

Measurement of Gas Flow Rates from Small-Scale Reactions

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Abstract:

The rate and total volume of noncondensable gas generation are important parameters in the safe, successful scale-up of chemical processes. Information regarding the evolution of noncondensable gas is used to (1) ensure the gas can be vented from the reactor without overpressurization, (2) calculate the concentration of flammable gases (or oxygen) to avoid creating an explosive mixture in the equipment, and (3) size the scrubber to ensure the capacity and heat removal rate are sufficient. The data are used in parallel with information regarding the heat of reaction from the desired chemistry, thermal stability of reaction mixtures/components, and an intimate knowledge of the process to analyze the risk associated with scaling up. If the level of risk is judged to be unacceptable, the analysis can be used to make rational process changes in order to reduce the risk to an acceptable level. Several techniques have been developed to study the gas hazards associated with a particular reaction. In general, these techniques suffer from at least one of two primary limitations: (1) the volume is not measured directly, causing the condition and/or composition of the gas to influence the accuracy of the measurement, or (2) the sensitivity is too low to take reliable measurements from small-scale reactions. The Pfizer Global Process Safety Network set out to develop a new device that could solve both of these problems and be used in conjunction with a microcalorimeter to provide heat of reaction data in parallel. This paper describes a new device that is used in series with a thermal mass flow meter to accomplish this goal. Detailed discussion of the error bounds on the flow rate from this device is also included.

Introduction

There are two key components for a comprehensive safety assessment of a desired chemical reaction:¹ (1) quantification of the heat output and (2) evaluation of the rate and quantity of gas evolution.² Techniques to study the gas hazards associated with the desired reaction have a long history, and include ingenious glassware devices,^{3,4} the simple U-tube (or gas burette),^{5–7} the Ritter Clock,⁸ mass spectrometry,⁹ and mass flow

meters.^{10,11} The Pfizer Global Process Safety Laboratories have aggressively pursued several continuous improvement initiatives in order to meet the challenges associated with compressed timelines and limited resources. For example, the incorporation of heat of reaction estimation techniques greatly improved our overall knowledge and efficiency without compromising safety.¹² When estimation is not appropriate, the use of a compound sparing reaction calorimeter, such as the OmniCal SuperCRC, has enabled us to maintain rapid turnaround times with small quantities (<15 mL) of material. Unfortunately, a convenient and robust device is not readily available to reliably measure gas flow rate under the desired conditions on this small scale.

Over the years we have come to rely on the use of a Ritter Clock coupled to an RC1 calorimeter to evaluate gas-evolving processes. Although this combination provides high quality calorimetry and gas flow rate in a single experiment, it is certainly not considered compound sparing or rapid. Therefore, we set out to develop a new technique that could be used in parallel with the SuperCRC, or other microcalorimeters, to reliably and efficiently provide gas flow rates and reaction calorimetry from small-scale reactions for a wide range of chemistries. This paper describes a new device that is used in series with a thermal mass flow meter to accomplish this goal. Detailed discussion of the error bounds on the flow rate from this device is also included.

Experimental Section

Reaction heats were measured using either an Omnical SuperCRC, or a Mettler Toledo RC1. The sensible heat of dosing has been removed. SuperCRC experiments: The heat flow curves have not been corrected for the cell time constant, τ , of the calorimeter. The reaction temperature was maintained isothermally by: (1) equilibrating the dose to the reaction temperature prior to injection using an injection preheating cylinder (available from Omnical). The cylinder is a brass fitting that is designed to accommodate a stainless steel needle, providing good heat transfer between the thermostatted SuperCRC block and the needle and (2) adding the dose in a

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Figure 1. Picture of the bag in a bottle device that translates all gas flow to air flow. Off-gas from the reaction flask enters the bag causing it to expand which in turn forces air out of the bottle and through the thermal mass flow meter.

controlled, linear fashion using a J-KEM syringe pump.¹³ The gas flow was measured using the device described in this report in series with an integrated thermal mass flow meter that was purchased from OmniCal. The millivolt signal from the thermal mass flow meter is displayed by the Turbo WinCRC software, and was converted to mL/min using a calibration curve. RC1 experiment: The reaction temperature was maintained isothermally by allowing the jacket temperature to fluctuate. Calibrations were performed before the addition and after reaction completion to obtain heat capacities and heat transfer coefficients. The heat flow curve was analyzed using WinRC NT version 7.11 (SR-6) with the following equation: $Q = Q_{\text{accum}} + Q_{\text{flow}} + Q_{\text{dose}}$. Heat-transfer coefficients were interpolated proportionally to virtual volume, heat capacities were interpolated proportionally to the reaction mass, and the baseline was interpolated proportionally to conversion. Total off-gas volume and rate were measured using a Ritter TG01 gas flow meter. A constant nitrogen purge rate of 16.2 mL/min was maintained, using a Matheson gas flow controller, and was subtracted from the Ritter data prior to analysis.

Results and Discussion

The use of a thermal mass flow meter for the evaluation of gas evolution hazards in batch processing was first reported by Lambert and Amery in 1987, and supplemented with several practical examples in 1992.^{10,11} Thermal mass flow meters have high sensitivity, making them well suited to measure gas flow rates in the single mL/min region.¹⁴ They are inexpensive,

simple to use, and safe. Unfortunately, the response is proportional to the heat capacity of the gas, and therefore, a different calibration curve is needed for each gas. One way around this issue is to calibrate for air or nitrogen and apply readily available correction factors to adjust the calibration curve to the gas of interest. Many chemical reactions produce gaseous mixtures whose proportions can change during the course of reaction. There is no simple way to correct a calibration curve for these situations. Furthermore, varying levels of water in the gaseous stream also affect the response factor. Highly corrosive gases present another problem for thermal mass flow meters. Even expensive Hastelloy units will eventually succumb to HCl, NO_x, and other corrosives. If a system could be designed that translated the off-gas to a single surrogate gas flow, air, these disadvantages could be eliminated. After many months of thinking about the problem and collecting ideas for potential solutions, we finally developed a simple solution that was the most promising, see Figure 1.¹⁵ A gas sampling bag is attached to the reactor vent line. The bag is in a bottle, and there is a second vent line from the bottle to the thermal mass flow meter.¹⁶ Off-gas enters the bag causing it to expand which in turn forces air out of the bottle and through the mass flow meter. All off-gas is converted to air flow which offers two distinct advantages: (1) calibration with one gas and (2) no corrosive gas enters the meter. A secondary benefit is that the gas is

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(15) The idea for the concept of using a bag in an enclosure to measure off-gassing came from a private conversation with Dr. Benoit Vanasse and Dr. Geoffrey D'Netto. They use this technique in their laboratory at Sanofi-Aventis.

(16) A bellows-type gas meter is available from Ritter that employs a deformable bellows within two twin chambers. Measurement of the gas occurs by filling and emptying these chambers which have a known, constant volume for each cycle. See www.ritter-app.com.

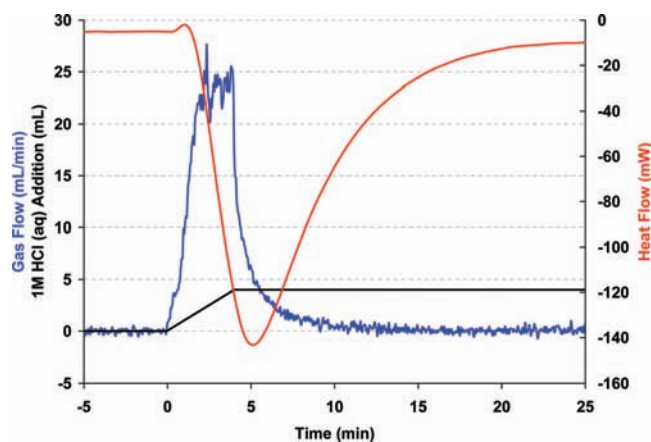


Figure 2. Gas flow (in blue) using the new device from a 4 min addition of 1 M HCl (dosing curve in black) to excess KHCO_3 . Heat flow (in red) from a SuperCRC calorimeter was collected in parallel.

conveniently contained in the gas sampling bag and can easily be analyzed for identity or concentration.

Proof of Concept: Measurement of Carbon Dioxide Off-Gas. In order to demonstrate the utility of the device, the rate of carbon dioxide off-gassing was measured from addition of 1 M aqueous HCl (4 mL, 4 mmol, 1.0 equiv) to excess aqueous 2 M KHCO_3 (5 mL, 10 mmol, 2.5 equiv) at 25 °C, see Figure 2. Heat flow data was collected in parallel by performing the reaction in a SuperCRC calorimeter. The linear addition of HCl (aq) was carried out over 4 min using a syringe pump. When the addition was started, the bag connected to the vent line began filling immediately, and the corresponding signal for gas flow began to rise. As expected, the gas flow rate is largely dose-controlled. The theoretical volume of gas from this experiment is 93.8 mL, and assuming a perfectly dose-controlled release of gas, we would expect the maximum CO_2 flow rate for the 4 min addition to be 23.5 mL/min.^{17,18} Integration of the area under the curve in Figure 2 gave a total volume of 88.7 ± 4.1 mL, and a maximum average rate of 23.6 ± 0.5 mL/min, -5.4% and $+0.4\%$ error, respectively, compared to theory. A statistical analysis of the error bounds associated with the data is discussed in the Calibration section below.

Inspection of the heat flow curve shows a small initial exotherm followed by a much larger endotherm. This is consistent with an exothermic acid–base reaction that quickly becomes endothermic due to the work being done by the expansion of CO_2 against the atmosphere. Integration of the heat flow curve gave $\Delta_r H = +16.6$ kJ/mol HCl. This is in good agreement with a heat estimation using heat of formation data which gave $\Delta_r H = +11.6$ kJ/mol HCl.¹⁹

Comparison to the Current State of the Art Ritter TG01 Gas Flow Meter. For comparison, the experiment was repeated in state of the art equipment, an 80 mL RC1 reactor with a Ritter

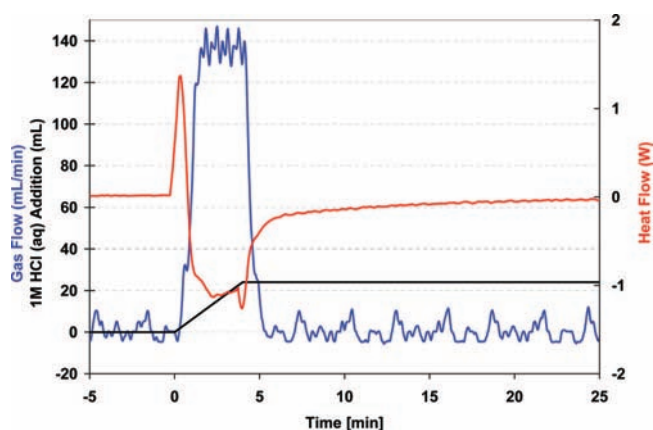


Figure 3. Gas flow (in blue) using a Ritter TG01 meter from a 4 min addition of 1 M HCl (dosing curve in black) to excess KHCO_3 . Heat flow (in red) from an 80 mL RC1 calorimeter was collected in parallel.

TG01 gas flow meter, see Figure 3. The rate of addition was identical (4 min), but the scale was 6 times larger in order to meet the minimum fill requirement of the reactor. Therefore, the theoretical volume of gas is 563 mL, and the theoretical maximum rate is 140.7 mL/min. Integration of the area under the curve in Figure 3 gave a total volume of 491 mL, and an average maximum rate of 136.6 mL/min, -12.8% and -2.9% error, respectively, compared to theory.²⁰ Therefore, the new small-scale gas flow device gave results that are slightly better than the current state of the art equipment.²¹ The Ritter flow meter works on the principle of positive volume displacement. The gas meter contains a revolving measuring drum, with four rigid chambers, and is filled with a packing liquid. The measuring drum measures volume by periodically filling and emptying the four chambers. The repetitive pattern in the baseline is normal, and is due to the filling and emptying of the chambers.

Inspection of the heat flow curve from the RC1, Figure 3, reveals a profile that is similar to that from the small-scale SuperCRC experiment, Figure 2. Integration of the heat flow curve gave $\Delta_r H = +12.9$ kJ/mol HCl. This is in good agreement with the value from the SuperCRC experiment, $\Delta_r H = +16.6$ kJ/mol, and a heat estimation using heat of formation data, $\Delta_r H = +11.6$ kJ/mol HCl.¹⁹

Measurement of a Low Gas Flow Rate Using the New Device. To determine if the new device could be used for measuring low gas flow rates, we repeated the small-scale experiment in a SuperCRC calorimeter, but extended the addition time of HCl (aq) to 40 min in order to achieve a theoretical CO_2 flow rate of 2.35 mL/min, see Figure 4. The experimental average maximum flow rate, 2.39 ± 0.23 mL/min, and total volume of evolved CO_2 , 86.4 ± 13.8 mL, were

(17) Theoretical volume = 4 mmol \times 22.4 mL/mmol \times 295/273 + 4 mL addition -7.0 mL soluble gas = 93.8 mL. Maximum theoretical CO_2 flow rate = 93.8 mL/4 min addition = 23.5 mL/min.

(18) The solubility of CO_2 in water, 25 °C, 1 atm (0.0330 mol CO_2 /kg water) was determined using the equation of state from Duan, Z.; Sun, R. *Chem. Geol.* **2003**, *193*, 257.

(19) The percentage difference is magnified because the heat of reaction is close to zero. The absolute difference is the important comparison. The absolute difference between the measurements and the estimation is very small, 1.3–5 kJ/mol.

(20) CalRix fluid was used as the packing liquid. Since CO_2 has a significant solubility in CalRix (1.2 mL of CO_2 gas/mL CalRix, the TG01 meter contains about 900 mL of CalRix), CO_2 was dissolved into the CalRix fluid up to the saturation limit prior to the experiment by running CO_2 through the meter at 43 mL/min for 2 h. The meter was reconnected to the vent line of the reactor (which had a 16.2 mL/min nitrogen purge) just prior to addition of the 1 M HCl (aq). It is unknown how much of the CO_2 was displaced by the nitrogen purge prior to and during the measurement of the CO_2 gas flow.

(21) The reported error for the TG01 meter is $\pm 0.5\%$ across the range of measurement, and the exact value for a particular meter is stated in individual calibration certificates.

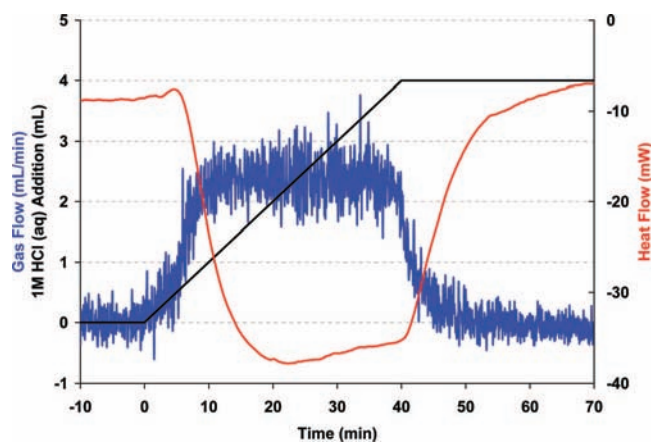


Figure 4. Gas flow (in blue) using the new device from a 40 min addition of 1 M HCl (dosing curve in black) to excess KHCO_3 . Heat flow (in red) from a SuperCRC calorimeter was collected in parallel.

in good agreement with theory, +1.7 and -7.9% error, respectively. Therefore, even at this low gas flow rate, the new small-scale gas flow device gave results that are slightly better than the current state of the art equipment.

Integration of the heat flow curve gave $\Delta_r H = +15.8$ kJ/mol HCl, consistent with the previous two experiments. A summary of the gas flow and heat flow data for the three experiments is presented in Table 1.

Calibration of the New Device Using Air. Since the thermal mass flow meter provides output in millivolts, the signal must be converted to units of rate using a calibration curve (see Supporting Information for full details regarding the calibration). Initial studies showed that this particular flow meter gave a linear response between 0 and 80 mL/min, a reasonable range for the small-scale experiments we intended to investigate. Once we had worked out the initial experimental difficulties, we designed and carried out a set of experiments to determine the error bounds for the calibration curve. The objective was to design a calibration study that estimates the linear calibration curve $y(x) = \alpha + \beta(x)$ with high precision and that accounts for as many pertinent sources of variability, as practically feasible, to be used in quantifying appropriate prediction bounds for future observations. Three calibration curves were generated while varying three factors: (1) a different operator for each curve, (2) a different bag for each curve, and (3) a wide range of dates to capture time-dependent variables such as humidity and other sources of drift in the thermal mass flow meter. The operator/bag/day combination constitutes an experimental run, and multiple calibration curves were generated within a run.

The investigated flow rates spanned 0–50 mL/min, and the experimental design originally focused on collecting data at the extreme values, due to the precision of the calibration equation being maximized.²² In addition to collecting millivolt data at those extreme flow rate levels, an intermediate level of 10 mL/min was added to the design. The addition of this midlevel flow rate actually compromises the aforementioned design optimality, albeit negligibly. However, the added benefits include checking

for any departures in linearity and the inherent scientific value that this particular flow rate has as it represents a required sensitivity limit based on the reactor with the worst-case vent rate in our pilot plant (see below).

Specifics on Data Analysis. The calibration data analysis was a weighted simple linear regression with mixed effects. The data-driven weights were included to capture changes in variance as a function of the changes in gas flow rate, as it is not uncommon to see an increase in dispersion as the response increases in magnitude. The mixed effects modeling incorporates the data structure, specifically the run-to-run and the within-run variability. SAS version 8.2 was used for all analyses.²³ More information on weighted regression with calibration data is found in Mullins,²⁴ and linear mixed effect modeling with calibration studies is referenced in Liao.²⁵ This work is a meld of both. The weights used in the regression analysis were the inverse of the observed millivolt variances at each flow rate level. This is a commonly used technique. Also, the observed standard deviations appear linearly related to flow rate through $\hat{\sigma} = 5.089 + 0.3225x$. For the weighted regression, the weights are $1/\hat{\sigma}^2$. Based on the analysis:

1. There was very little variability within run. That is, calibration curves from the same operator/bag/day combination were superimposable.

2. There was larger variation from run-to-run. That is, calibration curves from different operators were distinguishable. This run-to-run variability is largely captured through the variance component on the intercept, α , and to some degree through the slope, β .

3. The estimate calibration curve parameters are $\hat{\alpha} = 746.94$, and $\hat{\beta} = 49.01$.

4. The standard error of prediction for a future observation, $y(x_0)$, is a composite of variability in the response and variability in the calibration model, both being a function of x_0 . Once this is obtained, the lower prediction bound is written as $\hat{\alpha} + \hat{\beta}(x_0) - t_{df} SE_p(x_0)$, where $SE_p(x_0)$ is the standard error of prediction at x_0 , and t_{df} is the critical t value with corresponding degrees of freedom. Note that a lower bound on the calibration curve for $y(x_0)$ implies an upper bound on the inverse prediction, x_0 . Also, note that the upper bound on x_0 is analytically obtained by solving the equation $y(x_0) = \hat{\alpha} + \hat{\beta}(x_0) - t_{df} SE_p(x_0)$ for x_0 .

Application of the Calibration Curve: Data Handling and Reporting. When we applied the statistical models to the data from the 40 min addition of HCl to KHCO_3 , we immediately noticed that the baseline gas flow prior to addition of HCl was below zero for both the model equation and for the upper bound equation, -0.38 and -0.15 mL/min, respectively. We felt that the statistical analysis was sound, but questioned why this data set did not conform as expected. Potential reasons include: (1) the error limit is based on a 95% prediction bound, implying that 5% of the time, an event like this occurs, (2) the run-to-run sources of variability are underestimated, as only three operator/bag/day combinations were used in the study, and (3) there is a source of variability not captured in the original experiment. Our scientific intuition leads us to some blend of

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Table 1. Summary of gas flow and reaction heat data from three experiments adding HCl (aq) to excess KHCO₃ (aq)^a

experiment	theoretical average max off-gas rate (mL/min)	observed average max off-gas rate (mL/min)	% error	theoretical CO ₂ off-gas (mL)	observed CO ₂ off-gas (mL)	% error	theoretical $\Delta_r H$ (kJ/mol)	observed $\Delta_r H$ (kJ/mol)
SuperCRC, 4 min add	23.5	23.6	+0.4	93.8	88.7	-5.4	+11.6	+16.6
RC1, 4 min add	140.7	136.6	-2.9	563	491	-12.8	+11.6	+12.9
SuperCRC, 40 min add	2.35	2.39	+1.7	93.8	86.4	-7.9	+11.6	+15.8

^a The gas flow data for the SuperCRC experiments was collected using the new device described in this paper. The gas flow data for the RC1 experiment was collected using a Ritter TGO1 meter.

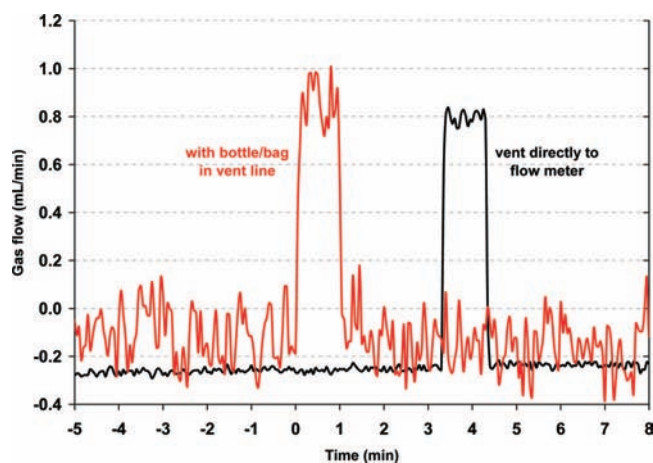


Figure 5. Signal from the thermal mass flow meter without the bottle/bag (black) and with the bottle/bag (red). The bottle/bag adds noise to the system because thermal fluctuations outside the bottle cause thermal expansion/contraction within the bottle.

(2) and (3) as the source of the inconsistency. Even though these deviations from zero are small, they can have a large effect on the determination of total volume upon integration of the rate curve. The effect becomes magnified as the flow rate decreases. We felt that correcting the baseline to zero was a practical way to ensure that the data is conservative for use in process safety analyses, without changing the structure of the error bounds. Therefore, we developed the following data handling and reporting protocol: (1) If the baseline of the model equation is below zero, we baseline correct up to zero and report the maximum rate of the baseline-corrected model with a prediction bound that is the difference between the value for the upper bound and that of the uncorrected model. The total volume is the integral values of the rate curve handled in this same manner. (2) If the baseline of the model equation is above zero, we baseline correct down to zero and report the maximum rate of the baseline-corrected model with a prediction bound that is the difference between the value for the upper bound and that of the corrected model. We do not take the prediction bound as the difference between the upper bound and the uncorrected model in this case because it is less conservative. The total volume is the integral values of the rate curve handled in this same manner.

Sources of Noise. It is interesting to note that the baseline noise level in the gas flow signal from the thermal mass flow meter increases significantly when the bottle/bag is connected in the vent line, see Figure 5. We hypothesized that thermal fluctuations outside of the bottle lead to small temperature changes inside the bottle and hence thermal expansion and

contraction of the air. Therefore, insulation of the bottle should help to reduce the noise, but it did not change significantly when the bottle was wrapped in heavy insulation or submerged in 3 L of water. We were puzzled by this result until we calculated that each noise spike represented about 48 μL , or a temperature fluctuation of only 0.014 °C. Even high-quality laboratory chillers would not be expected to significantly reduce the noise since they have thermal stabilities in the range of 0.01–0.05 °C. Another interesting effect of this thermal noise is that the use of a larger bottle leads to more noise. Given the high level of sensitivity to thermal fluctuations, it is not surprising that drafts created by the hood or simply touching the bottle with a warm hand also causes noise in the gas flow signal. Therefore, we place the bottle behind a shield in order to minimize noise. We initially thought that vibrations or resistance of the bag to expansion may contribute to the noise, but experiments ruled these out as significant sources.

Application of the Gas Flow Data to the Pilot Plant. We worked with an engineer in our pilot-plant facility in the UK to determine if the sensitivity of the device was sufficient to ensure safety upon scale up. The plant would be very concerned if an off-gassing reaction had a flow greater than 1.9 (L/min)_{gas} / L_{reactor volume} and would require process changes to avoid such high rates. For a 5 mL reaction volume the equivalent venting rate is 0.005 L \times 1.9 (L/min)_{gas} / L_{reactor volume} = 0.0095 L/min (9.5 mL/min). As demonstrated by the low flow HCl/KHCO₃ experiment above, we can easily detect a gas flow rate that is 4 times smaller than 9.5 mL/min. Note that this analysis does not consider foaming (level swell), condenser capacity, air treatment capacity, or scrubbing capacity.

Conclusions

The characterization of gas evolution has a very important place in the reactive chemicals hazard evaluation process in order to avoid pressurization and release to the environment. The use of a device that translates all gas flow to air flow has been shown to be a valid technique for low flow rates when used in series with a thermal mass flow meter. Coupling this new device with a microcalorimeter to collect heat flow data can save valuable time in today's global arena where the timelines to scale-up are compressed. The new device also conserves precious starting materials, since the average reaction volume needed to collect reliable data is about 5 mL. Efficiency, without compromising safety, can be achieved by allowing process safety professionals to make sound scientific judgment on how and when this new technique can be used.

One disadvantage of the new device is that an active nitrogen purge of the reactor is not practical since the bag will reach its maximum fill level in a relatively short period of time. For

example, a purge rate of 1 mL/min would fill the 100 mL bag in about 1.7 h. Therefore, this new technique may not work well for cryogenic reactions, or reactions that are highly sensitive to oxygen.

It should be noted that this new device is not limited to use with a thermal mass flow detector. In general, corrosive gases are a problem for many different types of gas flow detectors because the materials of construction are not sufficient to prevent damage over time. In addition, wet test meters also suffer from the fact that the gas of interest may be soluble in the packing liquid, resulting in erroneous measurements. Combination of this new device with many of these detectors could potentially overcome these problems.

We will continue to build on our knowledge, experience, and confidence in the new device as we explore other reactions. We will also search for new ways to reliably measure gas flow rates from small-scale experiments using appropriate laboratory instruments to support scale-up in our production facilities.

Acknowledgment

We gratefully acknowledge Dr. Benoit Vanasse and Dr. Geoffrey D'Netto for the concept of using a bag in an enclosure to measure gas flow. We also thank Steven J. Boucher and Li-Jen Ping for experimental assistance, Susan L. Orrill and Dr. John G. VanAlsten for helpful discussions, and Ivan Lines for calculation of the venting rates.

Supporting Information Available

Equipment set up with pictures, parts list with supplier and supplier part numbers, details regarding generation of the calibration curve, and the SAS input code. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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