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Reaction Calorimetry in Microreactor Environments – Measuring Heat of Reaction by Isothermal Heat Flux Calorimetry

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TOC Graphic

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Abstract

A novel set-up to analyze the heat of reaction of different single- and multiphase reactions carried out in continuous flow is presented. The measurement principle of the calorimetric system is based on true heat flow measurements and therefore ensures precise calorimetric data within 10 mW resolution. In addition to the investigation of simple mixing phenomena (ethylene glycol and water) a number of exothermic, industrially relevant chemical transformations including the nitration of phenol, the reduction of nitrobenzene, as well as several oxidation and reduction processes, were investigated as model systems. For these experiments a commercially available batch calorimeter (ChemiSens CPA202) was equipped with a glass static mixer (250 μ L) optionally connected to a tubular microreactor (PFA coil) allowing overall reaction volumes of up to ca. 5.5 mL. Experiments were performed by feeding individual streams with syringe pumps (alternatively substituting one liquid feed with a gaseous feed controlled by a mass flow controller) and mixing the feeds inside the glass static mixer contained in the thermostated reactor zone of the calorimeter. By adjusting the residence time, volume and flow rates, chemical transformations were driven to full conversion in order to obtain meaningful calorimetric data. A comparison with literature data indicates that the calorimetric flow system described herein provides comparable data to those obtained by standard batch calorimetry.

Keywords: Continuous Flow Synthesis, Heat Flow, Microreactor Technology, Multiphase Reactions, Reaction Calorimetry

Introduction

During the last two decades continuous flow chemistry has become increasingly popular in the field of organic synthesis.^{1,2} The advantages of this enabling technology are also progressively appreciated by the pharmaceutical industry and thus a growing number of scientists from research and academia to process chemists and chemical engineers in industry are now employing continuous flow technologies. The small internal volume of microreactors and their high surface area-to-volume ratios enhance mass and heat transfer, resulting in rapid mixing, enabling precise control over the reaction parameters, increasing overall process efficiency and safety.^{1,2} Furthermore, microreaction technology enables chemical transformations to be executed under conditions that are impractical or virtually impossible to perform using traditional batch conditions.^{1,2}

Despite all of the mentioned benefits of flow technology, there is still a need to obtain accurate thermal data for chemical reactions as a basis for appropriate reactor design for both laboratory and industrial scale applications. Chemical transformations are often accompanied by a significant heat release and must therefore be thoroughly understood to allow safe processing on industrial scale. In that aspect reaction calorimetry can be considered as powerful tool for providing information about the enthalpy of a reaction, heat capacity of the reaction mixture and activation energy.³ These parameters are of significant importance in order to obtain a fundamental understanding of the reaction behavior and kinetics.³ Currently, such calorimetric data are generally obtained in batch or semi-batch mode, using standard batch calorimeters such as the RC1 from Mettler Toledo and related instrumentation.⁴ This approach suffers from the fact that a comparatively large test volume (0.3 to 2 L) is typically required, which not only poses a severe safety hazard for fast and exothermic reactions (adequate control of temperature an mixing), but also limits the exploration of critical process parameters.⁴

In recent years, there has been growing interest in obtaining calorimetry data under continuous flow conditions, mainly using microstructured devices. Apart from numerous applications in biochemical research in the area of high throughput screening of drug-enzyme binding and the analysis of enzymatic reactions,⁵ seminal contributions to the field of process chemistry have been made by the Frauenhofer Institute for Chemical Technology (ICT) in Germany.⁶ The calorimetric device developed by ICT consists of a glass microreactor embedded between thermoelectric modules (so-called Seebeck elements) acting as direct heat-flow sensors allowing fast screening as well as determining the thermokinetic characteristics of chemical reactions.⁶

With the increase in popularity and use of flow technology from academic research institutions to process chemists, there is a growing need for measurement systems that allow the direct analysis of thermochemical behavior of chemical transformations inside flow (micro)reactors in real time. We herein present an experimental set-up that is able to generate real time reaction calorimetry data (Heats of Reaction) under continuous flow conditions employing microreaction technology. Key to the set-up is the use of a precision batch reaction calorimeter (ChemiSens CPA202) equipped with a glass static mixer (micromixer) and/or a coiled tubular reactor, to investigate the heat of reaction of chemical transformations carried out in continuous flow mode. Starting with the evaluation of simple mixing experiments,⁷ the focus of this work was to determine the heat of the reaction of several industrially important exothermic transformations involving both single- and multiphase systems, including liquid-liquid and gas-liquid chemistry.

Results and Discussion

ChemiSens CPA202 Reaction Calorimeter.⁸ The ChemiSens CPA, or Chemical Process Analyzer, is a pre-calibrated high-precision calorimeter for analyzing chemical processes. The absolute heat production from the process is presented on-line in real time without subjective interpretations of calibration pulses or unknown baselines. The main part of the CPA system is the reactor (250 mL volume) operating from -50 °C to 200 °C and up to 20 bar pressure with power resolution to 10 mW and glass sidewalls so the reaction mixture can be directly observed. Stirring is controlled (and variable) between 50 and 2000 rpm with a variety of impeller designs and a baffle insert. During operation the reactor is positioned in a precisely controlled thermostatic bath, which also acts as a safety shield. The CPA202 works on a unique principle called "True Heat Flow". The heat flow from the reaction process is directly measured using a constant-area thermopile comprised of hundreds of temperature sensors. This "True Heat Flow transducer" is pre-calibrated with all of the heat flow occurring at the well-defined bottom of the reactor (the rest of the reactor being insulated and immersed in the thermostatic bath, thus minimizing heat losses). Unlike other reaction calorimeters, the measured heat flow is not sensitive to changes in heat transfer coefficient or wetted heat transfer area. This means that evolved (or consumed) power is directly available on-line without any calibration or post processing. The temperature of the process reactants is controlled using a Peltier element which acts as a reversible heat pump to transfer heat to (or from) the thermostating liquid that is maintained at the same temperature as the process reactants. The True Heat Flow transducer is sandwiched between the Peltier element and the

bottom of the reactor vessel. The 13 L volume of the thermostatic bath surrounds the reactor, providing a large heat sink. The reactant volume in batch operation is typically in the range from 10 to 180 mL, substantially smaller than most traditional reaction calorimeters. In the circumstance of non-isothermal behavior, however, the True Heat Flow must be corrected by the accumulated heat that has either entered or left the reaction mass requiring knowledge of the reaction mass heat capacity and temperature change to do so.

Continuous Flow Calorimeter Setup. For the calorimetric measurements the ChemiSens CPA202 system was modified for continuous operation by placing either a glass static mixer or a T-mixer in combination with a tubular reactor inside the thermostated reactor zone. An image of the internal arrangements in the reactor zone of the calorimeter is shown in Figure 1. A schematic view of the setup for the calorimetric analyses is shown in Figure 2. Feeding of the liquids streams was performed using Syrdos dosing pumps from HiTEC Zang. For the control of the gas flow, a mass flow controller (MFC) was used (Bronkhorst) with a fixed value back pressure. Depending on the reaction conditions (gas development during reaction or reaction temperature higher than the atmospheric boiling point of the solvent) back pressure regulators (BPR) of up to 7 bar were applied. For the gas-liquid reactions we found that two BPRs connected in series with the algebraic sum of the nominal values of each BPR reduced the BPR-induced noise in the measured calorimetric signal, compared to using only one BPR of the double value. With two BPRs the noise in the signal was effectively reduced by up to 50%, thus allowing the recording of a more accurate signal. For reactions involving gases and one liquid feed a simple T-mixer was used, while for the experiments with two liquid feeds a glass static mixer was implemented in the setup. This microchip includes a micromixer with two inputs and one output with 250 μ L of overall residence volume. After the chip an additional residence time coil made out of perfluoroalkoxy polymer (PFA) with an outer diameter of 1.8 mm and inner diameter of 0.8 mm was added in order to increase residence time volume up to ca. 5.5 mL and thus to ensure that the investigated chemical transformations reached complete conversion.



Figure 1. Left: Overview of ChemiSens reaction chamber; middle: schematic view of microreactor and residence time coil setup, right: image of microreactor and residence time coil.



Figure 2. Setup for calorimetric measurements in the ChemiSens CPA202 calorimeter in continuous flow mode. The magnified heat flow sensor depicts the principle of operation where T2 is the temperature inside the reactor and T1 is the temperature of the thermostatic bath. 200 Seebeck elements are arranged in a cone shape and the temperature difference T2-T1 is measured across the Seebeck elements as the true heat flow.

Data Collection and Evaluation. The CPA202 calorimeter, owing to its large thermostatic bath, allows for preheating of the reactions feeds before entering into the reactor. For our experiments we decided to pump the reaction feeds (at room temperature) directly into the heated microreactor set-up thermostated at 50-130 °C without temperature pre-equilibration. This required the subsequent measurement of reference experiments where typically only "non-reacting" mixtures/solvents (i.e. without catalyst or reaction partner) were pumped through the system, thereby taking the "cooling" effect on the calorimeter into account. All of the experiments were performed in isothermal mode taking advantage of the long-term temperature stability of the thermostatic bath and the calorimetric system.

Calculations of Heat of Reaction were performed according to Eq 1 where H is the reaction enthalpy, P is the power in Watt obtained from the instrument (as the data output from the ChemiCall software), f is the flow rate in mL/s and c is the molar concentration of the limiting reactant in mol/mL. The power data from the instrument were obtained by averaging data from a linear region (or steady state of operation) with a minimum of 150 data points. In order to obtain meaningful calorimetric data power values were obtained for both the chemical reaction and for the "cooling" effect of the reaction mixture, which were subsequently subtracted in order to obtain the power value for the reaction only. These values were then used for the calculations.

$$H = \frac{P}{f \times c} = \left[\frac{\frac{J}{s}}{\frac{mL}{s} \times \frac{mol}{mL}} = \frac{\frac{J}{s}}{\frac{mol}{s}} = \frac{J}{mol}\right]$$
Eq. 1

What is actually being measured in the flow experiment is a "total heat flow." This total heat flow is a combination of the steady state enthalpy of reaction (per time) for the specific chemical transformation taking place (bond breaking/bond making) plus a variety of physical effects (heats of mixing of solvents, sensible heat effects due to streams of different temperatures, etc., per time) that occur simultaneously upon combining the streams. A series of reference experiments attempt to correct for some of these physical effects. A "heat of reaction" is then derived from the corrected steady state total heat flow, the flow rate and concentration of the streams and serves as the basis of comparison to previous work.

It has to be kept in mind that for a flow system, the "total heat flow" is what ultimately must be handled by the cooling system. Of the three contributions to total heat flow mentioned above (enthalpy of reaction, heat of mixing, sensible heat), in a real flow reactor system only the temperature of the streams (sensible heat) may be manipulated to help with heat transfer challenges (intentionally precooling a stream for example).

Mixing Experiments: Ethylene Glycol-Water. Mixing experiments in continuous flow mode are often performed in order to evaluate the performance of micromixing devices.⁹ The heat of formation of 1:1 ethylene glycol (EG) in water is -456.1 kJ/mol and that for pure EG is -454.8 kJ/mol. This suggests that the heat of mixing to make 1:1 EG:water would be -1.3 kJ/mol.¹⁰ In our initial experiments we wanted to compare the measured mixing enthalpy data for ethylene glycol and water obtained in the 250 µL glass static mixer with the values previously reported by Greiner and coworkers utilizing different micromixers but a similar general experimental set-up involving the ChemiSens CPA202 calorimeter.⁷ For the mixing experiment a setup using only the glass static mixer with an internal volume of 250 µL was used. Ethylene glycol and water with flow rates of 0.900 mL/min and 0.300 mL/min, respectively, were chosen in order to obtain the desired 1:1 molar ratio of liquids. The mixing was conducted at 60 °C in order to be well above room temperature for the thermostatic bath of the calorimeter and the cooling system to retain the temperature as stable as possible. In order to subtract the cooling effect of the mixing, a mixture of ethylene glycol and water was prepared and left overnight at room temperature; the mixture was then pumped through the system with a flow rate of 1.20 mL/min. An enthalpy of mixing of -1.19 kJ/mol was obtained which is in good agreement with the theoretically calculated value of -1.3 kJ/mol (diluting pure EG to 1:1 mole ratio in water) (Figure 3).¹⁰



Figure 3. Data obtained for the mixing of ethylene glycol (EG) and water. Before event point 1 there was no flow, providing the baseline of the experiment. Event point 1 represents both EG and water fed separately and mixed; event point 2 presents feeding of a pre-prepared mixture of EG and water, and event point 3 represents the stop of the flow. The appropriate power value was obtained by extracting data between point 1 and 2 and then subtracting the value of the cooling effect.

Reaction Calorimetry in Continuous Flow. In order to test our setup for the determination of the heat of reactions for chemical transformations carried out in flow mode, we first started with a simple model reaction, the hydrolysis of acetic anhydride with aqueous HCl, in order to compare the accuracy of the obtained data with literature values. We then moved to industrially more relevant reactions including single- and multiphase processes. All chemical transformations were previously developed (mainly in our laboratories) for continuous processing and (if necessary) the conditions were slightly modified in order to allow processing in the ChemiSens reactor.

Hydrolysis of Acetic Anhydride. The acid-catalyzed hydrolysis of acetic anhydride is often used as calibration reaction for calorimetric systems¹¹ and was therefore also selected for evaluating the performance and accuracy of the ChemiSens CPA202 flow system described above. The reaction was performed in the 250 μ L glass static mixer (Dolomite microreactor). Before investigating the actual reaction, a mixture of acetic anhydride (neat) and 5 M aqueous HCl was prepared and left overnight to react and reach the same temperature as the reactants. The pre-prepared mixture was subsequently pumped with a flow rate of 1.50 mL/min through the set-up in order to determine the cooling effect of the reaction mixture. The data obtained by this experiment were used for the calculation of the real Δ H_r without the need for calculating c_p of the reaction mixture. After the cooling effect experiment, reactants were pumped separately with a total flow rate of 1.50 mL/min (0.500 mL/min Ac₂O and 1.00 mL/min of 5M HCl) at 60 °C. With the obtained data a Δ H_r with a value of -179 kJ/mol) was calculated, which compares well with a literature value of -174.32 kJ/mol.¹² The result obtained in these experiments is somewhat higher because of the use of concentrated hydrochloric (5M) acid in order to obtain complete hydrolysis in such short residence time.

Nitration of Phenol. The procedure for the nitration of phenol with concentrated HNO₃ was adopted from the method reported by Durcy and Roberge¹³ with some modifications owing to the formation of solids and/or polymers (Scheme 1). These authors have studied the nitration of phenol by both batch and flow calorimetry using the RC1 calorimeter from Mettler Toledo.¹³ Despite the similar setup the results are not comparable since in our experiments a much larger molar excess of HNO₃ was leading to a higher proportion of dinitrated products.

Scheme 1. Nitration of Phenol Leading to Mono and Dinitrated Products.



ACS Paragon Plus Environment

The reaction setup included two pumps to transport the two feeds. One feed was the substrate solution that consisted of 23 wt% phenol dissolved in 71 wt% water and 6 wt% acetic acid (acetic acid was used to increase the solubility of the phenol in water). The second feed was 65 wt% (concentrated) nitric acid. Feeds were pumped with flow rates of 0.2 mL/min and 0.6 mL/min, respectively, producing a molar ratio of HNO₃ to phenol of 20:1. A PFA residence coil with 5.2 mL internal volume was used as reactor, the two feed streams were mixed in a standard T mixer, and a BPR with a nominal value of 7 bar. Because of gas evolution during the reaction the experimentally determined overall residence time of 6.5 min was slightly shorter than the one calculated from the nominal flow rates. According to HPLC analysis the major product formed was 2,4-dinitrophenol (92.5%), along with 2-nitrophenol (1.4%) and 4-nitrophenol (0.5%). In addition, trace amounts of higher substituted nitrophenols, unreacted phenol and polymers were obtained (total of 5.7%).

Two additional experiments were performed, the first one in order to determine the heat of dilution of nitric acid in water. For that purpose the first feed was concentrated nitric acid and second feed was distilled water. The flow rates were the same as in the nitration experiment. The second experiment was to determine the cooling effect, or rather the c_p , of the reaction mixture. Here the first feed was distilled water and the second was a solution of phenol in water and acetic acid. Again, flow rates were the same as in the nitration experiment. From all three sets of experiments the collected data were used to calculate a ΔH_r value. Calculation was performed using the equation 1 with the difference that in this case three values for power were obtained: power for the nitration (P1), power for dilution of nitric acid (P2) and power for the cooling experiment, c_p of the reaction mixture (P3). The overall value for power (P_F) vas obtained in following manner: $P_F = P_1 - P_2 - P_3$. With the final value of P_F and equation 1. ΔH_r was calculated to be -121kJ/mol for this particular nitration reaction. Somewhat similar results were previously obtained for the nitration of other aromatic compounds (i.e.,110 kJ/mol for the nitration of toluene, and 120 kJ/mol for the nitration of 3,4 disubstituted ethyl benzoate).^{6,14}

Reduction of Aromatic Nitrogroups by Hydrazine. The reduction of a nitro group is a very popular conversion in order to obtain amine functionalities, which are important in pharmaceutical applications. We have recently described a continuous flow procedure that allows the selective reduction of aromatic nitro groups employing hydrazine hydrate as reductant and in-situ formed Fe₃O₄ nanoparticles as catalyst (Scheme 2).¹⁵ This highly exothermic protocol can be performed safely using continuous flow technology within a few minutes at temperatures of 150 °C.¹⁵ For the current study nitrobenzene was selected as

substrate. The reaction mixture as one single feed was composed of nitrobenzene (30 mmol, 1 mol/L), hydrazine hydrate (1.2 equiv, 36 mmol) and 0.5 mol% Fe(acac)₃ as precursor for the iron oxide nanoparticles catalyst. The reaction was conducted at 125°C with a 1.00 mL/min flow rate of the single liquid feed employing a PFA coil of 5.2 mL affording a total residence time of 5.2 min. For this transformation it was necessary to use a BPR with a nominal pressure of 7 bar in order to keep the reaction mixture in the liquid state and to account for the development of gaseous nitrogen. Under these reaction conditions a conversion of 99% could be achieved according to GC-MS analysis. Additionally, cooling experiments were carried out to determine the cooling effect of the reaction mixture. These experiments were conducted in the same way as the main reaction but without any substrate (Figure 4). From the obtained experimental data ΔH_r was calculated to be -218kJ/mol.





Figure 4. Data obtained for the reduction of nitrobenzene with hydrazine hydrate and Fe_3O_4 nanocatalyst. The region before event point 3 represents flowing a solution of the substrate and hydrazine in methanol without the $Fe(acac)_3$ pre-catalyst through the calorimeter providing the "cooling" effect value. Event point 3 represents the start of flow of the reaction mixture with 0.5% Fe(acac)_3. Subtracting the cooling effect value from reaction value provides the heat of reaction.

Oxidation of Alcohols. The oxidation of alcohols using hydrogen peroxide as oxidant and tungsten-based catalysts enjoys great popularity in the synthetic community as it can be considered as a waste-free and green method, avoiding the use of stoichiometric (metal-based oxidants).¹⁶ For the current evaluation racemic 1-phenyl-1-propanol was used as a substrate, 25% H₂O₂ solution as oxidant and sodium tungstate (1.0 mol%) as catalyst (Scheme 3). Since 1-phenyl-1-propanol is not soluble in water, methyl trioctyl ammonium hydrogen sulfate was used as phase transfer catalyst (PTC).

Scheme 3. Oxidation of 1-Phenyl-1-Propanol with Hydrogen Peroxide. a) Oxidation of 1-Phenyl-1-Propanol with Hydrogen Peroxide. b) Decomposition of hydrogen peroxide with sodium tungstate



The chosen reaction temperature was 130°C and a reaction setup with two liquid feeds was used. Feed 1 consisted of 1-phenyl-1-propanol with 1 mol% of PTC and was pumped with a flow rate of 0.100 mL/min, the second feed was 25 wt% solution of hydrogen peroxide with 1 mol% of sodium tungstate dihydrate. The flow rate was set to 0.476 mL/min, providing a molar ratio of 4.4:1 (H₂O₂/substrate). The oxidation was performed in the glass static mixer with an internal volume of 250 μ L in addition to a 2.36 mL PFA residence time coil attached to it, providing a total volume of 2.61 mL and a thus a residence time of 4.53 min. After the reaction coil, outside of the calorimeter, a BPR with 7 bar nominal pressure was used. At the end of the reaction, the formation of the ketone product was confirmed by GC-MS and HPLC analysis (92.3%, area% at 215 nm). In order to determine the Δ H_r of the reaction, we conducted again the cooling effect experiment where the flow rates were the same as in original experiment. The only difference was the absence of any catalyst and PTC. For this experiment, the conversion was confirmed to be 0% by HPLC and GC-MS. A Δ H_r value of - 245kJ/mol was calculated for the oxidation reaction.

Olefin Reductions Using Diimide. We recently have reported the highly selective reduction of olefins to alkanes using in-situ generated diimide (HN=NH) under continuous flow

conditions.¹⁷ In this process the diimide is generated at elevated temperature and pressure directly from hydrazine hydrate and pure oxygen in a catalyst-free procedure. At temperatures of 100-120 °C selective olefin reductions can be obtained within minutes. This protocol has proven to be very useful in the context of API manufacturing, i.e., for the selective reduction of artemisinic acid¹⁸ and thebaine.¹⁹ For the current evaluation of this intensified gas-liquid reaction system allylbenzene was used as substrate. The reaction was performed in the glass static mixer (internal volume of 250 μ L) in addition to a 5.2 mL PFA residence time coil attached to it, providing a total volume of 5.45 mL and a thus a residence time of ca. 2.5 min. The reaction procedure was slightly modified by increasing the concentration of hydrazine hydrate from 4 to 6 equiv. The flow rate of oxygen was increased from 2.00 mL/min to 4.00 mL/min (6.0 equiv). Allylbenzene was dissolved in 1-propanol (10.4 mol/L) and the temperature inside the reactor was 100°C. Compared to our original protocol¹⁷ the amount of hydrazine hydrate and oxygen was increased in order to drive the reaction to complete conversion in desired residence volume. The liquid feed was pumped with a flow rate of 0.400 mL/min and the oxygen feed at 4.00 mL/min. Since a noisy signal was obtained with only one BPR due to the opening and closing of the BPR, two 7 bar BPRs were used yielding total of 14 bar backpressure (see above). For this reaction, cooling experiments were performed with 1-propanol and hydrazine hydrate without the substrate allylbenzene. The flow rates of the liquid feed and oxygen were the same as in the main experiment. The cooling experiment has been performed in order to cancel out any effect of undissolved oxygen and the formation of diimide during the reaction. The effect of the large amount of undissolved nitrogen is only on the flow pattern of the reaction mixture which by employing two BPRs can be minimized to not affect the calculations. Under the conditions described above conversion to product was confirmed to be 99% by GC-MS. A ΔH_r value of -501kJ/mol was calculated for this gas-liquid process.

Scheme 4. Reduction of Allylbenzene with In-Situ Generated Diimide. A) reduction of allylbenzene with diimide. b) Generation of diimide from hydrazine and molecular oxygen.



Conclusion

The commercially available calorimeter system ChemiSens CPA202, equipped with a glass static micromixer and a tubular reactor, was successfully tested for the investigation of exothermic reactions in continuous flow. With this novel set-up the heat of reaction can be derived from the measured total heat flow under continuous flow conditions in a safe manner. The tested model reactions included industrial relevant applications including single- and multiphase reactions. However, it should be emphasized that the results presented herein were obtained under conditions optimized for continuous flow processing. This typically means realization of reaction times (residence times) that are in the order of a few minutes, generally achieved by processing at elevated temperatures and/or using a larger excess of reagent(s). These data are therefore not necessarily comparable with those obtained by standard batch calorimetry using the RC1 or related calorimeters. In addition, flow processing involving gases as reagents or products in microstructured environments induces specific flow regimes, i.e. segmented flow patterns. In order to minimize the influence of these effects on the flow rate back-pressure regulators (BPRs) need to be employed. In this way the influence on the calculation of calorimetric data can be reduced and valid data can be generated.

In summary, the novel set-up described herein proves to be a very attractive alternative to existing calorimetric systems, especially for microreaction applications in flow. Future efforts will take advantage of temperature pre-equilibration so as to simplify the experimental protocol to not have to run reference experiments to account for the "cooling" effect. In this manner, the evaluation of the thermochemistry will be less complex.

Experimental Section

General. ¹H-NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, GC-MS spectra were recorded using a Thermo Focus GC coupled with a Thermo DSQ II (EI, 70 eV). A HP5-MS column (30 m \times 0.250 mm \times 0.025 µm) was used with Helium as carrier gas (1 mL min⁻¹ constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C the temperature was increased in 25 °C min⁻¹ steps up to 300 °C and kept at 300 °C for 4 minutes. Analytical HPLC (Shimadzu LC20, diode array detector) analysis was carried out using a C18 reversed-phase (RP) analytical column (150 \times 4.6 mm, particle size 5 μ m) at 25 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1 % TFA) and B (MeCN + 0.1 % TFA) at a flow rate of 1.0 mL min⁻¹. The following gradient was applied: linear increase from solution 30% B to 100 % B in 8 min, hold at 100% solution B for 2 min. Melting points were determined on a StuartTM SMP3 melting point apparatus. Reagents and solvents were purchased from commercial sources and were used without further purification. Conversion of starting materials and the amount of product were determined by GC-MS and/or HPLC at wavelength of 215 nm (unless otherwise mentioned).

Continuous Flow Calorimetry. The experimental setup consisted of the ChemiSens CPA202 calorimeter⁸ and a Huber 240 mini cryostat connected to the calorimeter as the source of cooling liquid. The cooling liquid inside the cryostat was Galden HT200 thermoliquid cooled to 20°C and circulated through the calorimeters thermostatic bath. The liquid for the thermostatic bath of the calorimeter was diethylene glycol (>99%) kept at 50-130 °C depending on the specific experiment. Inside the thermostatic bath the reactor was reactor filled with Galden HT200 thermoliquid. The flow reactor set-up either consisted of a 250µL glass static mixer with three inputs (one blocked) and one output (Dolomite, 250µL inner volume), or a standard PTFE T-mixer, optionally connected to a residence volume coil (2.36 - 5.20 mL) made from fluoropolymer tubing (PFA, 1/16" o.d., 0.8 mm i.d.) (Figures 1 and 2, the detailed set-up for each of the experiments is given in the Supporting Information). SyrDos dosing pumps (1 mL syringe volume, HiTEC Zang) were used for liquid feeds, and oxygen gas from a gas cylinder (5.0) was fed into the system via a calibrated mass flow controller (Bronkhorst). The stirrer speed in the reactor was 500 rpm for all experiments and the data were collected with the ChemiCall v2 program via a connected laptop. All the experiments including the cooling experiments were run for a minimum of 30 min in order to achieve steady state operation and to extract a sufficient amount of data for the analysis. This

required ca. 30 mmol of reagent owing to the high sensitivity of the instrument. The specifics of each experiment are described in the Supporting Information.

Supporting Information

Diagrams of the obtained data for calorimetric experiments, additional experimental information and supplementary figures.

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