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Development and Semicommercial Implementation of an Environmentally Benign, Hydrogen Peroxide Mediated Oxidation of Aliphatic Alcohols

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Abstract:

A process for the oxidation of an aliphatic alcohol (primary alcohol in C12−C15 region, substrate selected on the basis of a customer requirement) was developed and scaled up from laboratory (100 mL and 1 L scale) to bench (CR26 reactor) and to semicommercial scale (1000 litre) for toll manufacturing purposes. This oxidation was performed using hydrogen peroxide and a transition metal catalyst under phase transfer conditions. Although hydrogen peroxide mediated oxidation is a potentially hazardous process, the process was successfully scaled up using additional experimental data (from laboratory and bench scale), simple mathematical modelling, and simulation of the hydrodynamics of the multiphase system. The product acid from a C13 primary alcohol could be obtained at alcohol conversions exceeding 95% in selectivities approaching 100%.

Introduction

The oxidation of primary alcohols with hydrogen peroxide catalysed by transition metal catalysts under phase transfer conditions has been described in the chemical[1,2] and patent[3] literature. To date, however, only laboratory scale success has been claimed although this type of oxidation has been demonstrated to be very efficient (high conversion and selectivity to main product is achieved) and relatively cheap. Consequently, the large scale operation of this type of protocol constitutes a valuable alternative to a chromium(VI) mediated process (the effluent and toxicity issues add to the attractiveness). Additionally, the process employs no materials which are either costly or limited in supply, enabling the process to be implemented rapidly as distinct from processes employing speciality catalysts or oxidants.

The reaction proceeds in a multiphase reaction system under tungsten salt catalysis (sodium tungstate) and phase transfer catalyst (PTC, Aliquat 336 as the feed). The system can, in principle, be described by the following reaction scheme which is illustrated by simple linear aliphatic alcohols:

$$CH_3-(CH_2)_n-CH_2OH + 2H_2O_2 \rightarrow CH_3-(CH_2)_n-COOH + 3H_2O$$

The oxidation is proposed to proceed through addition to a metal peroxide complex as described by Jacobsen[1] (Scheme 1). The large excess of hydrogen peroxide required in the literature procedures is a result of simultaneous decomposition of the peroxide under the required reaction conditions.

$$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$$

Both the alcohol oxidation and hydrogen peroxide decomposition are exothermic and, therefore, can be considered inherently unsafe on large scale applications.

Generally the process consists of the following steps:

(1) Preparation and activation of catalyst and PTC (at pH 1.5)

(2) Oxidation of organic alcohols to organic acids (which proceeds through a quantifiable aldehyde intermediate) by simultaneous addition of alcohol and hydrogen peroxide in semibatch mode with strictly controlled temperature

(3) Phase separation (with or without the added requirement of solvent extraction)

(4) Acid purification

The tungsten salt (Na_2WO_4) required activation prior to the reaction in 15% hydrogen peroxide for a predetermined period of time. Failure to observe this activation period resulted in a period of inertia where buildup of both substrate and hydrogen peroxide resulted in a potentially hazardous situation early in the reaction process. During the activation of the catalyst a phase transfer catalyst (aliquat 336) was present. During the actual oxidation process it was critical to maintain $pH < 4.5$ or no product formation was observed (after catalyst activation at pH 1.5, no additional acidification was necessary).

The laboratory investigation of the multiphase oxidation was relatively simple and safe because of easy temperature control attributable to the relatively large surface area available for heat transfer with respect to the volumes of reagents used. Similarly, the available surface area for condensation of water vapour (with the concomitant cooling effect) was relatively large. Results obtained from the laboratory scale experiments, while encouraging, could only answer basic questions about the process feasibility, catalyst activity and selectivity, and mode of reaction (batch or semibatch). However, information on the process rate, hydrogen peroxide decomposition, etc. was insufficient for a safe process scale-up. The reason was mainly that the hydrodynamics would be different in the multiphase system on scale-up and that it was difficult to sample the different

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(1) Barak G.; Dakka J.; Sasson Y. *J. Org. Chem.* **1988**, *53*, 3553. Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386. Jacobsen, S. E.; Muccigrosso, D. A.; Mares, F. *J. Org. Chem.* **1979**, *44*, 921.

(2) Bortolini O.; Conte V.; Di Furia, F.; Modena G. *J. Org. Chem.* **1986**, *51*, 2661.

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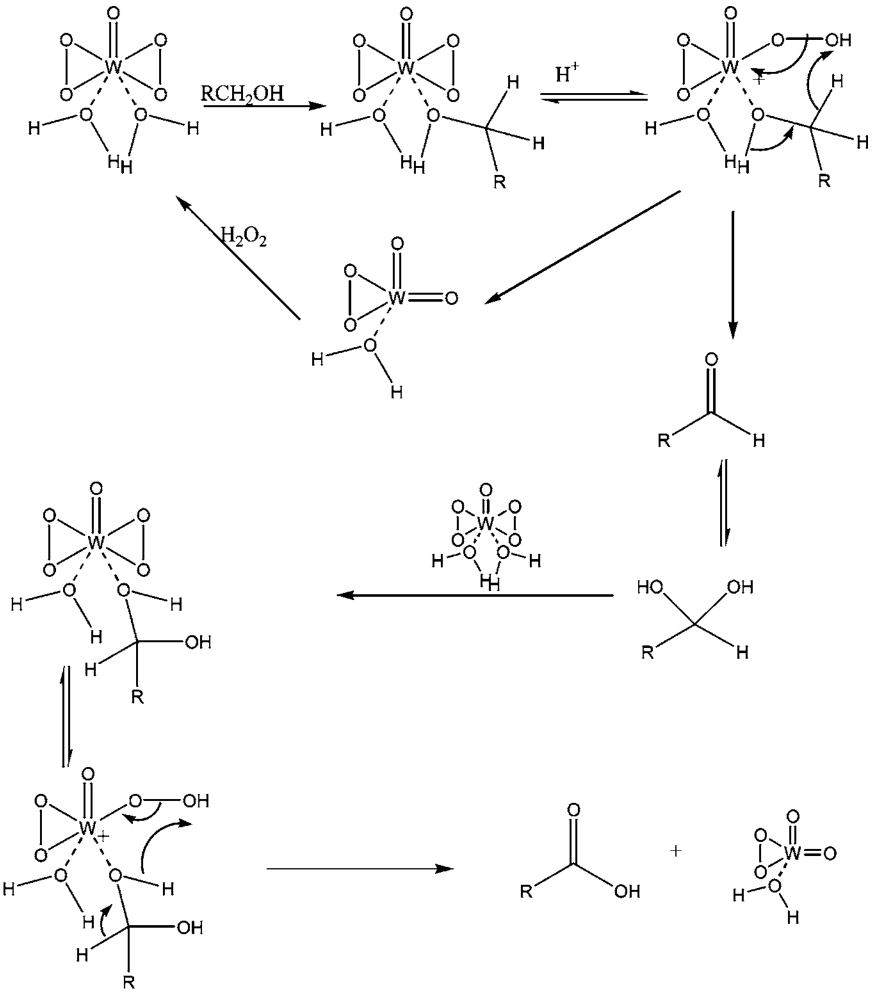
Scheme 1. **Oxidation of primary alcohols to carboxylic acids by tungstate salts**



phases. It was, therefore, very difficult (if not impossible) to measure reaction kinetics and thermodynamics accurately on the laboratory scale. For instance, an attempt to measure the heat of reaction using a calorimeter failed since there was insufficient mixing, i.e., no dispersion of organic phase. The heat of peroxide oxidation, including heat of peroxide decomposition, was estimated from bond energies to be 553 kJ/mol of alcohol. The bench scale experiments were therefore used to quantify the effect of process parameters on the system behaviour and to obtain the necessary data for scale-up.

Hazard Potential of Hydrogen Peroxide Oxidation

The multiphase reaction system for peroxide oxidation consisted of an organic phase (organic alcohol and acid); an aqueous phase (peroxide solution, dissolved sodium tungstate and water formed during the process); aliquat 336; and gas phase (water vapour, oxygen from peroxide decomposition, and nitrogen used for the system protection and vapour phase dilution). The mixing intensity (mass and heat transfer) and mode of operation (batch or semibatch) were important parameters in establishing the degree of safety using this multiphase system.

The main hazard potentials of the peroxide mediated oxidation of an aliphatic alcohol are temperature and pressure runaways. To estimate the hazard potential, the implications of batch operation using different sizes of agitated reactors were evaluated. On the basis of the earlier laboratory studies, it was assumed that activation of the tungsten salt catalyst proceeded in the presence of phase transfer catalyst and 10% H_2O_2 solution at 95 °C. Similarly, in concordance with a laboratory example it was also assumed that the full amounts of alcohol and hydrogen peroxide were loaded into the reactor and that the system was heated to the initiation temperature of 95 °C. The amounts of alcohol and water present in the system and the amount of water which needs to be evaporated in the system to compensate for the heat of reaction at isothermal conditions are illustrated in Table 1.

Table 1. **Masses and volumes for the different reactors used in scale-up**

reactor volume [L]	mass of alcohol [kg]	mass of water present [kg]	mass of water evaporated [kg]
26	10	6.6	12.5
75	20	13.2	25
1000	273	172	325

Hydrogen peroxide mediated oxidation is a fast process and can be complete within a few minutes. The reaction is spontaneous above a certain temperature, and an increase in the temperature would result in an increase in the rate of the highly exothermic hydrogen peroxide decomposition. In terms of heat removal, this fast process is practically adiabatic and the heat of the process can be only absorbed by water evaporation (as heat of vaporisation). The hypothetical pressure, as a result of the water evaporation needed to remove the heat of the reaction at isothermal conditions, would be approximately 450 bar. The potential for a temperature and pressure run-away in this type of process excludes, therefore, batch operation as a feasible safe process.

The only safe mode in which to operate the process would be a semibatch operation during which the substrate and peroxide are added simultaneously at very well controlled flow rates to make the process safer. The rate of addition of the alcohol and peroxide was determined by the following factors:

(1) A reasonable reaction volume in the reactor was required so that sufficient agitation of the multiphase system could take place and so that the foaming could be controlled.

(2) The alcohol addition rate was determined by the rate of water vaporisation to compensate for heat generation, heat capacity of a condensing system and its hydrodynamic conditions, flow rate, and temperature of reflux to control liquid volume in the reactor.

(3) A minimum concentration of hydrogen peroxide is required to maintain catalyst activity (if the concentration drops to low the catalyst is deactivated), and the correct pH domain in the reaction mixture must be maintained to avoid high rates of decomposition of hydrogen peroxide, i.e., less than pH = 2.5.

The experiments carried out on laboratory and bench scale helped to determine the critical process parameters and characteristics for a safe oxidation process. The following critical parameters were identified:

(1) The activity of the catalyst after a certain period (early in the process) was measured by analysing the conversion to the acid. This was done to establish if the reaction was proceeding at the expected rate (determined by the rate of addition of the alcohol and peroxide). Should the conversion of alcohol be below the established minimal level (as calculated), the run would be terminated, by stopping the addition of peroxide, alcohol, and heat, so as to avoid the buildup of large amounts of hydrogen peroxide and alcohol which, in the event of a sudden rise in catalyst activity, could initiate a runaway reaction.

(2) The level of hydrogen peroxide in the reactor must be above a minimum level; depletion of hydrogen peroxide could result in deactivation of the catalyst with subsequent hydrogen peroxide buildup (no peroxide would be consumed); reactivation of the catalyst could then result in a possible temperature and pressure runaway.

(3) The aqueous phase must be continuous, and the organic phase must be dispersed (better liquid−liquid mass transfer, water evaporation from continuous phase, and reduced potential for ester formation). Hydrodynamics is critical for mass transfer and consequent process rate.

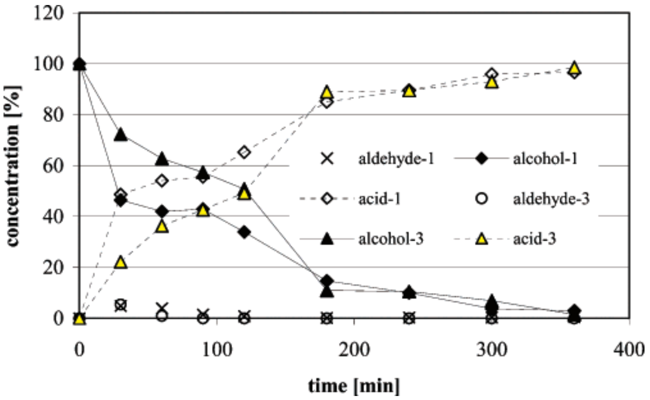


Figure 1. **Experimental concentration profile of alcohol, aldehyde, and acid in CR26 (alcohol addition rate, 5 kg/h; peroxide addition rate, 8 kg/h in batch 1; 6.4 kg/h in batch 3).**

Experimental Results and Design of Safe Process Operation

Scaling up an exothermic process safely is a complex problem and requires quantitative data. A lot of work has been applied to the safe scale-up of liquid−liquid processes with a runaway potential$^{4-7}$ demonstrating that experimental work at different scales cannot be avoided. Suitable experimental data for the hydrogen peroxide oxidation were obtained using a bench scale Büchi glass reactor system with total reactor volume of 45 L (CR26) using a condenser with a heat transfer area of 1 m^2 and a stirring rate of 155 rpm (pitch blade).

The experimental alcohol, aldehyde, and acid concentration profiles are shown in Figure 1. The higher rate of peroxide addition (batch 1) indicated faster oxidation. However, a higher rate of water evaporation was required to maintain the temperature. During this process, water vapour from the reactor entered the reactor condensing system and the condensate was partially returned to the reactor and partially removed from the system. Proper functioning of the condensing system required suitable hydrodynamics which was determined by the linear velocity of vapour in the tubes and pipes. Since the rate of evaporation in the reactor is restricted by the condensing system hydrodynamics, the rate of addition of reactants needed to be restricted in line with the limitations of the condensing system. The concentration profiles indicated that the rate of acid formation is related to the rate of alcohol addition. This fact is better presented in Figure 2, where the rate of formation of acid is linearly related to the rate of addition of alcohol. The data illustrate that the reaction profile is, essentially, reproducible.

The results indicated that after addition of 50 mol of alcohol only approximately 30 mol of acid had formed. Because of the linear dependence of the amount of acid formed and alcohol dosed, one can conclude that the efficiency of acid formation during alcohol dosing was 60% of the addition rate of alcohol. Based on the experimental data, a so-called "Effectiveness Factor (Φ)" was determined.

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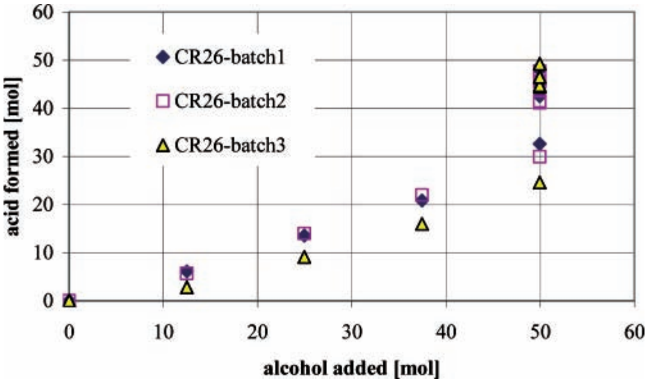

Figure 2. **Acid formation related to alcohol addition.**

The "Effectiveness Factor" can be defined as the amount of acid formed at the time of complete alcohol addition (mol of acid/mol of alcohol). Due to the defined phase boundary, it is probable that part of this effect is the result of the contribution of hemiacetal formation (intermediate aldehyde and starting alcohol) and subsequent oxidation generating esters. Hydrolysis of such species (and subsequent oxidation of the alcohol component) would result in overall retardation of acid formation. This empirical parameter of the process could be used for the process simulation, calculation of the rate of heat generation, and, subsequently, calculation of the amount of water evaporated from the reaction mixture to maintain isothermal conditions. On the basis of the rate of water evaporation and reflux rate, a suitable condensing system can be designed for a process at a certain scale or, as is often the case in custom manufacture, to establish the rate of water evaporation at certain experimental conditions and evaluate if the existing condensing system would be suitable.

Process Description

A multiphase liquid−liquid−gas catalytic system with a phase transfer catalyst is very complex. It is difficult, almost impossible, to determine reaction kinetics and mass transfer characteristics experimentally for this type of process, especially with time and money constraints.[4] The peroxide oxidation reaction in a multiphase system requires, to reduce the risk to acceptable levels, that the rate of the reaction, heat generation, and heat removal to be quantified so that conditions of temperature and pressure runaway can be avoided.

The overall mass and energy balances of the multiphase system can be expressed by the following equations (symbols are explained in List of Symbols):

$$\frac{\mathrm{d}m_\mathrm{r}}{\mathrm{d}\tau} = m_\mathrm{a} + m_\mathrm{p} - m_\mathrm{v} + m_\mathrm{c} \qquad (1)$$

$$\frac{\mathrm{d}(m_\mathrm{r}c_\mathrm{p}T_\mathrm{r})}{\mathrm{d}\tau} = \Phi \mathrm{m}_\mathrm{a}\Delta_\mathrm{R}H + m_\mathrm{a}c_\mathrm{pa}T_\mathrm{a} + m_\mathrm{p}c_\mathrm{pp}T_\mathrm{p} - m_\mathrm{v}(\Delta H_\mathrm{v} + c_\mathrm{pv}T_\mathrm{r}) + m_\mathrm{c}c_\mathrm{pc}T_\mathrm{c} - k_\mathrm{h}A(T_\mathrm{r} - T_\mathrm{j}) - Q_\mathrm{loss} \qquad (2)$$

This simple mathematical model was used to estimate the parametric sensitivity of the system. The main parameters of the process were the following:

(1) rate of heat removal from the reaction mixture, i.e., rate of water evaporation;

(2) "effectiveness factor";

(3) heat of reaction (since this is estimated from the bond energies it is important to know the system sensitivity);

(4) reflux temperature; and

(5) process hydrodynamics since the process is, very probably, governed by mass transfer (it is also important for the process scale-up).

The parametric sensitivity of the system was evaluated for the CR26 reactor. The process simulation showed that the reaction temperature was most sensitive to the rate of water evaporation and the "effectiveness factor", less sensitive to a change of the heat of reaction for the current reaction system, and almost insensitive to reflux temperature. These results indicated that it was very important to have sufficient cooling capacity and proper geometry of the condenser (heat transfer area, tubing size, etc.) ensuring the capability to handle the expected water vapour and condensate flux for the system scale-up since condenser system characteristics usually do not change proportionally to reactor volume.

Simulation of Multiphase Reactor Hydrodynamics and Mass Transfer

The VisiMix package[8] was used to simulate the hydrodynamics and mass transfer in the multiphase reaction system at different scales of stirred tank reactors (from bench scale to production scale).

The substrate and hydrogen peroxide were simultaneously pumped into the reactor, and the ratio of organic to aqueous phase changed during the process. The organic phase was dispersed, and the concentration of organic phase in the aqueous phase strongly influenced the mass transfer area and droplet size distribution in the system.

The VisiMix package was also used to establish basic hydrodynamic characteristics of the CR26 reactor. Based on the multiphase CR26 system's hydrodynamics, mass transfer, and micromixing in droplets and in dispersed phase, the hydrodynamic characteristics in the larger reactors (75 L and in a 1000 L reactor) were calculated. The intensity of mixing was assigned (in the VisiMix package simulation) in such a way that the hydrodynamic characteristics were better and mass transfer characteristics comparable or worse in large scale compared to the bench scale runs (100 rpm in 75 litre and 60 rpm in 1000 litre reactor). Some of the results of simulation are presented in Figure 3.

Results Obtained in Large Scale Reactors

The experimental results from the CR26 reactor and the results of the process simulation were used to choose the experimental conditions for 75 L scale (condenser heat transfer area 2.5 m^2) and 1000 L scale (condenser heat transfer area 4 m^2) reactors. The most important consideration for the process scale-up was safety. Therefore all of the designed process parameters for larger scales were chosen

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(8) *VisiMix 2000*: *Mixing Simulation for Chemical & Process Engineers*; VisiMix Ltd., POB 45170, Jerusalem 91450, Israel, http://www.online.visimix.com.

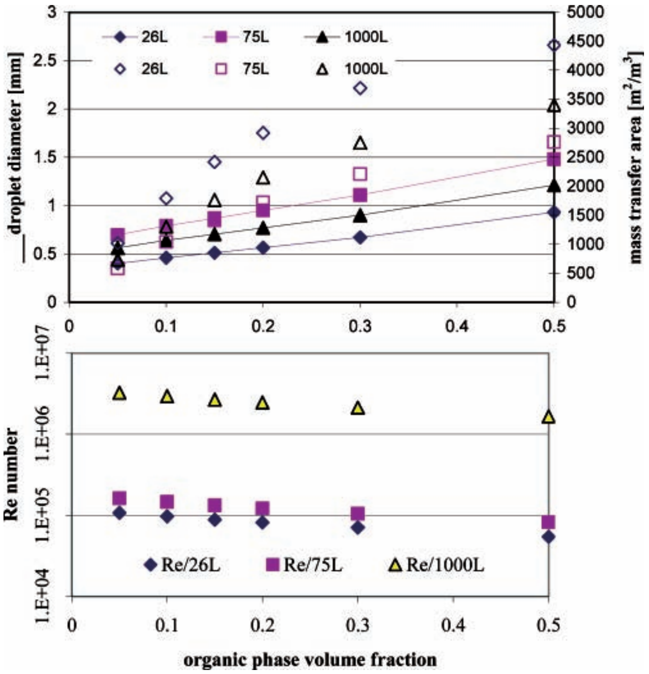

Figure 3. **Some hydrodynamic characteristics of a multiphase system in stirred tank reactors (CR26/155 rpm; 75 L/75 rpm; 1000 L/60 rpm).**

Table 2. **Experimental conditions proposed for large scale reactors**

reactor [L]	rpm	substrate addition [kg/min]	H_2O_2 addition [kg/min]	rate of evaporation [kg/min]
75	100	0.17	0.17	0.12
1000	60	1.4	1.3	1.3

very conservatively to achieve comparable or worse conditions for mass transfer and for better conditions for heat removal from the systems. On this basis the revolutions of stirrers and rates of addition of substrate and peroxide were chosen, and the rate of water evaporation was determined. The proposed conditions are tabulated in Table 2.

Another very important parameter for process safety is hydrogen peroxide concentration in the reaction mixture. The concentration of hydrogen peroxide in the reaction mixture depended on the rate of addition of hydrogen peroxide solution, rates of alcohol oxidation and peroxide decomposition, rate of water evaporation, and reflux. It is important to note that the hydrogen peroxide that was added into the reactor after complete addition of the alcohol was added at a reduced rate (approximately half of original rate). Comparison of predicted and measured hydrogen peroxide concentrations for the 75 L reactor is presented in Figure 4.

Experimental conversions obtained in different reactors are presented in Figure 5.

Comparison of acid formation as proportional to alcohol added for different scales is presented in Figure 6.

Experimental data confirmed that comparable or worse mass transfer characteristics in large scale reactors decreased the value of the "effectiveness factor" from 0.6 in CR26 to approximately 0.5 in 75 and 1000 L reactors. The use of this reduced figure ensured safe and robust operation of the 1000 L reactor at conversions of more than 95% and selectivities close to 100%.

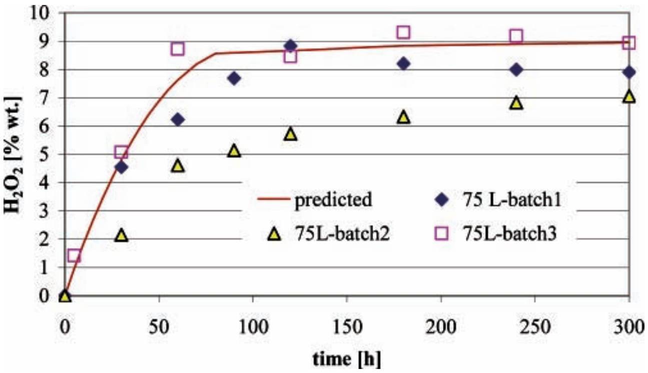

Figure 4. **Concentration of H_2O_2 in reaction mixture in 75 L reactor.**

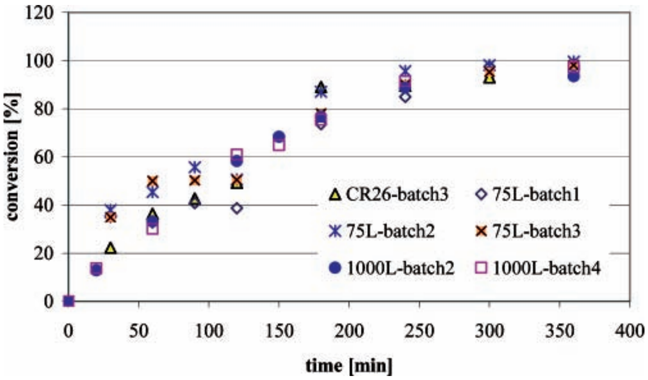

Figure 5. **Experimental conversions obtained in different reactors.**

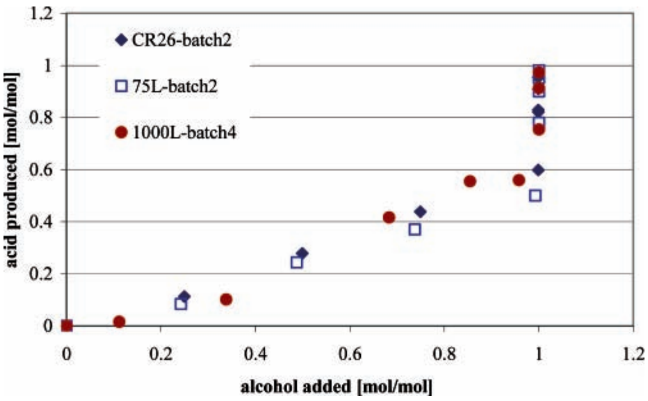

Figure 6. **Comparison of dimensionless rate of acid formation and alcohol addition in different reactors.**

Conclusion

The tungstate catalysed multiphase oxidation of an aliphatic alcohol using hydrogen peroxide and a quaternary ammonium salt phase transfer catalyst was investigated and successfully scaled up to a custom manufacture scale reactor (1000 L).

The laboratory scale investigation did not answer fundamental questions about multiphase reaction kinetics, mass transfer, and thermodynamics. The data from bench scale oxidation in the CR26 stirred tank reactor were used to answer these questions and used as the basis for evaluation of the process effectiveness, performance, and parametric sensitivity. It was found that the most important parameters were a so-called “effectiveness factor” of the process and the rate of water evaporation. These factors set the rate of addition of both hydrogen peroxide and alcohol. The hydrodynamic parameters of the multiphase system were simulated by the VisiMix package.

Both experimental data and results of simulation were used in the process scale-up to a 75 L reactor. Predicted hydrodynamics, the rates of addition of hydrogen peroxide and alcohol, and cooling and condensing requirements were confirmed experimentally on this scale and used to establish safe conditions for scale-up to the 1000 L reactor.

Due to the high boiling product, continuous removal of the product was not considered. Emulsion formation in the biphasic system did not prove problematic.

Designed process parameters for the 1000 L reactor were verified experimentally and applied for manufacture of 2000 kg of final product. Conversions higher than 95% and selectivities close to 100% were achieved.

Experimental Section

Initial Laboratory Procedure. Sodium tungstate dihydrate (11.5 g, 34.8 mmol) was added to a stirred solution of aqueous hydrogen peroxide (35%, 99 mL) and tricaprylmethylammonium hydrogen sulfate (8.0 g, 17.2 mmol) at 25 °C and stirred a further 10 min. The C13 primary alcohol (352 g, 1.76 mol) was added, and the resultant was heated to 96 °C. More hydrogen peroxide solution was added with time at a rate of 99 mL/h for 4 h, while removing water from the reaction through distillation (170 mL distillate collected). At this time approximately 99% of carboxylic acid was detected (GLC analysis). The solution was cooled and washed with water (3 × 100 mL) at which time no residual peroxide was detected in the organic phase.

Procedure at 1000 L. Sodium tungstate dihydrate (7.90 kg) was added to water (220 kg), hydrogen peroxide (35%, 87 kg), aliquat 336 (10.2 kg), and sulfuric acid (2.45 kg) at room temperature, and the resultant was heated to 90 °C. After the solution reached and maintained this temperature for 15 min, C13 primary alcohol addition (81 kg/h) and further hydrogen peroxide addition (35%, 77 kg/h) were initiated and continued for 4 h while conversion of the alcohol was monitored (30 min intervals). After addition of the alcohol was complete (4 h), hydrogen peroxide addition was continued at 45 kg/h for 3 h, at which time conversion to the required acid was greater than 98%. Agitation was ceased, the phases were allowed to separate, and residual hydrogen peroxide was removed from the organic acid by water washing. The phases were separated, and the product acid was collected for distillation.

Acknowledgment

This paper is dedicated to the memory of Vladimir Cukan, who passed away suddenly shortly after the completion of the programme.

LIST OF SYMBOLS

A	heat transfer area of reactor [m^2]
c_{pi}	specific heat capacity of (a) alcohol, (p) peroxide, (v) water vapour, and (c) condensate
ΔH_R	heat of reaction [kJ/kg]
ΔH_v	heat of vaporisation [kJ/kg]
k_h	overall heat transfer coefficient [W/m^2 K]
m_r	mass of reaction mixture [kg]
m_i	mass flow rate of: (a) alcohol, (p) peroxide, (v) water vapour, and (c) condensate (reflux)
Q_{loss}	heat loss [kJ]
T_i	temperature of (a) alcohol, (p) peroxide, (c) condensate, and (co) cooling medium
T_r	reactor temperature
T_c	condensate temperature
T_j	jacket temperature
Φ	effectiveness factor
τ	time [h]

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