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The Development of Continuous Process for Alkene Ozonolysis Based on Combined in Situ FTIR, Calorimetry, and Computational Chemistry

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Abstract:

Two continuous apparatuses were designed that are capable of safely scaling the highly energetic ozonolysis reaction to multikilogram scale where flow chemistry allowed excellent temperature control and minimized the inventory of the highly unstable ozonide intermediate. First, a continuous stirred tank reactor was developed and proven capable of generating product at a rate of 77 mmol of product per hour while maintaing <46 mmol of ozonide. Then, a larger-scale continuous bubble reactor was designed to deliver 770 mmol of product per hour while maintaing 950 mmol of ozonide present at any given time, and the latter was utilized to deliver 2.5 kg of product. The development of these reactors relied on careful evaluation of the thermal stability and heat of reaction of ozonolysis using computational chemistry and calorimetric measurement. In addition, the reactor design benefited from in situ ATR/FTIR monitoring of the rate of ozonolysis under nonflow conditions which allowed for the flow of substrate to be matched with ozone generation, enabling complete reaction of the alkene with minimal excess of ozone.

Introduction

Ozonolysis is a very useful synthetic noncatalytic reaction where alkenes and alkynes can be selectively oxidized to form carbonyl compounds, and thus ozonolysis is widely used in natural product and drug synthesis.[1] However, the utility of this reaction at large scale has been hindered by three factors, namely, (a) ozone toxicity, (b) the thermal instability of reactive intermediates (ozonides and/or hydroperoxides), and (c) the inherent exothermicity of the reaction. On the basis of the well-accepted mechanism[2] for the ozonolysis of alkenes (Scheme 1), the reaction proceeds by the addition of ozone to the alkene to form the highly energetic primary ozonide (POZ).[1] This POZ is very unstable and has been isolated at temperatures as low as −238 °C.[3] At temperatures relevant to this study, ∼−50 °C, the POZ cleaves to form an aldehyde and carbony1oxide[2] which recombine to form the more stable secondary ozonide (SOZ).[3] Indeed, computational modeling carried out in this study indicates that SOZ is more stable than POZ by 64 kJ/mol. The SOZ can be further manipulated to form the desired products, either through oxidation to form carboxylic acids or by reduction to afford ketones, aldehydes, or alcohols.

The formation of hydroperoxides,[4] especially in protic solvents such as methanol,[4] cannot be ruled out but was not considered herein in light of the fact that ozonolysis of various olefins, especially highly substituted olefins, in methanol still furnished the SOZ as a major product. Indeed, the high stabilities of SOZ in methanol[5] and THF[6] have been reported even at the reflux temperatures of each solvent.

Ozone addition and the subsequent quench are very exothermic, −381 and −122 kJ/mol respectively as experimentally measured in this study, see Results and Discussion. The formed ozonides are extremely reactive[7] creating an explosion hazard at high concentrations. These challenges associated with ozonolysis made the development of continuous process that improves temperature management and reduce the inventory of hazardous intermediates very attractive. Recent examples of continuous ozonolysis include carrying out the reaction in microstructured reactors[8] which furnished excellent conversions; however, an ozone-to-substrate ratio of ∼1.4 was required, and smaller total gas-flow rates (0.1 L/min) were used, and the setup can generate up to 1 g/h of product.[9] In another example[10] ozone was introduced to alkenes via gas-to-liquid transfer through semipermeable Teflon AF-2400 tubing. The latter setup was not efficient in absorbing ozone and can generate about ∼0.1 g/h of products.[9] Ozone is toxic, and its release to the atmosphere is regulated, and thus the use of excess ozone, i.e. high ozone-to-substrate ratio, poses serious challenges, from an industrial perspective, in terms of handling large quantities of unreacted ozone when operating in continuous mode.

In this study, ozonolysis of a drug candidate intermediate, whose structure cannot be revealed due to IP, was suggested as a better alternative to the current osmium tetroxide-based oxidation process. The structure of the drug intermediate can be classified as an isobutylene, $R1R2C{=}CH_2$. Due to the high cost of the substrate of interest, styrene was used as a model compound to understand the reaction kinetics and utility of a scalable continuous ozonolysis. Herein, we report semi-batch studies on the heat of reaction and kinetics of ozonolysis which were used to develop a continuous stirred tank reactor (CSTR) capable of generating about 8 g/h of product with nearly 100%

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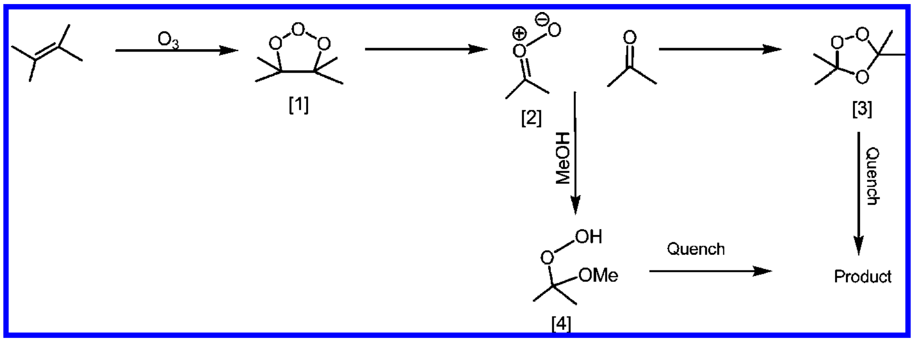
Scheme 1. **General reaction mechanism of alkene ozonolysis**



efficiency in ozone adsorption. To increase the throughput, a continuous bubble reactor was also developed in-house and shown to be capable of generating 80 g/h of product at the kilolab scale.

Results and Discussion

Heat of Reaction. In the intrinsically exothermic ozonolysis reaction, operational safety parameters rely upon accurate measurement of the heat of reaction. To corroborate experimental data generated through calorimetric measurements, which can be complicated by concurrent events such as gas dissolution and evolution, computational chemical methods were used to calculate the heat of reaction. To evaluate the relative energies of the intermediates and the heat generated from the reaction, we used the CBS-QB3[11] method implemented within Gaussian 03[12] to calculate the relative stability of SOZ to POZ and heat of reaction for the ozonolysis of the alkene of interest. For the computational modeling, isobutylene was used as a model compound for the drug intermediate, i.e. assuming $R_1 = R_2 = CH_3$. Geometric optimization of the corresponding POZ and SOZ was carried out using Gaussian 03, solvent effect was ignored, and results showed that SOZ is 64 kJ/mol more stable than POZ. The low temperature requirement to isolate POZ indicates that its formation, fragmentation and subsequent recombination to form the SOZ is fast and inconsequential to the overall observed reaction at our conditions. Therefore, computational modeling was used to investigate the heat of reaction of the relevant kinetic steps namely, the formation of SOZ and its subsequent quench to the desired product with dimethylsulfide.

Computational modeling results indicate that ozone addition to form the SOZ is very exothermic with heat of reaction of −445 kJ/mol. The results are in excellent agreement with calculated energy for the reaction of ethylene with ozone where the heat of reaction to form the secondary ozonide was −427 kJ/mol.[13] The subsequent quench with DMS was also exothermic, −110 kJ/mol. The latter results from computational chemistry are also in good agreement with the results from Ragan and cowokers at Pfizer where experimental calorimetry data for the ozonolysis of an allylic compound were −535 and −131 kJ/mol for ozone addition and the subsequent quench, respectively.[14]

Next, a Mettler-Toledo RC1e calorimeter was used to experimentally measure the heat of reaction of the drug intermediate. It is worth mentioning that the experimental value includes not only the intrinsic heat of reaction but also the heat of oxygen delivery, heat of ozone addition, and any evaporation of the solvent during the addition. During ozone addition, the observed total heat evolution was −381 kJ/mol in reasonable agreement with one obtained from computational modeling (−445 kJ/mol). The lower experimental value for the heat of reaction appears to be due to the induced solvent vaporization during ozone addition. Both experimental and computational method showed that ozone addition is very exothermic. In order to obtain a tangible sense of the consequences of the generated heat in the lab or at plant scale, the adiabatic temperature rise (ΔT_{ad}) associated with the exothermic event is calculated on the basis of eq 1. ΔT_{ad} reflects the temperature increase if generated heat is retained within the vessel due to absence and/or loss of cooling.

$$\Delta T_{ad} = \frac{\Delta H_{net}}{m_{total} C_{p,r}} \tag{1}$$

where ΔH_{net} is heat evolved (in J); m_{total} is total moles of reactor contents; $C_{p,r}$ is average heat capacity of the reactor contents (in J mol^{-1} K^{-1}).

Based on eq 1, the observed total heat during ozone addition corresponds to an adiabatic temperature rise ΔT_{ad} of 187 °C, i.e. if the energy of the reaction were released and the heat were not removed, the reaction mass could self-heat by 187 °C which reflects the intrinsic danger of running ozonolysis even at cold temperatures. For example, if the reaction was carried out at −50 °C, in the event of loss of cooling, temperature can rise to

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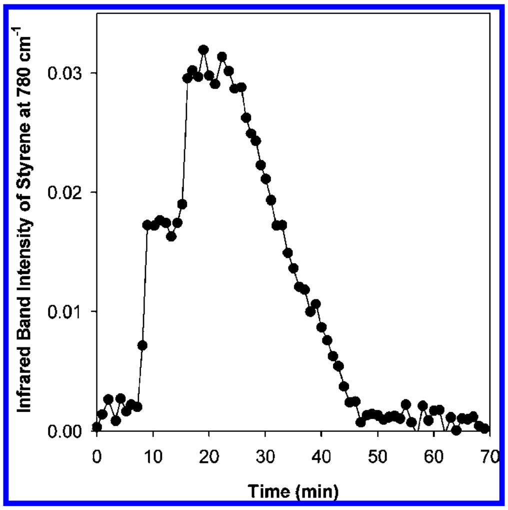

Figure 1. **Infrared band intensity of styrene at 780 cm^{-1} during ozonolysis in batch mode.**

137 °C which is well beyond the boiling point of typical organic solvents used for this reaction such as methanol and dichloromethane. The measured total heat of reaction during the quench with dimethylsulfide was also exothermic (−122 kJ/mol), which is consistent with the computationally predicted value of −110 kJ/mol. A differential scanning calorimeter (DSC) was utilized to assess the thermal stability of the reaction mixture after introducing ozone; prior to quench an exothermic decomposition, presumably of the ozonide, was observed (−12 kJ/mol) with an onset temperature near 42 °C. The observed heat during the subsequent quench corresponds to an adiabatic temperature rise of 52 °C. In addition to the highly exothermic reactions of the synthesis and reductive quench, there is evidence from the RC1 testing that measurable heat was being generated as low as −30 °C, presumably by the decomposition of SOZ.

Ozonolysis Kinetics in Semi-Batch Mode. We initially investigated the kinetics of the ozonolysis reaction in a nonflow regime (i.e. in a semi-batch mode) where styrene was used as a model compound due to its strong HPLC and FTIR signals and the scarcity and expense of the substrate of interest. For these experiments, a lab-scale ozone generator (Polymetric, Inc.) was used with the appropriate setting to generate 2.3 mmol/min of ozone according to the manual, see Experimental Section. The ozone was introduced under the impeller's blades in order to enhance mass transfer. The reactor was also equipped with an FTIR fiber-optic probe to monitor reaction progress. A solution of 3 mL of styrene in 200 mL of methanol at −50 °C resulted in an infrared band at 780 cm^{-1} (Figure 1).

When an additional 3 mL of styrene was added to the reactor, the FTIR band at 780 cm^{-1} approximately doubled as shown in Figure 1, indicating that FTIR is a viable analytical tool to quantitatively monitor styrene concentration. Ozone was introduced to the reactor (∼25 min), and the concentration of styrene dropped linearly as evidenced from FTIR absorbance. Strikingly, the rate of styrene reaction with ozone (2.2 mmol/min) based on the FTIR signal, is almost equivalent to the ozone supply 2.3 mmol/min. This indicates that the reaction is limited only by ozone supply and the current setup is allowing sufficient gas−liquid contact for mass transfer to absorb ozone from the supplied gas stream.

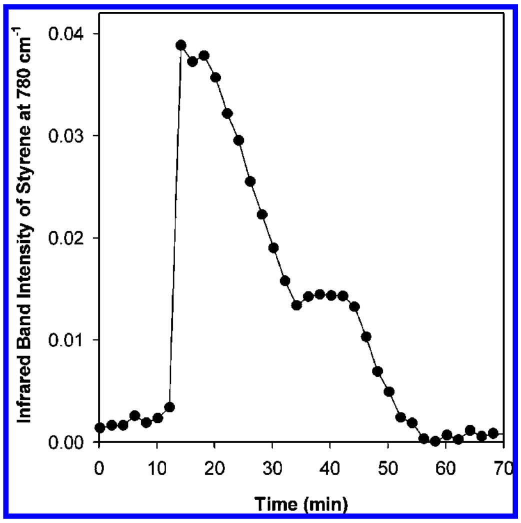

Figure 2. **Infrared band intensity of styrene at 780 cm^{-1} during ozonolysis in batch mode with ozone supply interruption.**

The semi-batch experiment indicates that ozone reaction with styrene is fast, and thus, no ozone accumulation is expected in the reaction mixture. This was experimentally evaluated using the same setup described earlier with the exception that ozone supply was purposely stopped before complete styrene consumption. As in the previous batch experiment, 6 mL (63 mmol) of styrene in 200 mL of methanol at −50 °C, was set up, and again infrared signal was observed at 780 cm^{-1} as shown in Figure 2.

Afterward, ozone was introduced to the reactor and in agreement with the previous semi-batch experiment, styrene concentration dropped linearly at a rate of about 2.2 mmol/min. After 35 min (i.e., 15 min after introducing ozone) ozone supply was disrupted by turning off the ozone generator; concurrently the reaction ceased, as evidenced by the styrene concentration reaching a steady value as shown in Figure 2. After 10 min, the ozone generator was turned back on, and the reaction immediately started again at approximately the same rate observed prior to ozone interruption. These results indicate that there is a fast reaction between ozone and the styrene in the liquid phase and that both the ozone absorption rate and olefin conversion do not depend on ozone mass transfer with current reactor geometry.

Styrene Ozonolysis in a Continuous Stirred Tank Reactor (CSTR). Encouraged by the high efficiency to ozone adsorption by standard lab reactor in the previous section, we retrofitted these existing reactors to allow continuous operation by adding an overflow valve. An overflow design was selected because of its simplicity in terms of fabrication where the existing reactor could be easily modified. This also avoids the need for a second pump to transport the CSTR contents to a third tank, usually a quench, and simplifies the level control in the reactor to maintain a constant volume in the reactor. Prior to using these modified reactors, a residence time distribution (RTD)[15] analysis was employed to examine the hydrodynamics of these reactors. As an example, the RTD test used to evaluate the performance of the retrofitted 100-mL reactor will be discussed. First, the 100-mL continuous reactor was filled with

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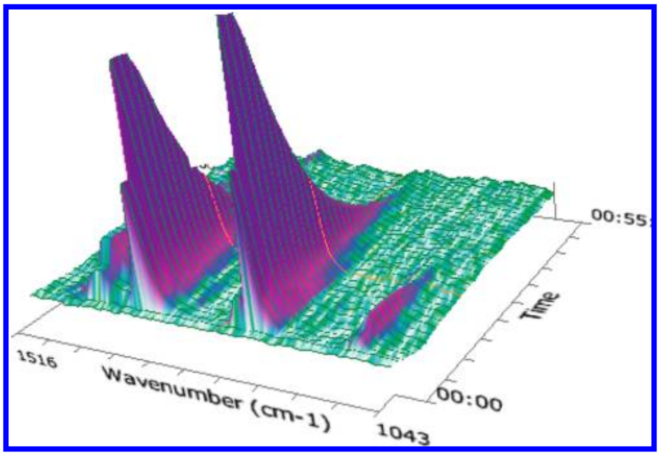

Figure 3. **Infrared spectra of acetone in heptane during residence time distribution experiment.**

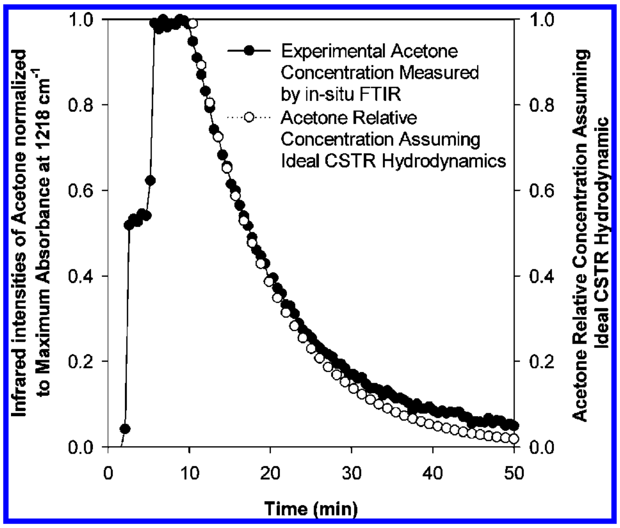

Figure 4. **Acetone relative concentration. (•) Experimentally measured by FTIR; (○) predicted assuming CSTR hydrodynamics.**

100 mL of heptane, and then 2 mL of acetone was added to CSTR. On the basis of the strong FTIR intensity of acetone at 1218 cm^{-1}, its concentration was monitored by in situ FTIR, (Figure 3). Next, an additional 2 mL of acetone was added to the reactor, and the infrared intensities of acetone at 1218 cm^{-1} doubled (Figure 4), indicating a linear response to acetone concentration.

By introducing pure heptane to the 100 mL CSTR and allowing liquid to overflow to a receiving tank, the acetone concentration should decay according to eq 2, assuming current reactor geometry followed ideal CSTR hydrodynamics

$$^{C(t)}/_{C_o} = e^{-t/\tau} \tag{2}$$

where $C(t)$ is relative concentration at time t, C_o is acetone initial concentration which was normalized to unity, and finally τ is the mean residence time of the reactor. Experimentally, pure heptane was transferred to CSTR via a piston pump at rate of 10 mL/min for a mean residence time, τ, of 10 min. The liquid from the reservoir was added right under the agitator at 300 rpm to enhance mixing. Figure 4 presents a comparison of acetone relative concentration experimentally measured by FTIR versus that predicted by eq 2 assuming an ideal CSTR. The excellent agreement between the two profiles suggests that the new reactor closely resembles an ideal CSTR and that behavior associated with channeling and/or dead volumes was not observed.

After ensuring ideal CSTR hydrodynamics, the CSTR was used for the ozonolysis of styrene in continuous mode. The setup employed the same ozone generator from the previous semi-batch experiments. The concentration was chosen so that at a flow rate of 10 mL/min from the reservoir, the styrene molar flow will be about equimolar to ozone supply, 2.3 mmol/min. The CSTR was equipped with an overflow valve in order to allow continuous operations and has a steady-state volume of 200 mL. An FTIR probe was used to monitor the concentration profile in the CSTR. A third quench reactor was attached to the overflow valve. A schematic diagram of the setup is shown in Figure 5.

Then, the temperatures of the CSTR and quench tank were set to −50 °C and −1 °C, respectively. The ozone supply from the ozone generator was connected to the CSTR in the same manner as in the semi-batch run, i.e. gas bubbles released under the mixing blades. Initially, 200 mL of the reservoir solution (46 mmol styrene) was transferred to the CSTR, and then observed FTIR intensity at 780 cm^{-1} was used to deduce number of moles of styrene inside the CSTR (Figure 6).

After 20 min, the pump was turned off (flow 0 mL/min), and the reactor overflow valve to the quench tank was closed; i.e. CSTR was operated in semi-batch mode. Next, the ozone generator was turned on, and gas was allowed to bubble in the CSTR. Ozone introduction resulted in consumption of styrene (46 mmol) in ~21 min. The rate of reaction was linear and at about 2.2 mmol/min, in excellent agreement with results obtained during the semi-batch experiments in the previous section. During ozone addition, the temperature inside the reactor rose from −50 °C to −38 °C due to reaction exothermicity. Next, the setup was operated in continuous mode by adding 15 mL/min from the reservoir solution [i.e. 3.5 mmol/min of styrene (50% excess styrene)] and opening the overflow valve in order to allow excess liquid to overflow into the quench tank. With an insufficient amount of ozone, styrene accumulated inside the CSTR to half of its original concentration, as expected for a 50% molar excess in substrate feed. The number of moles of styrene climbed to about 22 mmol which provided strong evidence of ideal CSTR hydrodynamics and the high efficiency of ozone adsorption. The flow rate from the reservoir was reduced to 5 mL/min, making substrate-to-ozone molar ratio 0.5. In the presence of excess ozone, the number of moles of styrene was experimentally observed to drop, as expected. The in situ FTIR capability to quantitatively monitor styrene was validated by several off-line HPLC measurements as shown in Figure 6.

The same CSTR setup was then used for the ozonolysis of a substrate of interest, an isobutylene-type drug intermediate. Despite the fact that the setup was very efficient in ozone adsorption, a ratio of about 1.2 ozone-to-substrate ratio was used to ensure 100% conversion of the substrate. The setup was operated in continuous mode in 12-h shifts for 4 days, generating ~90 g/day. The batches were combined and showed 98% conversion. Approximately 300 g of product was generated

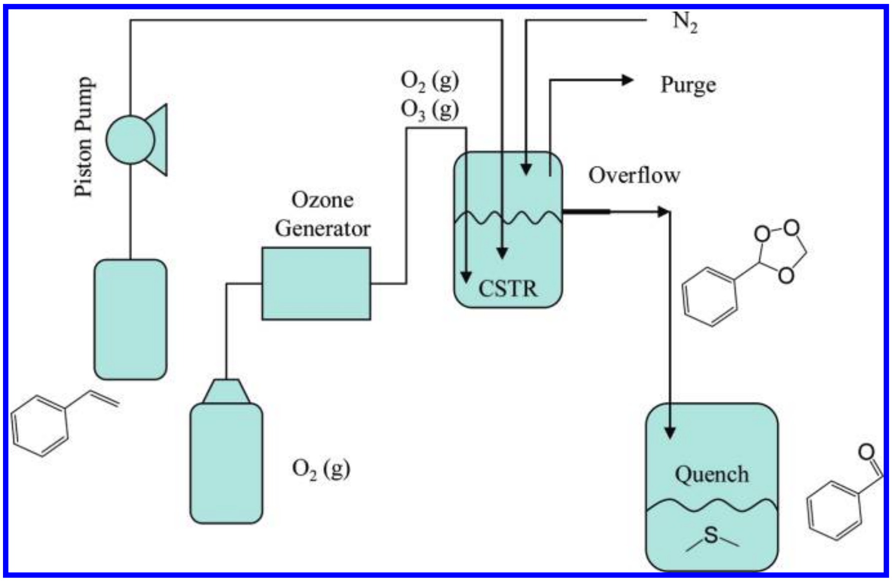

Figure 5. **Schematic diagram of the CSTR setup used for continuous ozonolysis of styrene.**

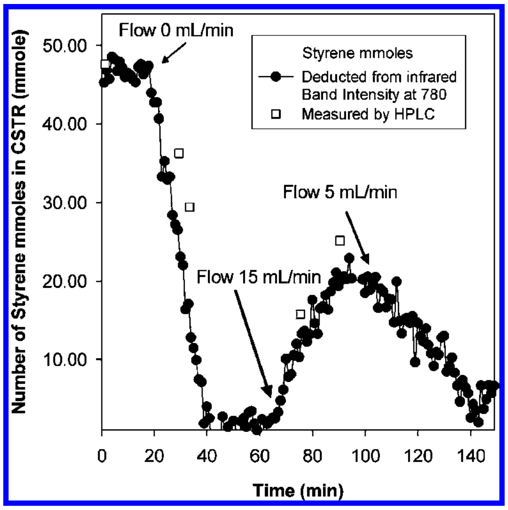

Figure 6. **Number of styrene mmole in the CSTR: (●) deducted from FTIR intensity at 718 cm^{-1}; (□) measured by off-line HPLC.**

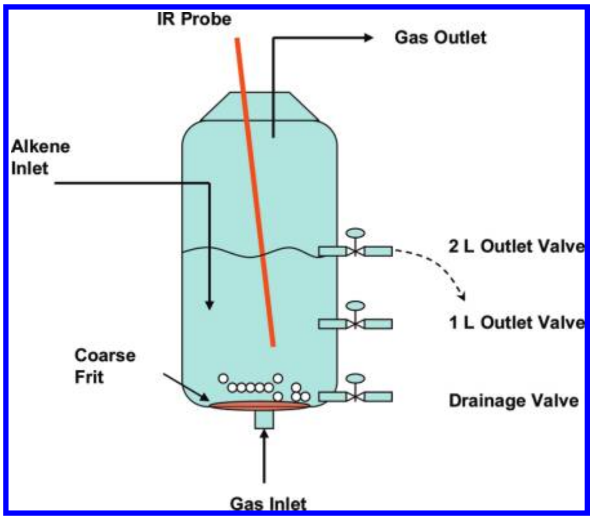

Figure 7. **Schematic diagram of the in-house-designed continuous bubble reactor.**

(81% isolated yield) after workup. Scaling up ozonolysis in batch mode would have required a larger reactor vessel which in general has smaller surface-to-volume ratio and thus less efficiency in removing heat from the reactor when compared to the described CSTR. Furthermore, carrying out the reaction in batch mode would require the conversion of all starting material to ozonide prior to the quench, potentially accumulating about 2880 mmol of the unstable ozonide, while operating in flow mode using the current CSTR keeps the ozonide concentration less than 46 mmol at any given time.

Styrene Ozonolysis in a Continuous Bubble Reactor. During CSTR and semi-batch the lab scale ozone generator was operated near its maximum capacity, however, throughput was limited by the amount of ozone generated. Therefore, a larger ozone generator, capable of producing 15 mol/hr of O_3, was employed to further scale up the ozonolysis reaction. The minimum total gas-flow rate of the larger ozone generator was 17 L/min, compared to a 2 L/min flow rate for the lab-scale ozone generator, and thus bubbling the gas stream from the larger ozone generator is not feasible as the gas-flow rate is very high and might entrain solvent if the standard batch setup was used. Therefore, a bubble reactor was designed and constructed for the ozonolysis as the bubble column would accommodate high-rate gas flows and maximize the gas/liquid contact. In addition, the designed bubble column allowed continuous operation, ease of cleaning, and the use of PAT tools (Figure 7). The reactor is jacketed to allow temperature control, and a coarse frit is incorporated at the bottom to allow a high gas-flow rate as well as to produce fine gas bubbles in order to enhance gas−liquid contact. Three valves were connected to the side of the reactor. The bottom valve is predominately for drainage and cleaning purposes. The other two valves function as overflow valves to allow continuous operation at a constant volume.

The efficiency of the new continuous bubble reactor (CBR) in utilizing ozone at these high gas-flow rates and the feasibility of operating the bubble reactor in continuous mode were evaluated using a solution of styrene in methanol at −33 °C (lowest temperature attainable). The new ozone generator was operated with air as a feed gas and appropriate settings that would generate 11 mmol/min of ozone according to the manual,

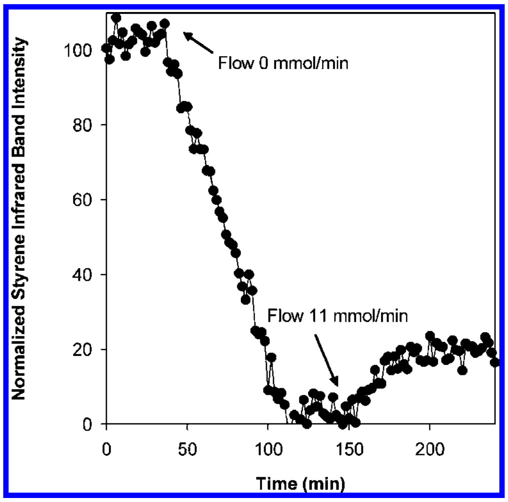

Figure 8. **Normalized styrene concentration based on FTIR band intensity inside a continuous bubble reactor.**

see Experimental Section. Upon introducing ozone, the number of moles of styrene dropped linearly at a rate of 9 mmol/min until completion (Figure 8).

The amount of styrene inside the CBR is 84.4 g (810 mmol), and at the current ozone feed of 11 mmol/min, the duration of the styrene consumption should have been 75 min, assuming 100% efficiency in ozone adsorption. The extra time required, 88 min rather than 75 min, indicated that the custom designed CBR was 85% efficient despite high gas flow rate (based on calculated O_3 production). The reactor temperature increased from −33 °C to −12 °C due to reaction exothermicity and the addition of the starting material solution at ambient temperature. The −12 °C was still below the observed onset temperature for the decomposition of ozonide observed at 42 °C DSC. By operating at higher temperatures (compared to temperatures for laboratory-scale experiments) ozone solubility is reduced, and thus CBR efficiency in absorbing ozone is also reduced. Next, continuous operation was initiated by adding styrene from the reservoir at 11 mmol/min and opening the 2-L overflow valve to allow excess reaction mixture to overflow to the quench tank. As the CBR is about 85% efficient in ozone absorption, a gradual increase in the concentration of unreacted styrene was expected. Indeed, at 150 min when the setup was operating in continuous mode, we observed the styrene concentration increase gradually until reaching a steady state of about ∼20%, indicating that ozone supply was not sufficient (Figure 8).

For ozonolysis of the substrate of interest (an isobutylene-type drug intermediate) an ozone-to-substrate ratio of 1.3 was used to compensate for the CBR inefficiency. The setup successfully operated in 9-h shifts over a 4-day period. The resulting delivery of 2.5 kg of product at a rate of about 80 g/h with 99% conversion was achieved. Inside the CBR, the steady-state level of moles of ozonide was about 950 mmol, compared to a maximum of about 24000 mmol if the reaction were to be operated in batch mode. Thus, the CBR significantly reduced the hazard associated with the reaction, allowed better temperature control by operating in smaller reactors, and allowed excellent gas−liquid mass transfer.

Safety and Precautions. The developed continuous setups in this study were successfully implemented for the substrate of interest and the model compound styrene; nevertheless, their utility should not be extended to other substrates without a careful evaluation of the thermal stabilities of the substrate and formed ozonide and the heat of reaction associated with these potentially highly energetic intermediates. In particular, the temperature in this study climbed as high as −12 °C, a temperature sufficient to induce violent decomposition of some ozonides. Two major contingencies have been considered during the large-scale ozonolysis run, namely the accidental release of toxic ozone and loss of cooling due to power failure. In terms of accidental release of ozone, the ozone generator is equipped with an ozone detector/alarm and an accessible emergency shutdown. Two additional hand-held detectors (Eco Sensors) were also utilized during the reaction to alert personnel in the event of unsafe levels of ozone. In case of power failure, the addition-controlled reaction can be safely stopped by shutting down substrate supply and/or ozone supply and draining the reactor contents into the quench pot situated in ethanol whose temperature was maintained at ∼0 °C by adding dry ice. The latter contingency scenario would result in a temperature rise of 33 °C inside the quench due to the sudden addition of reactor content.[16] To minimize any fire hazard, no flammable solvent was allowed inside the fumehood where the reaction was carried out other than that used in the reactor and quench pot. All pumps, electronics, and the feed reservoirs were kept outside the hood, and agitation was powered by pressurized air. Finally, the headspace of the CBR reactor was purged with 20 L/min of N_2 to keep oxygen concentration below the minimum oxygen concentration (MOC) for combustion of the solvents used.

Conclusion

The heat of reaction and kinetics of the ozonolysis of an alkene were investigated using computational chemistry, calorimetry, and in situ FTIR. The results demonstrated that the heat of reaction for ozone addition and the reductive quench are very exothermic. In addition, the ozonide intermediate is thermally unstable and poses a potential process safety hazard. Two flow chemistry setups were developed to reduce the severity of thermal hazards associated with this highly exothermic reaction by limiting the inventory of the unstable ozonide intermediate and by improving temperature control by carrying out the reaction in smaller reactors. This allowed ozonolysis to be used to produce larger amounts of product with less danger than that associated with standard batch equipment.

Kinetics showed that standard lab reactors offered excellent efficiency in ozone absorption and that the rate of reaction was limited by ozone supply. These reactors were retrofitted for continuous operation as CSTRs, and their performance was evaluated using the ozonolysis of styrene as a model compound. This lab-scale setup successfully produced 300 g of product in continuous mode. Finally, a continuous bubble reactor was designed to accommodate the production of 2.5 kg of product. The new setup allowed the reaction to be scaled up successfully with 85% efficiency in ozone absorption and produced the required material with 99% conversion.

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(16) The calculations assume worst-case scenarios where (1) the entire content of the bubble has converted to ozonide, (2) bubble reaction temperature of the content reaches 0 °C, and (3) no heat is removed from the quench pot due to power loss.

Experimental Section

General. All materials were obtained from commercial suppliers and were used without further purification. Experiments were conducted on various scales, ranging from 100−5000 mL using Chemglass jacketed glass vessels equipped with overhead agitators (retreat curve) and a K-type thermocouple for temperature measurements. The description of a representative experiment in each setup utilized in this study is shown below.

Reaction Calorimetry (RC1). A solution of the isobutylene drug intermediate (5 g), dichloromethane (65 g), and methanol (8 g) was charged into the 80-mL RC1 reactor equipped with a turbine agitator and an ozone generator and cooled to −45 °C. After calibration, the outlet line of the ozone generator was bubbled into the reactor for approximately 70 min. After approximately 60 min, the solution turned blue. After the ozone generator and calibration were turned off, the reactor contents were slowly heated to 0 °C over 45 min. After stabilization and calibration, DMS was added via pressure transfer over 20 min. Again after stabilization and calibration, the test was concluded. On the basis of calibration, the average heat capacity ($C_{p,r}$) and the overall heat transfer coefficient for the reactor (U_A) were found to be 1.25 J/K/g and 1.38 W/K, respectively.

Semi-Batch Mode. A solution of methanol (200 mL) was cooled to −50 °C, and a spectrum of the solvent was recorded using an FTIR fiber optic probe (ReactIRIC10 Mettler-Toledo) immersed in the liquid phase. Styrene (6 mL) was added to the reactor in two portions, and several spectra (5−10) were recorded after each addition. For the semi-batch experiments, a lab-scale ozone generator (Polymetric, Inc.) was used with the settings of 90 V and 8 psi of O_2 pressure and gas flow of 2 L/min. According to the ozone generator manual, these conditions result in converting 2.76% of the oxygen flow into ozone or 6.5 g/h (2.3 mmol/min) of ozone. Ozone was introduced to the reactor until complete consumption of the styrene was evident by FTIR. The ozone was turned off along with the chiller to allow the reactor to warm up to room temperature on its own. Then the reactor contents were quenched by adding DMS until less than 1 ppm peroxide was found using J.T. Baker “Testrips for Peroxide”.

Continuous Stirred Tank Reactor Mode (CSTR). The reservoir tank was prepared by mixing 30 g of styrene in 1.2 L of methanol. The quench reactor was attached to the overflow valve and was charged with 500 mL of methanol, 19 g of DMS. The CSTR jacket temperature was set to −50 °C while the quench solution was cooled to −1 °C under nitrogen. Methanol (200 mL) was transferred to the CSTR via a piston pump. Collection of FTIR spectra of CSTR content was initiated. Ozone was introduced until complete consumption of the styrene was evident by FTIR. The setup was operated in continuous mode by setting the pump at an appropriate flow rate and opening the overflow valve in order to allow excess liquid to overflow into the quench tank. At the end of the experiment, ozone was turned off, and the content of the CSTR was drained and manually added to the quench pot. Then DMS was added to the quench until less than 1 ppm peroxide was present.

Continuous Bubble Reactor Mode (CBR). The styrene reservoir was prepared by mixing 300 g of styrene with 5 L of methanol. The styrene reservoir was transferred to the CBR via a Teflon gear pump. FTIR spectra began to be recorded from inside the bubble reactor. The 2-L valve at the bubble column reactor was connected to the quench tank whose temperature was set to ∼0 °C. The 10-L quench reactor contained 500 mL of methanol and 257 mL of DMS. The ozone generator was operated, using 0.5 kW power, with air as a feed gas at 17 L/min and 2.5 bar pressure. According to the manual, these conditions generate 31 g/h of ozone which correspond to 11 mmol/min and was connected to the bottom of the bubble reactor. The reactor was operated in batch mode until styrene consumption in the CBR was complete. Then continuous operation was initiated by turning on the pump to 16 g/min and opening the 2-L side valve on the CBR to allow excess volume to flow into the quench tank. At the end of the experiment, ozone was turned off, and the content of the CBR was drained into the quench tank via the bottom valve of the CBR. Finally, DMS was added to the quench until less than 1 ppm peroxide was present.

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