me, Br, and $NO_2$) were prepared by $NaBH_4$ reduction of the appropriate acetophenones. GC and GCMS analysis were performed using an HP-5790 gas chromatograph with a 5% diphenyl 95% dimethyl capillary column (25 m/0.31 mm). IR spectra were recorded on an Analect FTIR FX-6200 instrument. UV-vis spectra were recorded on a Cary-17 UV spectrophotometer. $H_2O_2$ decomposition was monitored by measuring the amount of oxygen liberated. Peroxide content in the reaction was monitored by iodometric titration.[57]

*TEM and EDAX measurements.* TEM measurements were conducted on a JEOL 200 CX instrument. Platinum masks of the reaction mixture were prepared by freezing solution samples in liquid nitrogen, breaking the sample at -150 °C and under high vacuum ($10^{-5}$ torr), and coating the fracture with a platinum mask supported on carbon. This "freezed fracture etching" technique preserves the structures in the sample solution, and allows their observation by TEM. EDAX measurements were performed on a LINK 860 series 2 instrument. In this method, a specific site of a dried sample of the reaction is bombarded with an electron beam. The beam excites the atoms of the sample and they emit radiation which enables the determination of their identities.

*Oxidation of 1.* $RuCl_3$ (0.077 mmol, 20 mg), **1** (41 mmol, 5.00 gr), DDAB (1.2 mmol, 1.0 ml of a 50% soln in PhMe) and DCE (solvent, 10 ml) were mixed at 90 °C in a 100 ml reaction flask equipped with a syringe pump for dispensing $H_2O_2$ and an oxygen meter. After a homogeneous solution was obtained (ca. 10 min), 30% aq $H_2O_2$ was added continuously at a rate of 0.22 ml/min. The reaction progress was monitored by GC. After all of the substrate has reacted, the solvent was evaporated *in vacuo* and 15 ml of hexane were added to precipitate the catalytic complex, which could be filtrated and reused. The hexane was evaporated from the colorless filtrate leaving 4.48 gr **2** (92% yield based on **1**). Styrene, tetralin, and aniline were similarly oxidized.

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