

Controlled Multiphase Oxidation for Continuous Production of Fine Chemicals

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Abstract— The feasibility of an integrated continuous biphasic oxidation process was studied, incorporating (i) electrochemical generation of an oxidant, (ii) membrane emulsification and an Oscillatory Flow Reactor (OFR) to facilitate mass-transfer in a biphasic reaction system and (iii) product extraction to enable regeneration of the oxidant. The biphasic, organic solvent-free dihydroxylation of styrene by ammonium peroxydisulfate solutions (including electrochemically generated peroxydisulfate) was investigated as a model reaction, both in batch and in an OFR. Heating of peroxydisulfate in a strongly acidic solution was demonstrated to be essential to generate the active oxidant (Caro's acid). Membrane emulsification allowed mass-transfer limitations to be overcome, reducing the time scale of styrene oxidation from several hours in a conventional stirred tank reactor to less than 50 min in a dispersion cell. The influence of droplet size on overall reaction rate in emulsions was studied in detail using fast image capturing technology. Generation of unstable emulsions was also demonstrated during the oxidation in OFR and product yields >70% were obtained. However, the high-frequency/high-displacement oscillations necessary for generation of fine droplets violated the plug flow regime. Membrane emulsification was successfully integrated with the OFR to perform biphasic oxidations.

Key words: Biphasic Liquid-Liquid Oxidation, Intensification, Flow Chemistry, Oscillatory Flow Reactor, Electrochemistry

I. INTRODUCTION

In recent years, greater awareness of environmental and safety issues has led to increasingly stringent regulatory controls on manufacturing processes, fuelling demand for 'green' chemical technologies that can deliver greater atom, process, and economic efficiency [1]. Currently, chemical technologies adopted in pharmaceutical industries are largely based on multi-purpose batch/semi-batch reactors used in the sequential multi-step synthesis, with each step requiring a further unit of operation for product separation. As a result, the production of fine chemicals and pharmaceuticals suffers from very poor E-factors (mass of waste per mass of product [2], typically 25→100) and high costs. Low space-time yields, insufficient temperature control leading to poor selectivity and difficulties in process control (scale-up in particular) are amongst other disadvantages of batch manufacturing processes. A particular challenge for the pharmaceutical industry is the development of environmentally benign oxidation methods. Oxidation chemistry is currently under-utilised in the pharma manufacturing industry (3.9% of reactions cf. 14% for reductions) due to the difficulties of process implementation at scale, and therefore manufacturing routes avoid oxidation if possible [3].

In order to address these issues, there is growing interest in the development of fully integrated continuous

processes for scalable and efficient multi-phase chemical synthesis [4]. Manufacturing in flow reactors confers multiple benefits of process intensification, scalability and novel opportunities in process design and control [4–11]. Moreover, in a recent survey of key green engineering research areas, 'continuous processing' was identified as the top priority for delivering improved cost-effectivity.

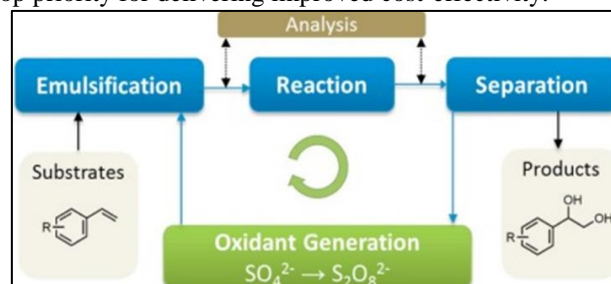


Fig. 1: (A) The basic analysis of manufacturing of fine chemicals by using multiphase continuous oxidation.

The OFR is a tubular reactor with periodically spaced compartments separated by inner structures, such as baffles or smooth periodic constrictions [7–9], to provide mixing via the generation and extinction of eddies created by the interaction of flow oscillations with the constrictions [11–13]. Thus, each compartment of an OFR acts as a Continuous Stirred Tank Reactor (CSTR) and a small steady flow component allows a required residence time to be obtained [2–6]. Owing to excellent axial and radial mixing in each compartment, these reactors provide a better alternative reactor for a wide range of processes such as continuous crystallization, biphasic production of biodiesel and suspension polymerisation [2,3,13].

II. METHODS

A. Chemicals

All reagents were used as received without further purification: deionised water (18 MΩ cm), (NH₄)₂S₂O₈ (98%, Sigma-Aldrich and Acros), H₂SO₄ (96%, Fisher Scientific and VWR), H₂O₂ (30% w/w in H₂O, VWR), KHSO₅·0.5KHSO₄·0.5K₂SO₄ (Merck), sodium dodecyl sulfate (≥99%, Sigma-Aldrich), IGEPAL® CA-720 (Sigma-Aldrich), styrene (≥99%, Sigma-Aldrich and Acros), 1-Phenyl-1,2-ethanediol (97%, Sigma-Aldrich and Merck), (NH₄)₂SO₄ (≥99%, Sigma-Aldrich), ethyl acetate (99% Acros Organics), meso-tetraphenyl porphyrin (≥99%, Sigma-Aldrich), isopropanol (≥99.7%, Sigma-Aldrich).

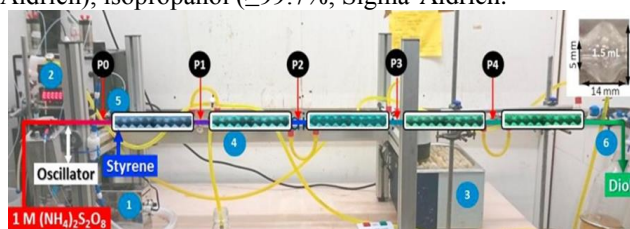


Fig. 2: Photo of the OFR rig with component scheme overlay

B. Batch oxidations of styrene

A solution of 1 M or 0.4 M $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (50 mol) in 2 M H_2SO_4 (50 mL) was pre-heated at 50 °C for 16 h in a 250 mL 3-neck round-bottomed flask (80 mm diameter). Potassium peroxomonosulfate triple salt (a stabilized salt form of Caro's acid, $\text{KHSO}_5 \cdot 0.5\text{KHSO}_4 \cdot 0.5\text{K}_2\text{SO}_4$) and H_2O_2 were used directly without thermal pre-treatment. After the pre-treatment, the oxidant solution was allowed to cool until the aluminium heating mantle stabilized at 50 °C, before styrene (20 mol) was added and the vessel stirred at 600 rpm by a PTFE half-moon stirrer blade (52 mm diameter, impeller $\text{Re} = 27,040$). The mantle temperature was maintained at 50 °C for up to 6 h during which time the reaction progress was measured by HPLC analysis of samples taken periodically.

C. Oxidation of Styrene in Dispersion Cell Reactor

Oxidation of styrene was carried out in a dispersion cell (Micropore Ltd) designed for low energy controllable generation of emulsions (see Fig. 1) [1,4]. The dispersion cell consists of two cylindrical compartments, a small 4 mL compartment at the bottom of the cell for the dispersed phase and a large glass compartment of 3.8 cm internal diameter (150 mL) at the top for the continuous phase. The two compartments are separated by a flat micro-sieve stainless steel membrane (1) with a circular area of 5 μm pores (total area of the porous ring is 1.85 cm^2 and surface porosity is 0.19%). The compartment at the bottom of the cell is equipped with the inlet port for injection of the dispersed phase into a continuous phase through the membrane. Above the membrane, there is a double-bladed paddle stirrer (blade diameter is 3 cm) equipped with 24 V DC motor (2) which produces shear stress at the surface of the membrane for droplet detachment during rotation. Thus, droplet size for a particular system can be controlled by the injection rate of the dispersed phase, rotation speed and pore diameter of the membrane.

D. Oxidations of styrene in OFR

Continuous oxidation of styrene was carried out in the OFR Rig (Fig. 2) consisting of a flow oscillator (1) (custom-built bellows pump with the flow oscillations range of 1–10 Hz and displacement of 0–3 mL, Williamson Manufacturing Company) and a set of 5 consecutively connected jacketed tubular glass flow reactors (4). Each tube has a volume of 27 mL and contains 16 periodically spaced bubble-shaped compartments with smooth periodic constrictions (bubble length is 14 mm, the maximum bubble diameter is 15 mm, constriction between bubbles diameter is 5 mm, and the volume is 1.5 mL, see the inset in Fig. 2). The total length and volume of the reactor rig are 152 cm and 135 mL correspondingly. The reactor is equipped with sample ports (P0-P4) situated along the reactor between the tubular sections. Dispersed and continuous phases (styrene and oxidant) were supplied to the reactor by a VICI pump (2). Styrene was continuously pumped into the reactor via a PTFE capillary (1 mm ID) inserted into the first bubble-shaped segment of the OFR via a custom made T-connection attached to the inlet of the reactor (5) and product was collected from the outlet (6). The rig was thermostated at 50 °C during all the oxidation tests using a recirculating heating bath (3).

E. Cross-flow membrane emulsification module

A cross-flow membrane emulsification module was provided by Micropore (see Fig. 3). The module consists of a stainless steel tubular case (1) with the inlet for the dispersed phase (styrene) (2), two compression fittings with ferrules and nuts (3) and two stainless steel tubular segments (4) with grooves and O-rings (5) for holding a Shirasu Porous Glass (SPG) tubular membrane (6) ($L = 10$ cm, $\text{ID} = 8$ mm, wall thickness of 1 mm, average pore size of 10 μm , SPG Technology). The membrane assembly was situated vertically, with an inlet for the continuous phase (7) connected to the outlet tube of the bellows flow oscillator and the outlet of the membrane emulsification module (8) connected to the OFR by a PTFE elbow tubular connection

The solution was then pumped using a VICI pump with the superimposed oscillations of flow through the inner space of the SPG membrane emulsification module. Pure styrene was pumped through the membrane by the VICI pump.

F. Continuous Extraction of the Diol

Continuous extraction of the diol product was carried out in a smaller volume OFR at 20 °C ($\text{VR} = 12$ mL). A solution mimicking the composition of the reaction mixture after the completion of the oxidation (0.3 M of 1-phenyl-1,2-ethanediol, 2 M H_2SO_4 and 2 M $(\text{NH}_4)_2\text{SO}_4$) was pumped through the OFR at different flow rates using the VICI pump. At the same time, ethyl acetate was pumped to the inlet of the OFR (see and Fig. 4 for more details). The aqueous phase flow was oscillated at a frequency of 5 Hz with 1.2 mL displacement using a custom-built bellows pump (Williamson Manufacturing Company). The amount of the diol extracted from the aqueous phase was measured by HPLC.

III. RESULTS AND DISCUSSION

A. Oxidation of Styrene in a Stirred Tank Batch Reactor

During the early development of this reaction in a stirred tank reactor, an induction period was observed in the conversion of styrene to its diol (fig. 3). The reaction of styrene with freshly prepared 1 M solutions of ammonium peroxodisulfate proceeded slowly over the first 30 min before the rate of diol formation increased and a maximum conversion (ca. 80%) was achieved after 6 h. Strongly acidic conditions were found to be necessary for the effective oxidation of styrene by peroxodisulfate. Under pH neutral conditions the oxidation was extremely slow and produced multiple by-products. It was also found that higher reaction temperatures (70–90 °C) accelerated the oxidation of styrene by acidic solutions of peroxodisulfate but at the expense of product yield and purity which were both reduced. In order to inhibit the undesired side reactions, all further oxidations were performed at 50 °C. It was subsequently found that preheating the acidic ammonium peroxodisulfate solution (50 °C for 16 h) accelerated the rate of styrene dihydroxylation, eliminating the induction period and reducing the reaction time to <2 h (fig. 3). The preheated peroxodisulfate solution oxidised styrene at a similar rate as solutions of the potassium peroxomonosulfate triple salt, a commonly used oxidant in organic synthesis (fig 3). It has been reported that acidic

solutions of peroxodisulfate undergo thermal decomposition to form peroxomonosulfate [7,8]. The observed induction period when using peroxodisulfate as the oxidant, and the improved reactivity of preheated peroxodisulfate solutions suggested that the dihydroxylation of styrene by peroxodisulfate actually proceeds via the generation of a peroxomonosulfate species as the oxidising agent. For the purposes of this study, a pre-treatment regime of 16 h at 50 °C was used to activate the peroxodisulfate solutions and ensure that the dihydroxylation of styrene was not rate limited by the in situ generation of peroxomonosulfate. A detailed analysis of the underlying reaction processes in the dihydroxylation of styrenes by peroxodisulfate is the subject of ongoing research and will be reported in due course.

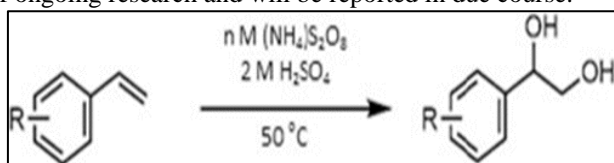


Fig. 3: The dihydroxylation of styrene by ammonium peroxodisulfate

For comparison, the oxidation was also performed using a solution of peroxodisulfate (0.4 M) generated by an electrochemical cell [13] (fig.3). In this case, the electrochemically generated peroxodisulfate (non-activated) appeared to be as reactive as the commercially procured peroxodisulfate of the same concentration (after it was activated at 50 °C for 16 h). It has previously been reported that electrochemically generated peroxodisulfate solutions were effective oxidants in organic transformations [9].

Assuming the reaction occurs at the interface, it was postulated that it should be possible to accelerate the reaction by performing the oxidation in micron-size emulsions, capitalising on their large interfacial area. For example, in the case of biphasic catalytic epoxidation of sunflower seed oil by hydrogen peroxide, no significant mass-transfer limitations were observed for average droplet sizes less than 15 µm [3,1]. To test this approach, the oxidation of styrene was carried out using energy efficient membrane emulsification in a dispersion cell (Fig. 1) and the result can be seen in (fig. 3). As expected, the efficient dispersion of styrene led to a nearly twofold increase in the initial oxidation rates (from $8 \times 10^{-5} \text{ M s}^{-1}$ in stirred tank to $1.4 \times 10^{-4} \text{ M s}^{-1}$ in the dispersion cell).

B. Oxidation of Styrene in Dispersion Cell

Following the promising results of the application of membrane emulsification to biphasic oxidations, a more detailed study of styrene oxidation was performed in a dispersion cell and the results can be seen in. At a rotation speed of 555 rpm, 7 µm droplets of styrene were generated (images of droplet size distributions measured by ViPA are shown in Fig. 3a). This average droplet size is considerably smaller than the 49 µm droplets predicted for this rotation speed and pore diameter by force balance model developed for emulsification in a dispersion cell [6,7]. The discrepancy could be due to the effect of multiple dripping from a single pore leading to the formation of much smaller droplets. Fast oxidation during the injection time (18.3 min) can also lead to the decreased droplet sizes as the first samples were taken for the analysis after styrene injection had completed, when

nearly 20% of it had already been oxidized to the diol and dissolved in the aqueous phase. Additionally, rapid coalescence of the unstable emulsion into two phases was observed after the injection, which could lead to the statistics missing large droplets. The addition of a small amount of sodium dodecyl sulfate (below critical micelle concentration) stabilized the droplets leading to a faster overall reaction rate during styrene injection as can be seen in the case of 555 rpm (Fig. 4). It should be noted here that the diol itself also has surfactant properties. According to our measurements, if half of the styrene is oxidized, the interfacial tension in styrene-peroxodisulfate/sulfuric acid system decreases from 27.7 to 14.2 mN m⁻¹ at 50 °C due to the formation of the diol. Still, rapid coalescence at this rotation speed led to the formation of a separate layer of the organic phase after the injection of styrene. The corresponding decrease of the interfacial area resulted in a significant reduction of the overall reaction rate and maximum conversion of styrene to the diol did not exceed 60% after two hours of oxidation as can be seen in (Fig 4) It is worth mentioning that it was not possible to measure the droplet size distributions at 218 rpm due to the fast coalescence of the droplets during styrene injection, and the dramatically decreased interfacial area resulted in a very low reaction conversion.

C. Oxidation of Styrene in OFR

1) Oxidation at Slow Flow Rates

The model biphasic reaction, developed in the dispersion cell reactor with membrane emulsification, was then transferred into a continuous OFR (Fig. 2). In order to generate unstable emulsions in this assembly, it was necessary to determine the optimal operational regimes for the reactor, which can provide enough energy for the efficient breakage of the organic phase to produce an unstable fine emulsion and to prevent its coalescence until the completion of the reaction. Following the results obtained in batch and dispersion cell tests, a timescale of two hours was initially selected for the reaction ($t_{\Sigma} = 119.8 \text{ min}$,) After preliminary tests of different oscillatory conditions, a frequency of 8 Hz and displacements of 1.7 or 0.8 mL were selected to generate adequate flow oscillations for the effective breakage of the droplets inside the OFR; displacements <0.8 mL at this frequency were not enough for the efficient breakage of bulk styrene phase into small droplets, and segregation of two phases was observed. Also, oscillatory frequencies <5 Hz were insufficient to maintain fine emulsions inside the OFR.

OFRs are fully characterised by net flow and oscillatory Reynolds numbers, Re_n and Re_0 , describing the intensity of mixing applied to the reactor, and Strouhal number measuring the effective eddy propagation inside the compartments [12,13]. According to the literature, two different regimes of operation exist for baffled reactors. In the region of “soft” mixing, where $50 < Re_0 < 500$ (upper boundary depends on dimensions of reactor and type of baffles) a reasonably good approximation to the plug flow regime is normally observed [3,5,8]. The ratios $\psi = Re_n/Re_0$ are in the range between $2 < \psi < 12$ for this regime [9]. In the case of $Re_0 > 5000$, a fully turbulent regime exists, corresponding to the mixed flow and the reactor is approximated by a single CSTR [15,12]. In the intermediate region, the flow is not fully mixed, representing a transition

between plug flow and CSTR regimes. High St numbers ($St > 0.2$) indicate insufficient eddy generation to effectively mix the compartment, whilst $St < 0.13$ indicate intense eddy formation and propagation into the neighbouring compartments [10]. It is worth mentioning that these ranges were only confirmed for monophasic flows and optimal oscillatory conditions will depend not only on the internal geometry of the reactor but also on the physico-chemical properties of the liquid-liquid dispersion. In our case, Re_0 of 5231 and 2615 were calculated for 1.7 or 0.8 mL displacements at 8 Hz and Reynolds numbers ratios, ψ were found to be about 1979 and 989. These numbers indicate that there is a high degree of back-mixing in the OFR and that the operating regime is far from the acceptable approximation to plug flow [5,3]. The non-plug flow operating regime was further confirmed by RTD analysis (see fig. 4). St numbers of 0.12 and 0.23 evidence that there are efficient eddy generation and propagation into the adjacent cavities [2].

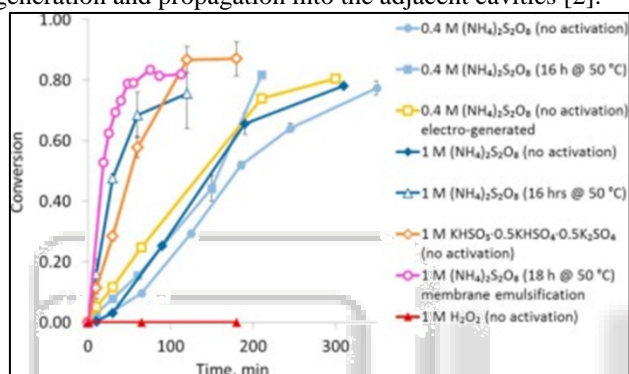


Fig. 4: Effect of oxidant type, its concentration and pre-treatment methods (shown in brackets) on the rate of styrene oxidation carried out in a stirred tank reactor at 50 °C.

Oxidation in the dispersion cell reactor using membrane emulsification is shown for comparison

2) Oxidation at Fast Flow Rates

In order to investigate the biphasic mixing and limitations of our OFR in greater detail, the dihydroxylation of styrene was performed at a shorter total space residence time of 20.8 min, corresponding to that of a single tubular reactor segment at slow flow rates. Three sets of oscillating conditions were studied: 8 Hz/1.7 or 0.8 mL and 5 Hz/1 mL. In the first two cases the corresponding Re_0 s were left unchanged (5231 and 2615) but ψ were decreased to 394 and 197 respectively. These numbers indicate that the flow regime is still far from the plug flow [15,12]. For the latter case, the values are in middle of the transitional region ($Re_0 = 1923$ and $\psi = 145$) and $St = 0.2$ indicates good mixing inside the cavities. However, the performance of OFR cannot be described as pure CSTR which is further confirmed by the analysis of RTD.

3) Oxidation with the Integrated Cross-Flow Membrane Emulsification Module

The other way to improve the performance of the system is to continuously generate the emulsion from the reaction mixture in a separate device (e.g. dispersion cell, cross-flow or azimuthally oscillating membrane emulsifier [11,44,6]) and pump it to the OFR at the same time. In this study, a cross-flow membrane module with the installed SPG tubular membrane (see Section 2.5 and Fig. 3) was integrated with

the OFR and tested. Preliminary tests of the water-styrene system with added surfactant allowed a high degree of plug flow to be obtained at 5 Hz/0.4 mL and total space residence time of 20.8 min (see Fig. 4). These oscillatory conditions correspond to St number of 0.44 indicating moderate mixing inside the cavities and Re_0 numbers from the transitional region ($Re_0 = 865$ and $\psi = 65$). Best fittings of the tanks-in-series model to the experimental results were obtained at $N = 4$ for a single tubular segment and $N = 19$ for the whole reactor system. The latter number indicates a plug flow operation regime which is established at residence times longer than 14 min.

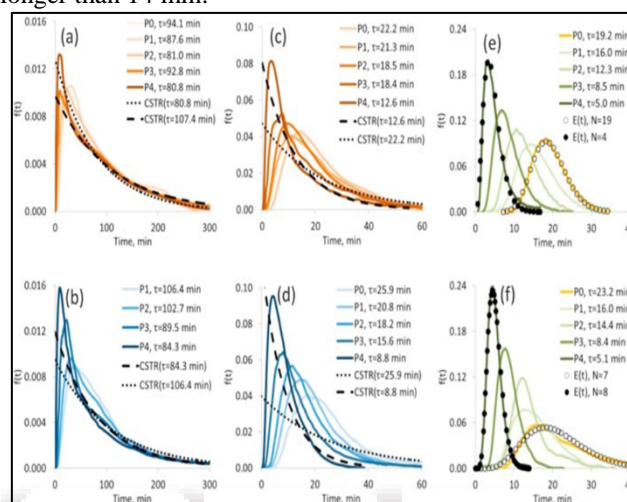


Fig. 5: Residence time distributions in OFR (a–e) and in OFR integrated with the cross-flow membrane module (e, f) for a water-styrene system with Igepal 720 surfactant (37.5 mg L^{-1}) measured at 50 °C by monitoring the response at the outlet of the OFR from the fluorescent tracer injected into P0–P4 ports. Oscillation frequencies are 8 Hz (a–d), 5 Hz (e), 10 Hz (f) and displacements are 1.4 mL (a, c), 0.8 mL (b, d), 0.4 mL (e) and 0.3 mL (f). Flow rates of water are $1.244 \text{ mL min}^{-1}$ (a, b) and $6.220 \text{ mL min}^{-1}$ (c–f); flow rates of styrene are $0.051 \text{ mL min}^{-1}$ (a, b) and $0.255 \text{ mL min}^{-1}$ (c–f). Residence times were calculated as first central moments, $\tau = \int t \cdot f(t) dt$, dotted and dashed lines denote RTD in CSTR for the residence times corresponding to P0 and P4.

IV. CONCLUSIONS

In this work, the feasibility of a continuous biphasic oxidation process has been demonstrated. It was shown that electrochemically generated peroxydisulfate is as effective as the commercially available equivalent oxidant. Significant benefits in using membrane emulsification in biphasic oxidations were demonstrated. Using a dispersion cell, mass-transfer limitations can be overcome, reducing the time scale of the reaction from several hours to less than 50 min. Subsequently, it was also shown that OFRs with smooth periodic constrictions can also facilitate the biphasic oxidation of styrene by the formation of unstable emulsions with a large interfacial area. Maximum conversions of styrene to the diol, of ca. 75% could be achieved in the OFR, which is comparable to the reaction performance in stirred batch reactors. An advantage of the OFR system is that it allows continuous operation with the productivity of ca.

0.5 mol day⁻¹ and it can facilitate biphasic oxidation processes across a range of scales. RTD analysis showed that it was not possible to achieve plug flow regime using the OFR assembly, even at fast flow rates and smaller displacements/frequencies. Efficient mixing provided by high-frequency and large displacement volume oscillations is necessary for the formation of the unstable emulsions inside the OFR at the expense of plug flow regime.

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