Development, Validation, and Application of a Custom-Made Mini-Reaction Calorimeter for Thermal Safety Screening

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ABSTRACT: Before scaling up to production, it is of high importance to evaluate the potential of a reaction to lead to an undesired thermal degradation event. The use of a large amount of compounds is usually required for a reliable calorimetry study. In this work, we report the development of a milliliter-scale reaction calorimeter for reaction screening applications. The setup was designed using laboratory equipment and characterized and validated with routine experiments. The results were sufficiently accurate enabling us to observe trends in the measured reaction enthalpies of a family of compounds reacting with strong bases as a function of the compounds' structures.. The use of the microscale tailor-made calorimeter is considered very valuable for potentially highly energetic reactions since reaction calorimetry studies can be performed accurately and safely with small amounts of valuable materials.

KEYWORDS: *calorimeter, sulfamidate, thermal safety, micro scale, reaction calorimetry*

INTRODUCTION

Chemical process development requires significant investment of time and resources to study the safety of a reaction step prior to scale-up. Many aspects of a chemical transformation need to be understood thoroughly for risk management purposes. This includes heat released during the reaction, chemical compatibility, thermal degradation and runaway conditions.[1]

To this end, multiple instruments have been developed over years and are nowadays typically used to determine the stability and the thermal hazard of each compound, and some of them became invaluable tools for chemists. For example, differential scanning calorimetry (DSC) or thermogravimetric analysis (TGA) enable rapid assessments and provide the thermal degradation profile of the products while only using very small quantities (∼5−10 mg). The application of these methods provides important thermal information such as the melting point, boiling point, or temperature of decomposition, as well as the amounts of energy that is absorbed or released during said phenomena. This gives a first insight into the temperature limits of the process and how dangerous the reaction can potentially be. However, DSC and TGA are two techniques that analyze dry materials and are therefore not representative of the overall process as this usually involves solvents, catalysts, or salts. To be able to evaluate the risk associated with a chemical step, including the heat released in a given solvent system, reaction calorimetry studies are necessary. At a laboratory scale, there are large reaction calorimeters available, such as Mettler Toledo's EasyMax and RC1, offering the measurement to be run under similar conditions as in the final process. While these calorimeters consider various reaction parameters, such as stirring or addition of reagents, the volumes required to perform the analysis are much larger (50 mL to 2 L), creating a risk of its

own when unknown reactions with potential runaway scenarios are studied.

In this work, we present a custom-made mini-calorimeter that offers the possibility to run calorimetry studies at the sub-milliliter scale. Comparable instruments are commercially available, for example, micro-reaction calorimeter from THT[2] and advanced reactive system screening tool (ARSST) from Fauske;[3] however, their cost can be prohibitive. The prototype we present was developed to address the need in our research laboratory to perform quick and accurate reaction enthalpy screening with very small reaction volumes. In particular, we were interested in assessing how a library of molecules would react with bases of different strengths.[4] As only very limited quantities of material were available for testing and because of the extreme exotherms observed in some cases, it was necessary to develop an instrument that used sub-milliliter volumes for the reactivity screening.

MINI-CALORIMETER DESIGN

Remaining reproducible and accurate while working with much smaller volumes than in a standard calorimeter setup was the principal design challenge that we faced. To address our needs of performing multiple measures in a safe setup, the final design included (a) a double-jacketed glass test tube (max 2 mL) fitted with a rubber stopper and acting as a measurement cell; (b) a thermocouple (type K) inserted through the rubber

cap, equipped with a LabVIEW program (National Instruments, Austin TX, USA) used to record the temperature throughout the reaction; (c) a magnetic stirrer (with a submersible magnetic plate); and (d) a thermostatic water bath set at a constant temperature in order to minimize the effect of ambient temperature variations. As mentioned above, the aim was to measure the heat of reaction between two reagents, and so a syringe was used as the method of reagent addition.

This entire setup, presented in Figure 1, was built in our research laboratory with material readily available, except for
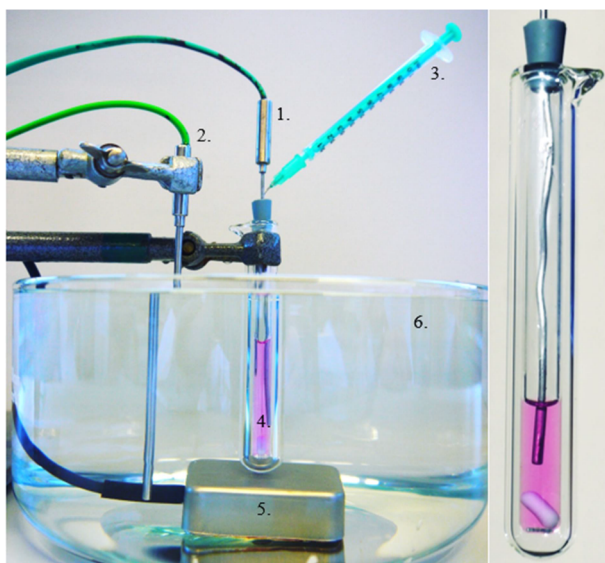

Figure 1. Setup of the mini-calorimeter used for the reactivity tests between cyclic sulfamidates and bases: double-jacketed glass vessel (4) equipped with a thermocouple (1), magnetic stirring (5), and dosing syringe (3) immersed in a thermocouple-equipped (2) thermostatic bath, and (6) a LabVIEW program, as shown in the graph.

the double-jacketed glass tube that was made specifically for the prototype. As already mentioned, such a device can be rather expensive when purchased as a standalone instrument (e.g., 30,000−60,000 USD). The cost estimation for our tailor-made mini-calorimeter is about 5000 USD with all the components bought individually, offering a rather inexpensive and competitive alternative.

■ THEORETICAL BASIS

The unit was designed and characterized such that the reaction could be performed under fully defined thermal conditions. With little energy exchange with the environment, most of the heat of reaction is accumulated in the reactor and can be calculated through the temperature rise measured by the thermocouple. To determine the reaction enthalpy, a heat balance had to be established as presented in the following list of equations.[5] The heat generated by the reaction (Q_r) can be calculated by adding the four terms representing the energy accumulated in the reaction mixture (Q_{acc}), introduced during dosing (Q_{dos}), dissipated through heat losses (Q_{loss}), and accumulated in the glass wall (Q_{wall}) (eq 1).

$$Q_r = Q_{acc} + Q_{dos} + Q_{loss} + Q_{wall} \tag{1}$$

The heat accumulated in the reaction mixture is obtained using the reaction mass, the heat capacity of the mixture, and the final and initial temperatures (eq 2):

$$Q_{acc} = m_r \cdot cp_r \cdot (T_f - T_i) \tag{2}$$

Both Q_{loss} and Q_{wall} terms include parameters that are specific to the device (eqs 3 and 4). The overall heat loss coefficient α takes into account the total heat dissipated from the calorimeter to the surroundings, and the heat capacity of the calorimeter c_w takes into account the heat accumulation in the walls of the vessel.

$$Q_{loss} = \int \alpha \cdot (T_r - T_{amb}) \tag{3}$$

$$Q_{flow} = c_w \cdot (T_f - T_i) \tag{4}$$

The dosing term (Q_{dos}) is calculated by multiplying the mass of the added reagent, its heat capacity, and the difference between the temperature of the reagent and that of the reaction mixture (eq 5):

$$Q_{dos} = m \cdot cp \cdot (T_r - T_{dos}) \tag{5}$$

Because the reagent that is added to the mixture is preheated prior addition, using in the same water bath as the calorimeter, we assume that the temperature is identical and therefore remove this term from the final equation.

Finally, the heat capacity of the final reaction mixture (cp_r) being measured for each experiment by DSC, the reaction enthalpy, and adiabatic temperature increase can be expressed as per eq 6.
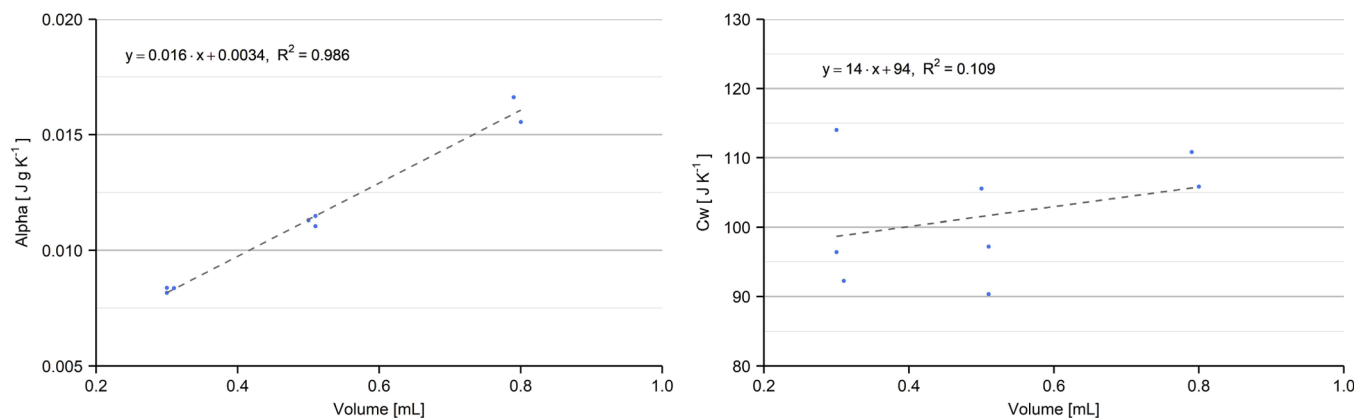

Figure 2. Characterization of mini-calorimeter—equations and results for α and c_w.

$$\Delta_r H = \frac{Q_r}{n}; \; \Delta T_{ad} = \frac{Q_r}{cp_r} \tag{6}$$

MINI-CALORIMETER DEVELOPMENT, CHARACTERIZATION, AND VALIDATION

The calorimeter was characterized by calculating the heat loss coefficient α and the heat capacity of the calorimeter c_w. The heat loss coefficient α [W/K] considers the loss of energy toward the surrounding environment, while the heat capacity c_w [J/K] of the calorimeter considers the energy required to warm up the unit to a specific temperature. The determination of c_w and α (eqs 7 and 8) was performed according to the standard protocol by introducing hot water into the reactor and waiting for the temperature to stabilize at room temperature. This characterization was performed with three different volumes of water to be able to account for the influence of the volume in the following measurements. The experiments were performed in triplicate to calculate the standard deviation and obtain more accurate values. As shown in Figure 2, α has good linearity between the three volumes tested, but the calculation for c_w seems to be less precise for small volumes, resulting in a greater deviation between the points with the smaller volume. The experiments were therefore performed using volumes between the two higher points, 0.5−0.8 mL to ensure more repeatable results.

The calibration of the device was of very high importance to ensure reliable and accurate results. The characterization of our device was validated by comparing the calculated enthalpies of the hydrolysis of acetic anhydride and of the dilution of sulfuric acid with values from the literature obtained using established methods (Table 1). In both experiments, 390 μL of water was

Table 1. Validation Experiments − Comparison between Experimental and Literature Values

	experimental value		literature value
	ΔT_{ad} (°C)	$\Delta_r H$ (kJ/mol)	$\Delta_r H$ (kJ/mol)
Ac$_2$O hydrolysis	27 °C	−54 ± 5.7	−58.6 ± 0.4[6]
H$_2$SO$_4$ dilution	44 °C	−56.8 ± 10.5	−61.8 ± 0.5[a]

[a]Values of previous EasyMax/RC1 experiments, HEIA-FR.

first placed in the mini-calorimeter, and temperature was stabilized. For the hydrolysis experiment, 90 μL (0.95 mmol) of acetic anhydride was then added instantaneously using a

syringe, while for the dilution experiment, 75 μL of sulfuric acid (1.40 mmol) was then injected. The temperature profiles for both reactions are shown in Figure 3.

Both experiments were performed in triplicate to confirm reproducibility and obtain a standard deviation that will be used during sample measurements. As shown in Table 1, the values are rather accurate although rather imprecise − the mean value is close to the reported data, but the relative standard deviation is in the order of 10−20%. In order to limit the impact of the standard deviation related to the microscale device, all further experiments were performed in triplicate to obtain a more reliable mean value.

Heat loss coefficient α [W/K]

$$\alpha = \int \frac{m \cdot cp}{(T_r - T_{amb})} \cdot \frac{dT}{dt} \tag{7}$$

Heat capacity of the calorimeter c_w [J/K]

$$c_w = \frac{m \cdot c_p (T_i - T_f) - Q_{loss}}{(T_f - T_i)} \tag{8}$$

APPLICATION IN THERMAL SAFETY SCREENING OF REACTIONS

The main objective of the study was to perform reaction screening and compare the reactivity of various compounds.[4] During the course of the project, many molecules had to be synthesized in-house; therefore, a significant advantage of the developed mini-reaction calorimeter resided in the small quantities of products (approximately 120 mg per test) required to perform all measurements. All experiments were performed following the same procedure and in triplicate, ensuring comparability and accuracy. The purpose of the screening study was to collect evidence of the influence of various substituents on the reactivity and degradation of cyclic sulfamidates. The measured enthalpies and adiabatic temperature increases are shown in Figure 4 for the compounds tested in our mini-calorimeter. Depending on the nature of the substituents on the cyclic sulfamidates, reaction enthalpies of various magnitude were expected; indeed, mostly steric and electronic effects of the substituents strongly impact the reaction enthalpy. Nevertheless, our mini-calorimeter was a successful and useful tool for the reaction screening of our library of molecules, allowing for an initial estimation of each compound's thermal potential.
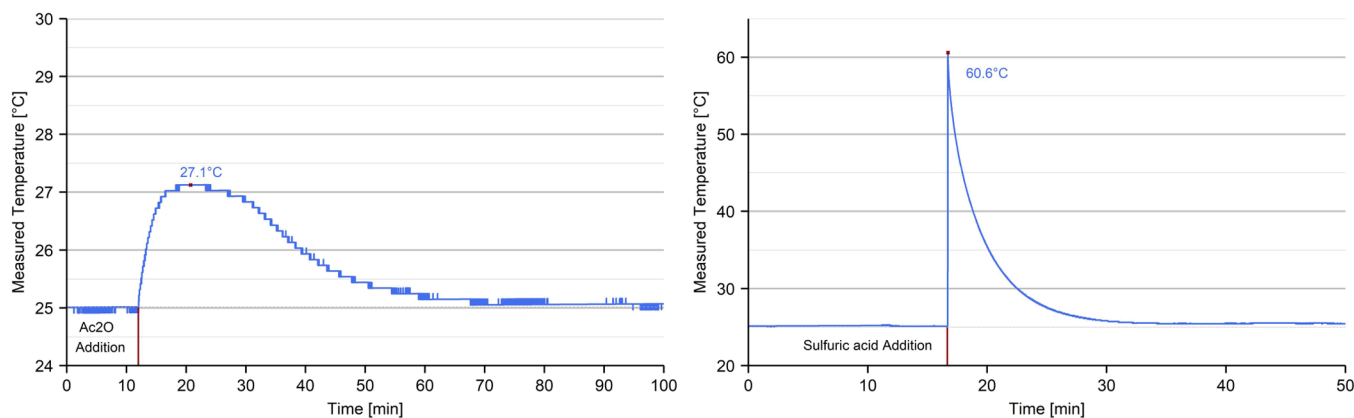

Figure 3. Temperature profiles of acetic anhydride hydrolysis and sulfuric acid dissolution.

1
$\Delta_r H = 589.9 \pm 62.8$ kJ//kg
$\Delta T_{ad} = 39.0 \pm 4.0$ K

2
$\Delta_r H = 320.5 \pm 16.7$ kJ//kg
$\Delta T_{ad} = 32.8 \pm 1.9$ K

33
$\Delta_r H = 274.0 \pm 13.7$ kJ//kg
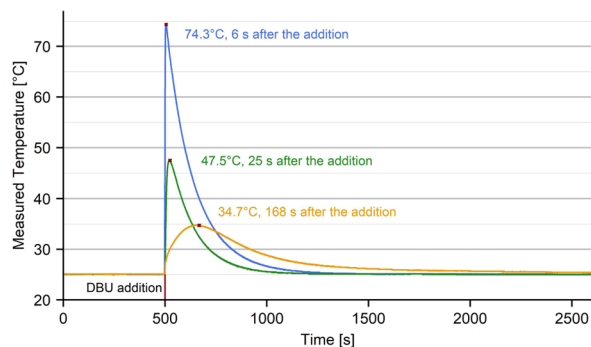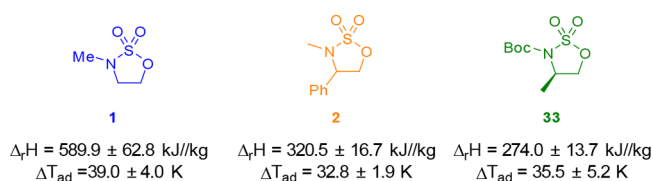$\Delta T_{ad} = 35.5 \pm 5.2$ K

Figure 4. Temperature profile of cyclic sulfamidate **1** (blue), **2** (orange), and **33** (green) measured in the mini-calorimeter (in acetonitrile as a 50% (m/m) solution and an excess amount of DBU (solution 50% (m/m) in acetonitrile) is added in one go using the syringe).

CONCLUSIONS AND OUTLOOK

In this work, we present the possibility of building a simple setup to perform reactivity screening in a research laboratory at the sub-milliliter volume scale. The prototype can be easily built at a relatively moderate cost and used to measure the heat flow profiles of potentially highly exothermic reactions. The mini-calorimeter was successfully characterized and validated with known reactions: acetic anhydride hydrolysis and sulfuric acid dilution. Following characterization, reaction enthalpy analysis of cyclic sulfamidates on a 100 mg scale was carried out. The application of the micro-calorimeter for the thermal assessment of highly active compounds was proved to be safe and very straightforward. The accuracy of the results relies on a proper characterization of the reactor with the reaction solvent, as well as working within the characterized volume of 0.5−0.8 mL. An average error of 12% on the enthalpy was reported, which is certainly higher compared to commercial calorimeters. However, our approach offers a significant advantage for a research laboratory, where products are often synthesized in small quantities. The results are sufficiently accurate to allow comparison between different compounds and reactions and might be applied in reaction screening. As demonstrated with the application described above, the mini-calorimeter allows researchers to process thermal safety assessment in a fast, safe, and economical manner.

EXPERIMENTAL SECTION

General Information. All solvents and reagents used were of bulk quality.

Analytics. DSC was measured with a Mettler Toledo DSC2 STARe System, weighing ~10 mg of the reaction mixture in aluminum crucibles (40 μL) and following an isotherm and ramping program between 30 and 40 °C, with a heating rate of 10 °C per minute under a nitrogen atmosphere (80 mL/min).

Chemicals. All chemicals used in this work were purchased from common suppliers and used without further purification.

The compounds for the reactivity tests were synthesized in-house.[4]

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.2c00128.

> Experimental procedures; reactor construction scheme and list of materials; and reactor characterization and validation data (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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