

## PTFE-Membrane Flow Reactor for Aerobic Oxidation Reactions and Its Application to Alcohol Oxidation

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**ABSTRACT:** A “tube-in-shell” membrane flow reactor has been developed for aerobic oxidation reactions that permits continuous delivery of O<sub>2</sub> to a liquid-phase reaction along the entire length of the flow path. The reactor uses inexpensive O<sub>2</sub>-permeable PTFE (“Teflon”) tubing that is compatible with elevated pressures and temperatures and avoids hazardous mixtures of organic vapor and oxygen. Several polymeric materials were tested, and PTFE exhibits a useful combination of low cost, chemical stability and gas diffusion properties. Reactor performance is demonstrated in the aerobic oxidation of several alcohols with homogeneous Cu/TEMPO and Cu/ABNO catalysts (TEMPO = 2,2,6,6-tetramethyl-1-piperidiny-N-oxyl and ABNO = 9-azabicyclo[3.3.1]nonane N-oxyl). Kinetic studies demonstrate regimes where the overall rate is controlled by the kinetics of the reaction or the transport of oxygen through the tube wall. Near-quantitative product yields are achieved with residence times as low as 1 min. A parallel, multitube reactor enables higher throughput, while retaining good performance. Finally, the reactor is demonstrated with a heterogeneous Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> catalyst packed in the tubing.

## ■ INTRODUCTION

Significant advances have been made recently in the development of aerobic oxidation reactions that could be applied to pharmaceutical and fine chemical targets.<sup>1</sup> These reactions reduce waste and offer other advantages over reactions that employ traditional stoichiometric oxidants.<sup>2</sup> Large-scale applications of aerobic oxidation in the pharmaceutical and fine chemical industries raise safety concerns associated with the combination of flammable organic solvents and oxygen gas.<sup>3,4</sup> In 2010, we reported a continuous-flow tube reactor developed in collaboration with Eli Lilly, which used a dilute oxygen gas source (8% O<sub>2</sub> in N<sub>2</sub>) to avoid flammable oxygen/organic vapor mixtures during the reaction.<sup>5</sup> The reactor was originally demonstrated with homogeneous Pd-catalysts for aerobic alcohol oxidation, and it was later applied to homogeneous Cu/TEMPO-catalyzed aerobic alcohol oxidations.<sup>6</sup> Subsequently, a number of other flow-based methods and (micro)-reactors that enable safe use of O<sub>2</sub> in liquid-phase aerobic oxidation reactions have been reported by other groups.<sup>7,8</sup>

Membrane reactors present an intriguing alternative to slug-flow, bubble-flow and related continuous processes in which the gas and liquid flow together through the reactor.<sup>8–10</sup> In these reactors, a polymeric material provides a semipermeable barrier that permits passage of O<sub>2</sub> from the gas phase into the liquid-phase reaction on the other side of the membrane. Park and Kim used a sheet of poly(dimethylsiloxane) (PDMS) to supply oxygen to liquid-phase Pd-catalyzed oxidative Heck reactions in a dual-channel microreactor.<sup>8a</sup> Ley and co-workers have published a number of applications of Teflon AF-2400, a highly gas-permeable specialty polymer, in a tube-in-tube configuration to deliver O<sub>3</sub>, O<sub>2</sub> and other gases into the liquid-phase reaction solutions.<sup>11</sup> Additional aerobic applications of AF-2400 tube-in-tube reactors have been developed by other groups. For example, Buehler and co-workers used an AF-2400 reactor to deliver O<sub>2</sub> to a two-phase reaction for the biocatalytic production of catechols.<sup>8b</sup> And, the groups of

Kirschning and Gavrilidis used AF-2400 reactors in applications of nanoparticle Au and Au–Pd catalysts for aerobic alcohol oxidation.<sup>8c,d</sup>

While the highly gas-permeable AF-2400 material has attracted attention for use in aerobic oxidations, it presents several potential drawbacks. The limited temperature rating of the polymer means that the membrane is often used only to saturate the liquid phase with dissolved gas before conducting the reaction downstream at higher temperatures in metal tubing. Limited solubility of oxygen (or other gases) in the liquid may require that additional ambient-temperature AF-2400 gas-transfer segments be incorporated between heated reaction zones to ensure sufficient oxygen is available to complete the reaction.<sup>11b</sup> A recent quantitative model by Yang and Jensen highlighted scaling limitations associated with AF-2400 tube-in-tube reactors, particularly when the membrane is used only to presaturate the liquid-phase solution.<sup>12</sup> There is also an economic constraint, as the quoted price for Teflon AF-2400 (\$25,000/kg) is more than 3 orders of magnitude higher than the cost of more common fluoropolymers, such as poly(tetrafluoroethylene) (PTFE) or poly(ethene-*co*-tetrafluoroethene) (Tefzel).

In light of the issues just noted, we elected to explore other polymeric materials as oxygen-permeable membranes for aerobic oxidation reactions. The polymeric materials considered here cost only \$2–10/kg and are readily available in much larger quantities and a wider range of sizes than Teflon AF-2400. Gas–liquid cofeed slug-flow reactors constructed with PTFE were recently shown to be effective for the aerobic oxidation of alcohols using recently reported homogeneous Cu/TEMPO and Cu/ABNO catalyst systems<sup>6,13</sup> (TEMPO = 2,2,6,6-tetramethyl-1-piperidiny-N-oxyl and ABNO = 9-

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azabicyclo[3.3.1]nonane *N*-oxyl). The PTFE tubing was considered to be an impermeable, nonreactive alternative to stainless steel reactor tubing that avoided deleterious interactions between the Cu catalyst system and the steel tubing. Here, we show that PTFE has sufficient oxygen permeability to be used as a membrane in a tube-in-shell reactor that exhibits superior performance relative to the previously reported slug-flow tube reactor.<sup>6</sup> This reactor is also shown to be compatible with a heterogeneous Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> catalyst for aerobic alcohol oxidation,<sup>14</sup> resulting in high product yield and only moderate pressure drop. These results highlight the utility of abundant, low-cost polymeric materials as gas-permeable membranes for continuous-flow reactions that employ gaseous reagents.

## RESULTS AND DISCUSSION

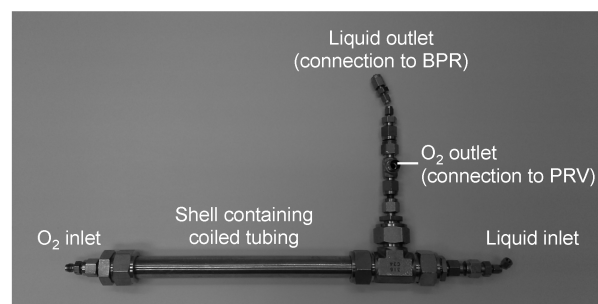
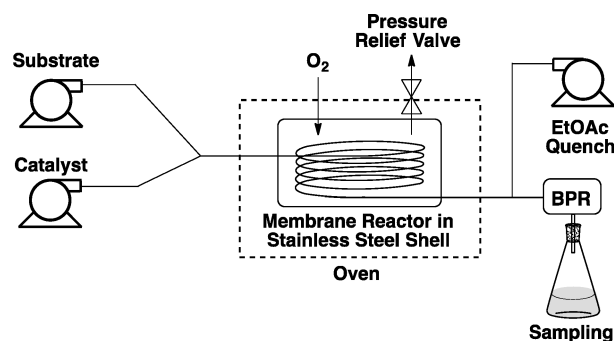
### Development and Testing of Membrane Reactor.

We recently reported a Cu/TEMPO catalyst system for aerobic alcohol oxidation<sup>13a,b</sup> that consists of the following components: 5 mol % [Cu(CH<sub>3</sub>CN)<sub>4</sub>]OTf (CuOTf), 5 mol % 2,2'-bipyridine (bpy), 5 mol % TEMPO, and 10 mol % *N*-methyl imidazole (NMI). The kinetics of catalytic alcohol oxidation with this system have been extensively studied under batch reaction conditions,<sup>15</sup> and the oxidation of benzyl alcohol exhibits a first-order dependence on oxygen pressure and copper catalyst concentration, and a zero-order dependence on the alcohol concentration. The significant amount of kinetic data available for this system made it well suited for probing the operating capabilities of the membrane reactor.

Preliminary reactions were conducted in Tefzel tubing with the Cu/TEMPO catalyst under static conditions to determine if oxygen permeability was sufficient to support the aerobic oxidation reaction, similar to the approach used previously to test the permeability of AF-2400 tubing to ozone.<sup>11a</sup> A narrow-diameter piece of Tefzel tubing (0.01" i.d., 0.0625" o.d.) at ambient temperature was charged with a solution of benzyl alcohol (0.2 M in acetonitrile) and the catalyst. Both ends of the tubing were capped, and the tubing was placed in a sealed round-bottom flask continuously purged with a stream of O<sub>2</sub>. A 43% yield of product was observed after 4 h and a >99% yield after 24 h. Use of Tefzel tubing with a larger inner diameter (0.03" i.d.) led to lower yields: 31% after 4 h and 85% after 24 h. This simple test demonstrated the ability of oxygen to permeate the wall of the polymeric tubing at a rate sufficient to support the catalytic reaction, but it also showed the strong effect of the geometric parameters of the tubing on the oxygen transport rate.

A membrane reactor configuration suitable for use in flow was then devised, as shown in Figure 1. A polymer tube, different options of which are listed in Table 1, was coiled into a 1/2" stainless steel shell and sealed with Swagelok fittings. The catalyst and substrate solutions were supplied by separate pumps and mixed just prior to entering the reactor. As the tubing exited the pressurized steel shell, the reaction was quenched with ethyl acetate. Samples were collected downstream from a liquid back pressure regulator (BPR).

Several considerations of transport in these long, narrow tubes suggest that the behavior in the reactor may be treated as ideal plug flow. Radial diffusion across the streamlines is rapid relative to flow down the tube: the radial diffusion time constants of 5–15 s are much smaller than overall residence times of 1–40 min. So, the conditions of the Taylor dispersion<sup>17</sup> apply and transverse variations of solutes are



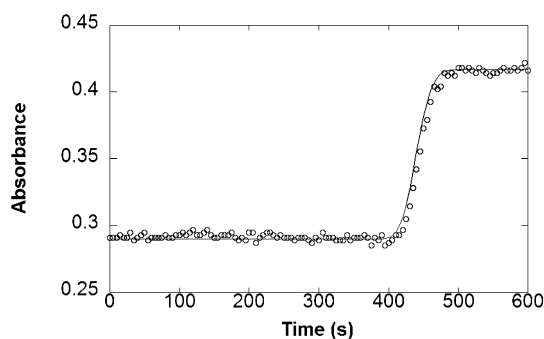
**Figure 1.** Diagram of the tube-in-shell flow reactor and a photograph of the 1/2"-diameter stainless steel shell and Swagelok fittings for gas and liquid inlets/outlets and attachments to the back pressure regulator (BPR) and pressure relief valve (PRV).

**Table 1. Tubing Compositions, Properties, and Designated Names**

Tubing Name	Polymer Material <sup>a</sup>	Oxygen Permeability (Barrer) <sup>b</sup>	Cost per Foot (\$/ft)	Outer Diameter (10 <sup>-2</sup> in) <sup>c</sup>	Inner Diameter (10 <sup>-2</sup> in) <sup>c</sup>
Tef <sub>SM</sub>	PTFE	4.3	1.39	6.25	1
Tef <sub>M</sub>	PTFE	4.3	1.12	6.25	3
Tef <sub>LG</sub>	PTFE	4.3	1.64	12.5	6.3
TefPFA	PFA	5.3	3.22	6.25	1
Tefzel	ETFE	0.6	1.94	6.25	1
PE	Polyethylene	0.40	0.14	12.5	6.2
PI	Polyimide	1.5	9.04	6.15	5.35

<sup>a</sup>Abbreviations: PTFE = poly(tetrafluoroethylene), PFA = perfluoroalkoxy, ETFE = poly(ethene-co-tetrafluoroethene). <sup>b</sup>Standard literature values, from ref 16. <sup>c</sup>Dimensions in units specified by the vendors (see Experimental Section for details).

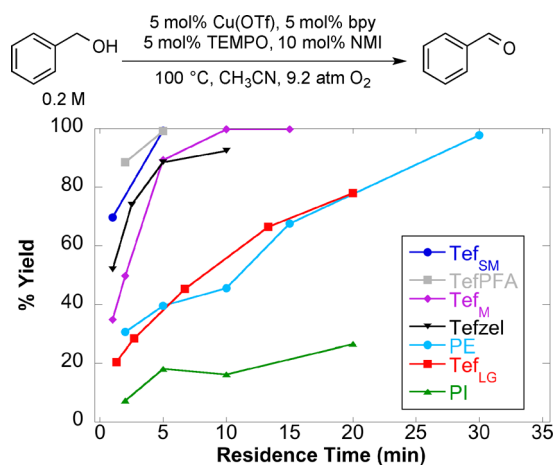
eliminated even though the laminar fluid flow has the parabolic velocity profile expected for low-Reynolds-number flow. A typical residence time distribution (RTD) determined from the effluent response to an inlet concentration step change of tracer is shown in Figure 2 with a fit to the axial dispersion model.<sup>18</sup> The wider, shorter tubes displayed larger dispersions, with values up to  $\mathcal{D}/uL = 0.0030$  indicating minor deviations from plug flow behavior of solutes. For reactions that exhibit first-order and zero-order kinetics, this low dispersion can be shown not to cause appreciable deviation from the reaction behavior modeled for ideal plug flow. Diffusion of alcohol substrate and dissolved oxygen will be more rapid than that of the larger phenanthrene tracer molecule used in the RTD study, so transverse concentration profiles of these reactants will also be unaffected by the laminar flow velocity profile under steady-state conditions. RTDs were measured for all tube reactors used for accurate determination of reactor volume, and all showed



**Figure 2.** Tracer step response RTD for an 8 m, 0.01" i.d.  $\times$  0.0625" o.d. Teflon tube reactor (Tef<sub>SM</sub>). Phenanthrene tracer measurement using an inline HPLC UV–vis detector. The fit to the axial dispersion model yields  $\tau = 445 \pm 1$  s with dispersion  $\mathcal{D}/uL = 0.0008 \pm 0.0001$ .

near plug flow behavior. Entrance effects can be neglected as another consequence of the Taylor dispersion conditions for all but the widest, shortest tubes used in this study. In similar fashion, comparison of reaction and diffusion rates using the Thiele modulus/effectiveness factor approach shows that radial diffusion in these narrow tubes is also sufficiently faster than the reaction rates that no transverse concentration variations will be generated by the catalytic reactions in use here. The most significant transport limitation will be oxygen permeation through the polymer tube wall, as characterized below. Therefore, the reactor can be modeled as a plug-flow tubular reactor.

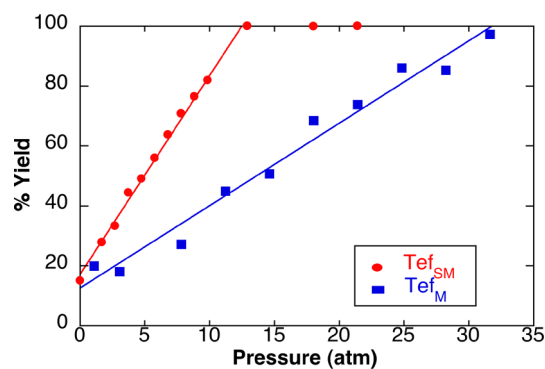
Teflon-PTFE, Teflon-PFA, Tefzel, polyethylene, and polyimide are readily available materials, and they were chosen for investigation based on their gas permeability, chemical compatibility, heat resistance, and low cost (Table 1). The oxygen permeability of 900 Barrer for Teflon AF-2400 is much higher than these materials, but this advantage is offset by its other properties as discussed in the Introduction. Tubing of each type was installed in the reactor and used to oxidize benzyl alcohol to the aldehyde. Figure 3 shows that the tube inner diameter (and resulting surface area/volume ratio) has the most significant influence on the overall reaction rate, and that the wall thickness is a secondary influence. The highest reaction rates were observed in the 0.01" i.d. tubes of differing materials.



**Figure 3.** Oxidation of benzyl alcohol to benzaldehyde with various membrane materials. The polyethylene (PE) reactor was run at 90 °C due to the lower melting temperature of the polymer. See Table 1 for definitions of the abbreviations.

The 0.05" i.d. polyimide tubing displayed the slowest overall reaction, even though it had the thinnest wall dimension. Teflon was chosen for future studies, as it was the least expensive material with good performance.

**Kinetic Modeling of Membrane Reactor.** In our previous work with the Cu/TEMPO catalyst in a slug-flow reactor, the use of diluted oxygen (9% O<sub>2</sub> in N<sub>2</sub>, to avoid flammable vapor mixtures) restricted the maximum achievable partial pressure of oxygen to 3 atm.<sup>6</sup> Containment of the organic solvent within the membrane reactor permitted use of pure oxygen as the applied gas. The pressure ratings of the tubing and the shell allowed oxygen pressures up to 35 atm to be used safely. A scan of oxygen pressures showed a first-order oxygen dependence (Figure 4), as seen in the previous batch



**Figure 4.** Oxidation of benzyl alcohol to benzaldehyde in Teflon tube-in-shell membrane reactors. Reaction conditions: 0.2 M benzyl alcohol in CH<sub>3</sub>CN, 5 mol % Cu(OTf), 5 mol % bpy, 10 mol % NMI, 5 mol % TEMPO, 60 °C, 20 mol % mesitylene as internal standard, 3.0 min residence time.

kinetic study.<sup>15a,b</sup> The yield increased linearly with an increase in applied pressure over a wide range of pressures. The linearity to high yield shows that the reaction is effectively zero-order in benzyl alcohol substrate over the full range of concentrations. The nonzero conversion seen in the absence of applied oxygen was found in batch experiments to be a consequence of the noncatalytic behavior of the Cu/TEMPO system under nonaerobic conditions.

In the operating membrane reactor, the local reaction rate is constant at every location along the length of the reactor tube. At any particular oxygen pressure, the rate in the small-bore tube is higher than that in the medium-bore tube, showing the effects of the different wall configurations on oxygen flux and resulting reaction rate. Since both the intrinsic catalyst kinetics and the oxygen transport affect the overall rate, it is useful to develop a simple model of the interaction of these two controlling processes. Both the reaction and the wall diffusion are first-order in oxygen pressure and produce a resistance-in-series behavior. Equation 1 shows the diffusion flux  $J$  through the cylindrical tube wall, where  $P$  is the wall permeability,  $p_{O_2}$  is the applied oxygen pressure,  $p_{iw}$  is the oxygen equivalent pressure on the inner wall, and  $r_i \ln(r_o/r_i)$  is the effective wall thickness for an annulus.<sup>17</sup>

$$J = P \frac{(p_{O_2} - p_{iw})}{r_i \ln\left(\frac{r_o}{r_i}\right)} \quad (1)$$

The intrinsic kinetics for benzyl alcohol oxidation under these conditions are zero-order in alcohol and first-order in oxygen

and copper,<sup>15a,b</sup> and the reaction rate  $\nu$  can be expressed as shown in eq 2.

$$\nu = k[\text{Cu}]p_{iw} \quad (2)$$

The oxygen equivalent pressure in solution ( $p_{iw}$ ) is treated as constant over the cross section throughout the liquid in the tube. The oxygen level at the inner wall is obtained by equating the oxygen wall flux with the reaction rate within the tube (eqs 3–5).

$$2\pi r_i J = \pi r_i^2 \nu \quad (3)$$

$$2\pi r_i P \frac{(p_{O_2} - p_{iw})}{r_i \ln\left(\frac{r_o}{r_i}\right)} = \pi r_i^2 k[\text{Cu}]p_{iw} \quad (4)$$

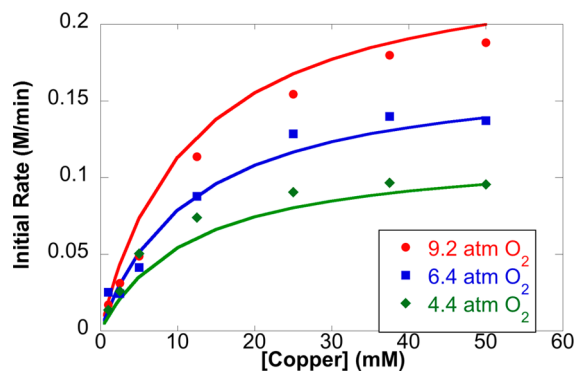
$$p_{iw} = \frac{2Pp_{O_2}}{2P + k[\text{Cu}]r_i^2 \ln\left(\frac{r_o}{r_i}\right)} \quad (5)$$

Thus, the overall reaction rate in terms of the external oxygen pressure, as shown in eq 6, exhibits the limiting behaviors for both kinetic control and oxygen transport control.

$$\nu_{overall} = \frac{k[\text{Cu}]p_{O_2}}{1 + \frac{k[\text{Cu}]r_i^2 \ln\left(\frac{r_o}{r_i}\right)}{2P}} \quad (6)$$

When permeation is fast and reaction is slow (high  $P$  and low  $[\text{Cu}]$ ),  $p_{iw}$  approaches  $p_{O_2}$  and  $\nu_{overall}$  reduces to reaction control. When the reaction is fast, with  $p_{iw}$  approaching zero,  $\nu_{overall}$  reduces to the flux limit.

To observe regions of control by oxygen transport and reaction kinetics, a range of copper concentrations was used to vary the intrinsic reaction rate. Figure 5 presents the results of



**Figure 5.** Oxidation of benzyl alcohol to benzaldehyde in reactor Tef<sub>SM</sub>. Reaction conditions: 0.5 M benzyl alcohol in CH<sub>3</sub>CN,  $X$  mM Cu(OTf),  $X$  mM bpy,  $2X$  mM NMI, 20 mM TEMPO, 100 °C, 20 mol % mesitylene as internal standard.

an initial-rate study conducted at short residence times, and it shows that the overall rate is linear in copper at low concentration, when the reaction is slow. At high copper concentration, when the intrinsic reaction kinetics are faster and exceed the oxygen flux limits of the membrane, the overall reaction rate shows saturation behavior. The flux limit is proportional to the applied oxygen pressure, as seen for the three oxygen pressures used. The lines in Figure 5 reflect a global two-parameter fit ( $k$  and permeability  $P$ ) of the kinetic data to the rate law in eq 6.

The oxygen permeability of the PTFE tubing, determined from the fit to the high-rate plateau, is 60 Barrer. This value is substantially higher than the ambient-temperature reference value for PTFE (4.3 Barrer; Table 1) and also the value estimated for 100 °C (9.5 Barrer).<sup>16</sup> Possible explanations for the difference between the reference values measured for well-defined PTFE films and the present permeabilities observed for the commercial tubing would include differences in molecular chain packing between the biaxially oriented films and the uniaxial extruded tubing, or simply the higher integrity and density of a carefully prepared slab compared to the normal tolerances and treatment of commercial chromatography tubing during manufacture. Regardless, the observation of such enhanced permeation through the tubing in use here relative to standard tabulated polymer property data illustrates the variability possible between different samples or sources.

**Applications to Aerobic Alcohol Oxidation.** The membrane reactor was tested with the Tef<sub>SM</sub> tubing in the oxidation of three representative alcohols that had been previously demonstrated in batch<sup>13</sup> and/or in the previously reported continuous slug-flow reactor<sup>6</sup> (Table 2). The

**Table 2.** Scope of the Tube in a Shell Reactor with a Copper Catalyst

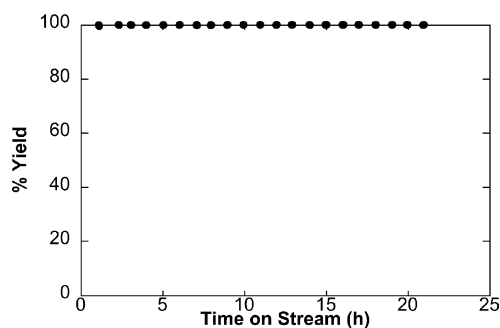
Entry	Alcohol	Nitroxyl/bpy	Residence Time	Yield
1		5 mol% TEMPO bpy	1 min	98%
2		1 mol% ABNO 4-MeObpy	1 min	99%
3 <sup>a</sup>		1 mol% ABNO 4-MeObpy	1 min	99% ee

TEMPO =	ABNO =	4-MeObpy =
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<sup>a</sup>Analyzed by <sup>1</sup>H NMR with tri-*tert*-butylbenzene as the internal standard. Enantiomer selectivity determined by HPLC analysis. See ref 13d for details.

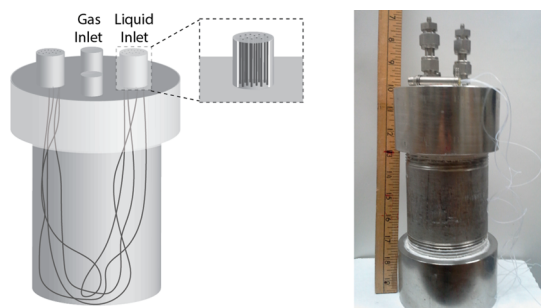
propargylic alcohol (entry 1) undergoes oxidation to the aldehyde in 98% yield under the indicated conditions. The shorter residence time relative to the previously reported result in the slug-flow reactor (1 min vs 5 min, respectively) reflects the substantially higher accessible O<sub>2</sub> pressure in the present reactor. Similarly short residence times (1 min) were achieved in the oxidation of the aliphatic alcohol (cyclohexylmethanol, entry 2) and the chiral, sterically hindered 2° alcohol (entry 3). The latter applications employed the recently reported Cu/ABNO catalyst system,<sup>13d</sup> which shows much higher activity for aliphatic and sterically hindered substrates, relative to Cu/TEMPO. With the previously reported slug-flow reactor, cyclohexylmethanol required a residence time of 45 min to reach completion when Cu/TEMPO was used as the catalyst.<sup>6</sup>



**Figure 6.** Oxidation of 10 g of benzyl alcohol to benzaldehyde in a Tef<sub>SM</sub> reactor. Reaction Conditions: 1 M benzyl alcohol in CH<sub>3</sub>CN, 5 mol % Cu(OTf), 5 mol % bpy, 10 mol % NMI, 5 mol % TEMPO, 33 atm O<sub>2</sub>, 100 °C, 20 mol % mesitylene as internal standard, 5 min residence time.

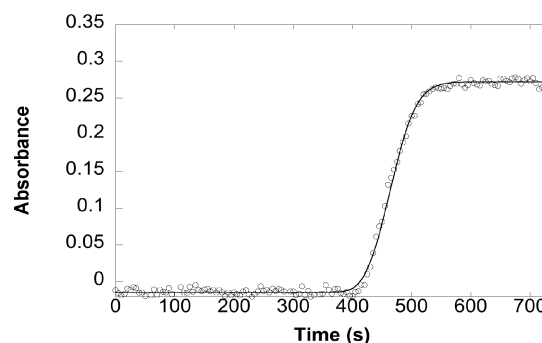
The stability of the membrane flow reactor in operation at a higher concentration of alcohol and over an extended period of time was tested in a 10-g-scale oxidation of benzyl alcohol (Figure 6). A 1 M solution of benzyl alcohol was oxidized with the Cu/TEMPO system at 33 atm of O<sub>2</sub> and a 5 min residence time. The steady-state yield held at >99% for the duration of the experiment.

**Multitube Membrane Reactor.** Scale-up of the aerobic oxidation reaction to yet higher quantities or flow rates while maintaining desirable residence time necessitates a proportional increase in reactor volume. The single tube reactors described thus far had volumes less than 1 mL. Increasing operational capacity by increasing the diameter or length of a single tube would reduce O<sub>2</sub> mass transfer or increase the pressure drop, respectively. Instead, it is practical to number-up the membrane reactor by assembling a configuration with multiple tubes operating in parallel. A prototype multitube reactor was constructed with 13 Cole Palmer PTFE #30 AWG Thin Wall tubes, each 25 ft in length (Figure 7), resulting in a total liquid reactor volume of 10 mL.



**Figure 7.** Schematic diagram and photograph of the multitube reactor. For clarity, only 4 of 13 tubes are depicted in the schematic diagram.

The polymer tube ends were sealed with epoxy into 2"-long sleeves of 3/8" tubing to pass through Swagelok fittings at the end of the pressure vessel, which was constructed from high-pressure 3" stainless steel pipe and caps rated to 2570 psi. The vessel was tested to 1000 psi to ensure compatibility with the operating pressures used (400 psi). A Parr or other commercial high-pressure reactor, modified to accommodate the membrane tube feed-through fittings, could also be used for this application.

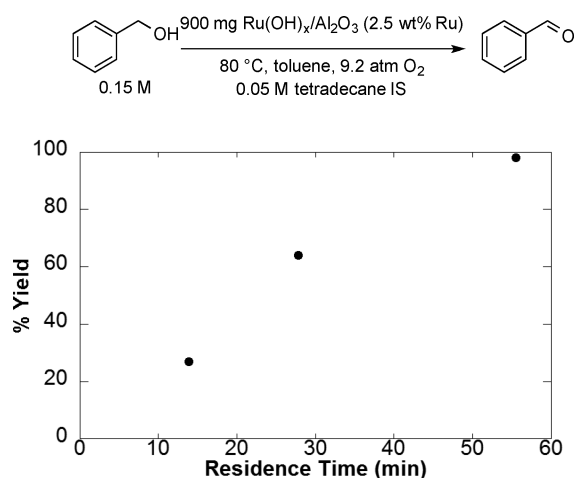


**Figure 8.** Tracer step response RTD for multitube reactor, with phenanthrene tracer measurement using inline HPLC UV/vis detector. The fit to the axial dispersion model yields  $\tau = 464 \pm 1$  s with dispersion  $\mathcal{D}/uL = 0.0027 \pm 0.0001$ .

A residence time distribution study showed that dispersion in the multitube reactor was only slightly larger than that seen in a single tube reactor (Figure 8; cf. Figure 2), indicating that the parallel tubes each had similar behavior and the end fittings caused only minor additional mixing or dispersion. The multitube reactor was then employed in the oxidation of 10 g of benzyl alcohol within 45 min, which may be compared to the 21 h run duration required in the single-tube reactor (cf. Figure 6). A steady state yield of >98% was observed throughout the reaction (conditions: 1 M benzyl alcohol in CH<sub>3</sub>CN, 5 mol % Cu(OTf), 5 mol % bpy, 10 mol % NMI, 5 mol % TEMPO, 28 atm O<sub>2</sub>, 100 °C, 20 mol % mesitylene as internal standard, 5 min residence time).

**Use of a Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> Heterogeneous Catalyst in the Membrane Reactor.** We considered whether the membrane reactor configuration described above could also be used to conduct aerobic alcohol oxidation reactions over a heterogeneous catalyst. The Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> catalyst, developed by Mizuno and co-workers, has been widely studied for alcohol oxidation.<sup>14</sup> A prior flow study of the Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> catalyst had been conducted by providing an acetonitrile solution of the alcohol and a 9% O<sub>2</sub>/N<sub>2</sub> gas mixture in slug flow to the catalyst in a packed bed.<sup>7o</sup> Three-phase reactors of the latter type can be difficult to characterize and operate with consistency, and the use of a diluent gas to avoid flammable vapor compositions requires high total operating pressures. The membrane reactor allows a bubble-free alcohol feed stream to pass over the catalyst while the oxygen is supplied through the permeable wall along the length of the reactor. This format removes the uncertainty of the effect of gas void volume on the liquid fill factor in the reactor and also allows operation with pure oxygen at more modest total pressures. Wider and shorter polymer tubing can be used to aid in loading powdered catalyst and avoid excessive pressure drop through the packed bed during flow. Larger diameter tubing also minimizes the possibility of preferential channeling of liquids along the reactor walls. Since Darcy flow through a packed bed naturally exhibits uniform axial velocity and plug flow, the Taylor dispersion criteria no longer apply.<sup>17</sup> Tube diameter is still limited by the radial diffusion of solutes, which must be faster than the reaction rate to avoid radial variations in the concentration of substrate and/or oxygen.

For demonstration purposes, an 18" length of the larger 1/8" o.d. (0.063" i.d.) Teflon tubing was loaded with 900 mg of a heterogeneous 2.5 wt % Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> catalyst and used to oxidize benzyl alcohol to benzaldehyde after an initial catalyst



**Figure 9.** Heterogeneous oxidation of benzyl alcohol to benzaldehyde in the Tef<sub>LG</sub> reactor.

pretreatment to stabilize the catalyst activity.<sup>70</sup> The benzyl alcohol was oxidized to completion (Figure 9) in reactor residence times of less than 1 h. The relatively slow reaction rate reflects the relatively low activity of the catalyst. Under these conditions, the Ru catalyst has been shown to have a turnover frequency of 2 mol substrate·mol Ru<sup>-1</sup>·h<sup>-1</sup>. The initial rate displayed in the permeable-tube reactor corresponds to a volumetric productivity of 3 mmol·L<sup>-1</sup>·min<sup>-1</sup>. The O<sub>2</sub> flux limit, estimated from the permeability parameter *P* taken from Figure 5 and the geometric parameter  $r_i^2 \ln(r_o/r_i)$  to account for the tubing dimensions, is 15 mmol·L<sup>-1</sup>·min<sup>-1</sup>. Thus, this reactor tubing may be used with catalysts of somewhat higher activity, while much more active catalysts will need appropriate changes in reactor tubing size or material parameters.

The pressure drop across the reactor was 1 atm at the low flow rate used for the longest (55 min) residence time. The pressure drop increased linearly with the flow rate, reaching a maximum of 11.5 atm at the fastest flow (14 min residence time). The mean particle diameter of the catalyst and overall void fraction were estimated to be 10 μm and 0.7, respectively. The Blake–Kozeny equation for flow through packed beds<sup>17</sup> satisfactorily describes the observed pressure-drop/flow-rate behavior. The observed pressure drop is well below the 1000 psi pressure limit of the Teflon tubing, demonstrating that this simple membrane reactor can provide adequate oxygen flux and acceptable overall pressure drops for use with heterogeneous catalysts.

## CONCLUSION

Membrane reactors show great promise for use in aerobic partial oxidation reactions. The results above demonstrate that inexpensive, commercial polymer tubing has sufficient oxygen permeability to provide the flux of O<sub>2</sub> needed to sustain rapid aerobic oxidation reactions. Of the materials tested, Teflon (PTFE) showed the best behavior in terms of reaction times, O<sub>2</sub> flux, and ease of use. And, the thermal stability of this material enables operation at elevated temperatures commonly desired for process intensification.

The reactor performance is influenced more by the ratio of tubing surface area to liquid volume than by the polymer type or thickness of the membrane itself. Simple reactor models may be used to evaluate the relative control of reaction rates by catalyst kinetics or the flux of gas through the membrane. Thus,

conditions may be chosen to operate under “kinetic control”, to assess the reaction kinetics, or under “diffusion control”, to maximize reaction productivity, as in scale-up applications.

In comparison to a slug-flow reactor with gas–liquid cofeed, the membrane reactor improves safety by eliminating vapor-phase organic/oxygen mixtures and lowers the overall pressure requirement of the system by eliminating the need for high pressures of an inert gas diluent. The higher accessible oxygen pressures can be used to increase reaction rates and improve reactor productivity.

The good performance of low-cost membrane materials under aerobic oxidations suggests that similar materials could be employed in reactions with other gaseous reagents, such as hydrogen, carbon monoxide, and syngas, among others.<sup>11d</sup>

## EXPERIMENTAL SECTION

**General Considerations.** Commercially available reagents and catalyst components were obtained from Aldrich and used as received, with the exception of the Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> catalyst, which was prepared as described in the literature.<sup>14</sup> Polymer tubing was obtained from VICI (PTFE - Tef<sub>SM</sub>), Supelco (PTFE - Tef<sub>M</sub>, Tef<sub>LG</sub>), IDEX (PFA), Upchurch Scientific (ETFE), Spectrum Chromatography (Polyethylene), and Cole Palmer (Polyimide). Tubing dimensions are listed according to catalog specifications, which are typically provided in units of inches. Acetonitrile was obtained from solvent purification columns, in which the solvent was passed through a column of activated molecular sieves. The catalyst solution was kept under a blanket of flowing nitrogen during the reaction. GC analyses were performed using a DB-Wax column (30 m) installed in a Shimadzu GC-17A equipped with a flame-ionization detector. A 22.5 min GC method was used consisting of 1 min at 70 °C, ramp at 20 °C/min to 200 °C (6.5 min), and 15 min at 200 °C. The injector and detector were held at 225 °C, and the column flow was 1.5 mL/min of He with a split ratio of 20. Retention times were as follows: mesitylene (3.7 min), benzyl alcohol (7.7 min)/benzaldehyde (5.7 min), cyclohexylmethanol (5.8 min), cyclohexanecarbaldehyde (3.9 min), 3-phenyl-2-propyn-1-ol (12.3 min), 3-phenyl-2-propynal (8.1 min).

**Representative Procedure for Alcohol Oxidation in Flow (Homogeneous Catalyst).** The substrate (4 mmol, 0.4 M) was prepared as a stock solution in acetonitrile (9.5 mL) with mesitylene (0.11 mL, 0.8 mmol, 0.08 M) as an internal standard. The catalyst stock solution consisted of [Cu(CH<sub>3</sub>CN)<sub>4</sub>]OTf (75 mg, 0.2 mmol, 5 mol %), bpy (31 mg, 0.2 mmol, 5 mol %), TEMPO (31 mg, 0.2 mmol, 5 mol %), and NMI (32 μL, 0.4 mmol, 10 mol %) dissolved in acetonitrile (10 mL). The liquid back-pressure regulator (BPR) was set 1 atm higher than the desired gas pressure to avoid the formation of oxygen bubbles. The gas was set to the desired pressure (24.8 atm) by a cylinder pressure regulator. The oven and tube-in-shell reactor were allowed to equilibrate at the operating temperature for 1 h. The solutions were run through the system with each HPLC pump providing half of the total liquid flow. The ethyl acetate quench was set to 10–50 times the liquid feed flow rate. The product was collected at the exit of the liquid back pressure regulator.

For the pressure scan reaction, the reactor pressure was changed using the oxygen pressure regulator on the tank. Each pressure was given 30 min to equilibrate before sampling. For the catalyst concentration dependence experiments, the stock catalyst solution was diluted with CH<sub>3</sub>CN by an HPLC pump operating in gradient mode to yield different copper

concentrations. The initial rates were determined using a 2 and 3 min residence time.

**Representative Procedure for Alcohol Oxidation in Flow (Heterogeneous Catalyst).** The Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> (900 mg) was placed into a 45 cm tube using a slurry (900 mg Ru(OH)<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> + 20 mL acetone). The packed bed was dried overnight using air. The substrate (30 mmol, 0.15 M) was prepared as a stock solution in toluene (200 mL) containing tetradecane (1.96 mL, 10 mmol, 0.05 M) as an internal standard. The substrate solution was fed into the reactor using an HPLC pump. The reactor operating procedure was the same as for the homogeneous catalyst, but with toluene as the quench solvent.

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### Notes

The authors declare no competing financial interest.

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