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Streamlining Process R&D Using Multidimensional Analytical Technology

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Abstract:

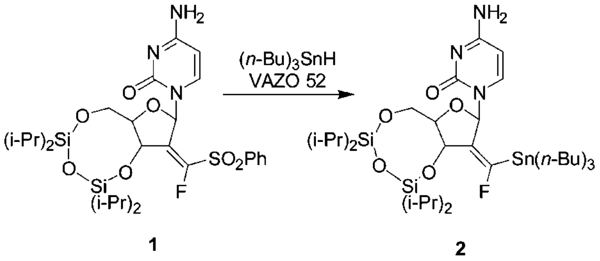
The combination of multidimensional analytical technology to form a single *n*th-order analyzer can produce reaction process data more efficiently and may provide data that are inaccessible using conventional techniques. A 3rd-order analyzer was assembled utilizing a Mettler RC1 calorimeter, Applied systems, Inc. ReactIR and Hewlett-Packard 5971A mass selective detector. The 3rd-order analyzer was utilized to simultaneously perform reaction calorimetry, in situ infrared spectroscopy, and in situ mass spectrometry on the conversion of a vinyl sulfone to a vinyl tributylstannane. The goal of complete material and energy balance, coupled with knowledge of scale-up issues, was achieved in a single experiment and in real time.

Introduction

Taking a product candidate from discovery to market is a multistep process that may typically take between 3 and 12 years. To make timely and informed decisions regarding taking the candidate from one process step to the next, the decision-maker relies heavily on data from such diverse sources as the marketplace, the government, and the company's technical base. The responsibility of the technical base is to provide high-quality data as quickly as possible so that the best possible decisions can be made in the most timely manner. For the manufacturing technical base, material and energy balance data, as well as reaction thermodynamics and kinetic data, are frequently required. In addition, high-quality data are required for considerations that include reactive chemical hazard evaluation, environmental emissions, waste handling, reaction efficiency, reaction pathways, and identification of side reactions and byproducts. In Dow's Custom and Fine Chemicals Services the goals are to streamline the Research and Development process, and to provide a complete set of data for process modeling and scale-up in as few experiments as possible.

To promote a better understanding of the conversion of the vinyl sulfone **1** to the vinyl tributylstannane **2** (Scheme 1) prior to pilot plant scale-up an *n*th-order analyzer, or analyzer^n, was assembled to obtain all of the desired data during a single experiment and in real time.[1] For characterizing a sample or process, an analyzer^n is distinguished from "*n*" separate analytical techniques by the ability to simultaneously obtain the data in an integrated fashion. In the present case, where $n = 3$, the analyzer^3 was used to perform the following: (1) reaction calorimetry, (2) in situ infrared spectroscopy, and (3) in situ mass spectrometry. The entire set of data obtained by this analyzer^3 provided a very clear picture of the reaction profile.

Scheme 1



Instrumentation

The choice of the components used in assembly of the analyzer^3 was determined by the ease of use of the equipment hardware and software, the ability to obtain quantitative information, the availability of versatile sampling interfaces for a wide variety of applications, the compatibility with the other components and strong support from the supplier. The reaction calorimeter (RC) was a Mettler Toledo[2] RC1, the Fourier transform infrared spectrometer (FTIR) was an Applied Systems, Inc. ReactIR, and the mass spectrometer (MS) was a Hewlett-Packard 5971A mass selective detector. These analyzers are described in detail below. The assembled analyzer^3 is depicted in Figure 1.

Reaction Calorimeter. The RC is an automated batch reactor which is used to conduct isothermal and adiabatic reactions.[2] The data acquisition system allows for the monitoring of physical parameters and for the determination and evaluation of thermal data and constants, including reaction temperatures, heat of reaction, temperature−time data, heat flow−time data, reaction rate, overall heat transfer coefficient, specific heat, heat of mixing, and heat of solution.[3] The complete RC system is composed of the automated reactor and a dosing controller. The RC reactor consists of four functionally separate modules:

(1) an electronic control and monitoring system, which includes a microprocessor control unit and the power electronics and electromechanical control

(2) a thermostat, which is used to control the reactor temperature

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[1] Proceedings from *ASI Applied Systems Annual Forum*; Baltimore, MD, 1996. *On-line Analytical Tools for Reaction Engineering*; LaPack, M. A.; Barton, K. P.; Bell, K. A.; Foulds, B. S. See also the following website: http://www.rxeforum.com.

[2] Details on the reaction calorimeter can be found at http://www.mt.com.

[3] For an application see: Blackmond, D. G.; Rosner, T.; Pfaltz, A. *Org. Process Res. Dev.* **1999**, *3*, 275.

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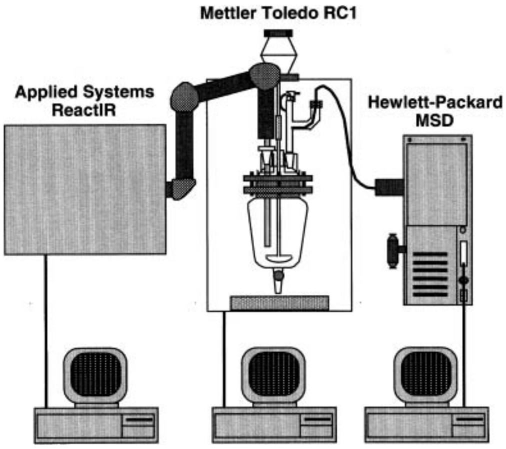

Figure 1. **Schematic illustration of the analyzer[3] consisting of reaction calorimetry, infrared spectroscopy, and mass spectrometry.**

(3) a reaction vessel, consisting of a jacketed, cone-bottom glass vessel (choice of 1-L or 2-L capacity), reactor cover with five ports for external fittings, choice of stirrer (an anchor agitator was used for these experiments), operating pressure range, 0.05 bar to standard pressure

(4) a measuring system. Every 2 s the RC measuring system sends the PC a set of measured values. The PC calculates additional quantities from these measured values. For the calculation of more complex expressions, various parameters such as specific heat can be entered in the PC.

The dosing controller allows for continuous addition of reagents or solvents. The heat flow due to the dosing action is automatically accounted for in the overall energy balance for the system. The PC is used to communicate with the RC reactor and the dosing controller. A selected operating system, QNX, and a special hardware configuration are utilized. The energy balance for the reaction system is described by eq 1,

$$Q_r = Q_f + Q_a + Q_d + Q_l = \sum r_i \cdot \Delta H_i \tag{1}$$

in which:

Q_r = reaction heat flow

Q_f = measured heat flow = $UA(T_r - T_j)$

Q_a = accumulated heat = $mC_p\, dT_r/dt$

Q_d = heat flow from dosing = $dm/dt\, C_p\, d(T_r - T_d)$

Q_l = heat losses

$\sum r_i \cdot \Delta H_i$ = sum of heat production rates of all reactions

and

A = heat exchange area [m^2]

Q_f = heat flow [J/s = W]

T_j = temperature of heat exchange medium [°C]

T_r = temperature of the reaction mass [°C]

U = overall heat transfer coefficient [W/m^{2}K]

r_i = reaction rate i [mol/s]

ΔH_i = reaction enthalpy [J/mol]

dm/dt = dosing rate [kg/s]

T_d = temperature of the dosed material [°C]

Most of the quantities defined above are acquired continuously (and in part calculated) as measured values during operation of the RC. The reaction enthalpy is evaluated off line, after completion of the experiment.

Infrared Spectrometer. An FTIR is used to monitor the liquid phase during the reaction. The FTIR is advantageous, because by itself it is a multidimensional analyzer. It provides information for chemical identification and quantification, and since the data can be collected in real time, it can provide reaction rate data.[4−6] The sample interface is an attenuated total internal reflectance (ATR) probe that is commercially designed to be inserted into the Mettler Toledo RC1 reaction calorimeter. With the ATR probe, no samples are required to be withdrawn from the reactor, which minimizes problems with suspended solids that may be encountered with off-line techniques. The metal probe body is Teflon-coated to ensure inertness. Probes comprising various ATR materials are available from the supplier. For most applications, a diamond−zinc selenide composite (DiComp) ATR probe and a liquid nitrogen-cooled mercury cadmium telluride detector provide the best combination of physical ruggedness and analytical sensitivity. This FTIR configuration provides liquid-phase analyses in the midinfrared region (4000−750 cm^{-1}). The fingerprint region yields chemical information and allows for quantitative analyses with PLS, P-matrix and K-matrix programs as standard features. The major drawback with the DiComp ATR probe is the transmission cutoff in the 2000 cm^{-1} region, which prohibits the monitoring of bonds that absorb in that region (e.g., triple bonds). For quantitative studies, standards are typically prepared in a matrix that best represents the process being studied. In the current study, high performance liquid chromatography (HPLC) analysis of small aliquots of the reaction solution were utilized for quantification.

Mass Spectrometer. The experimental system is also outfitted with a mass selective detector (MSD) modified for in situ analyses.[7,8] Like the FTIR, the MSD provides an array of chemical information in real time. This analyzer is used to monitor the gas phase during a process. Typical instrumental conditions are given in Table 1. A variety of sampling inlets may be employed for interfacing the process headspace with the mass spectrometer.[8,9] Fused silica capillaries, Teflon tubing, and membrane introduction devices have been used.

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Table 1. **Summary of MSD conditions**

ionization mode	electron impact
ion source temperature	100 °C
scan mode	total ion scan, 1−150 D
scans/s	1
electron multiplier voltage	1500 V

Since the mass spectrometer operates under high-vacuum conditions, very low sample consumption is required. The sample inlet used in the present study was a 0.050-mm i.d., 30-m long fused silica capillary. The flow of the gas sample through the capillary was less than 1 cm^3/min. The vacuum in the mass spectrometer was maintained at 3.0×10^{-5} Torr. Argon was introduced as an inert internal standard into the RC headspace at a rate of 10 cm^3/min. Gas standards were prepared in 10-L gas sampling bags.

Proposed Rate Expression. The simplified mechanism shown in Figure 2 was used to develop a rate expression. In solution, the pentanenitrile, 2,4-dimethyl, 2,2′-azobis (VAZO 52) initiator **3** decomposes on heating, forming two free radicals **4** and liberating nitrogen.[10] The VAZO 52 radical **4** reacts with tri(*n*-butyl)tin hydride **5** to form a tri(*n*-butyl)tin radical **6** which then reacts with the vinyl sulfone **1** to form the vinyl tributylstannane **2** and the phenylsulfonyl radical **8**. The key termination step is the formation of phenylsulfonyl-tri(*n*-butyl)tin **11**. Abbreviations for the various chemical species are indicated below:

[I]	VAZO 52 initiator concentration
$[I^\bullet]$	VAZO 52 free radical concentration (2,3-dimethyl butyronitrile radical)
$[N_2]$	nitrogen concentration
[P]	product concentration
[R]	reactant concentration
$[S^\bullet]$	phenylsulfonyl radical (species **8**, Figure 2) concentration
[TH]	tri(*n*-butyl)tin hydride concentration
$[T^\bullet]$	tri-(*n*-butyl)tin radical concentration

The following assumptions were made in the development of the rate expression:

1. The quasi steady-state assumptions are valid, that is, the net rates of free radical formation are zero and the propagation rates (r_3 and r_4) are equal to each other:

$$d[I^\bullet]/dt \cong 0, \text{ etc.} \tag{2}$$

$$r3 \cong r4 \tag{3}$$

2. By stoichiometry, the concentration of initiator is equal to the initial initiator concentration minus the concentration of N_2:

$$[I] = [I_0] - [N_2] \tag{4}$$

3. By stoichiometry, the concentration of tri(*n*-butyl)tin hydride is equal to the initial tin hydride concentration minus 2 times the concentration of product:

$$[TH] = [TH_0] - 2[P] \tag{5}$$

First, rate equations were developed for the product and intermediates, according to the form given in eq 6 below:

$$\frac{d[C_i]}{dt} = k[C_j]^a\,[C_k]^b \tag{6}$$

$$\frac{d[P]}{dt} = k_3[T^\bullet][R] \tag{7}$$

$$\frac{d[I^\bullet]}{dt} \cong 0 = 2fk_1[I] - k_2[I^\bullet][TH] - 2k_8[I^\bullet]^2 \tag{8}$$

$$\frac{d([T^\bullet] + [S^\bullet])}{dt} \cong 0 = k_2[I^\bullet][TH] - 2k_6[T^\bullet][S^\bullet] - 2k_5[S^\bullet]^2 - 2k_7[T^\bullet]^2 \tag{9}$$

Equations 7, 8, and 9 were combined and simplified, to yield the following proposed rate expression:

$$\frac{d[P]}{dt} = k_3(fk_1)^{1/2}\,[I]^{1/2}\,[R]\left\{\frac{1}{k_7 + \frac{k_6k_3}{k_4}\frac{[R]}{[TH]} + \frac{k_5{k_3}^2}{{k_4}^2}\left(\frac{[R]}{[TH]}\right)^2}\right\}^{1/2} \tag{10}$$

Results and Discussion

Two separate runs were performed according to the following procedure:

1. 0.05 g-mol of VAZO 52 initiator was charged to the reactor.
2. 0.14 g-mol of the vinyl sulfone (**1**) in cyclohexane was added to the reactor, and agitation was started.
3. 0.60 g-mol of tri(*n*-butyl)tin hydride was added while stirring.
4. The contents of the reactor were heated to about 55−60 °C. Heating was continued, and the contents were allowed to react until HPLC analysis indicated greater than 90% conversion.

Calorimetric Data. The heat of reaction and adiabatic temperature rise for the reaction were evaluated from the two experiments. Typical temperature and heat profiles for this reaction are shown in Figure 3, and the results are summarized for both experiments in Table 2.

Concentration−Time Data. Throughout both experiments the reactor headspace was monitored by in situ mass spectrometry, and the liquid-phase concentrations were monitored by in situ FTIR. Profiles of cumulative mols of nitrogen and hydrogen and the mols of reactant consumed and product produced during run 2 are shown in Figure 4. For the liquid-phase measurements of compounds **1** and **2**, the measured absorbance responses were converted to mols by calibration with HPLC data. For the evolved nitrogen and hydrogen, mass spectrometric response data were converted to mol/min on the basis of the flow rate of the argon internal standard into the reactor. The data for mol/min were then numerically integrated to calculate the cumulative molar rate data. The rate data were assumed to be equal to the evolved amounts (mol of gas per L of reaction mixture) of nitrogen

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[9] DesJardin, M. A.; Doherty, S. J.; Gilbert, J. R.; LaPack, M. A.; Shao, J. *Process Control Qual.* **1995**, *6*(4), 219.

[10] For discussions on the decomposition of azoalkanes. see: (a) Bawn, C. E. H.; Mellish, S. F. *Trans. Faraday Soc.* **1951**, *47*, 1216. (b) Kochi, J. K. *Free Radicals*; Wiley: New York, 1973; Vol. 1, p 143.

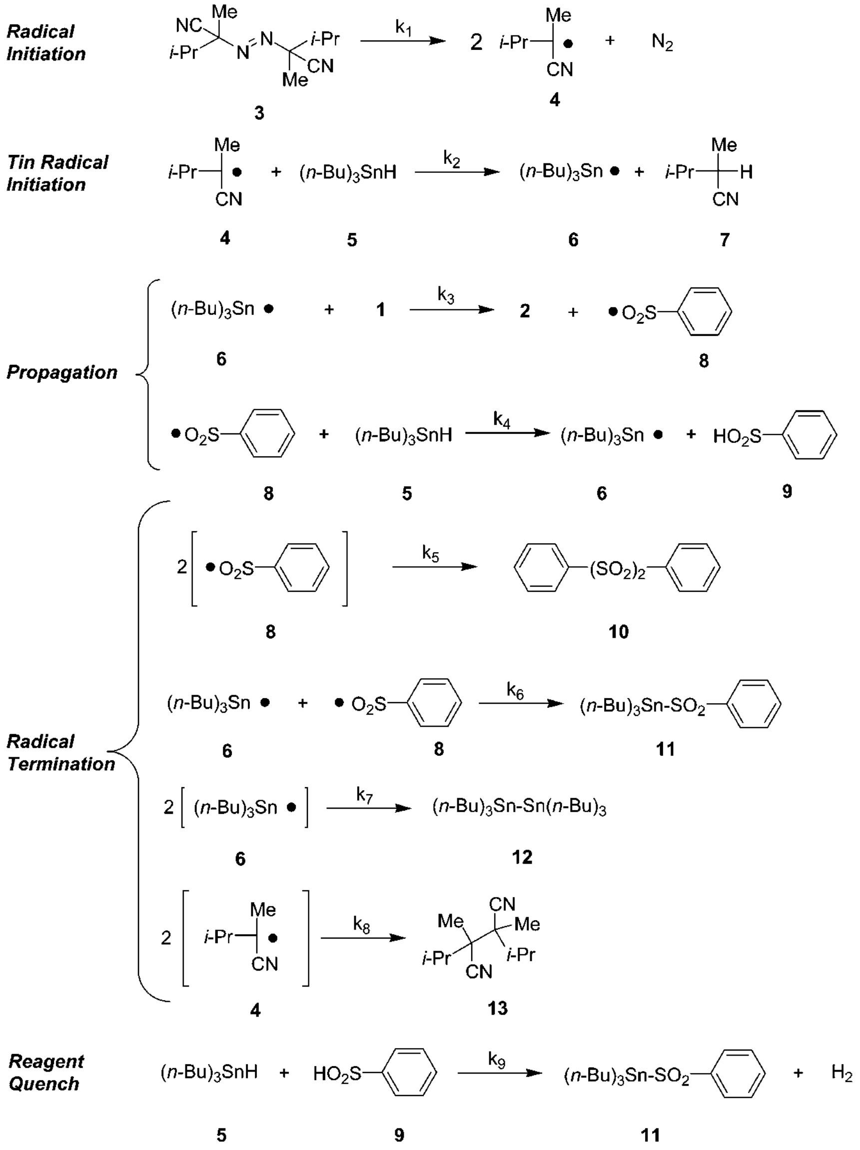

Figure 2. **Simplified mechanism.**

and hydrogen from the reaction mixture. The data were not corrected for vapor/liquid equilibrium.

The proposed reaction mechanism (Figure 2) predicts that there is a mol of hydrogen evolved per mol of reactant. For this application it was important to verify the hydrogen evolution, particularly for reactive chemical hazard evaluation and vent gas handling issues for scale-up. The theoretical amounts of hydrogen and nitrogen evolution, predicted by stoichiometry, are: 0.14 mol H_2 and 0.05 mol N_2 per L of reaction mixture. As can be seen from Figure 4, the total measured amounts of hydrogen and nitrogen as measured by the in situ MSD technique, agreed well with the amounts predicted by the proposed reaction mechanisms.

Comparison of Observed and Modeled Rates. Equation 10 was numerically integrated, using the quantitative experimental data for compound **2** [P], VAZO 52 [I], compound **1** [R], and tri(*n*-butyl)tin hydride [TH]. Then the observed concentration−time profile of compound **2** was compared with that predicted by eq 10. Figure 5 is a comparison of the experimentally measured concentrations of **2** and those predicted from integration of eq 10. The three terms in the denominator of eq 10 represent the various termination mechanisms. The relative values of those three sets of rate constants were varied, and in general the best agreement was found when the combined rate constants were of the same order. However, for this study the fitting of the rate constants was not optimized. The rate constants used for the predicted rate curve for the formation of compound **2** in Figure 5 are:

$$k_3 \approx 0.065 \text{ in appropriate units}$$

$$k_7 \approx k_6k_3/k_4 \approx k_5k_3^2/k_4^2 = 1 \text{ in appropriate units}$$

The data show generally good agreement with the predicted rate, although there is evidence of an initial induction period. One possible cause of this behavior is the presence of a radical quenching species present in the feed solution which is consumed during the early stage of the reaction. This initial behavior should be addressed in any further development and modeling of the reaction kinetics.

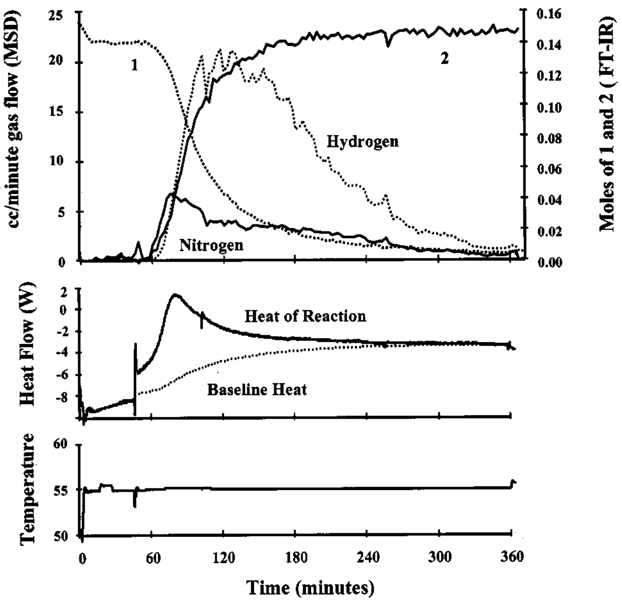

Figure 3. **Run 2 data from the analyzer[3].**

Table 2. **Summary of RC1 Heat Evaluations[a]**

run	step	ΔH (kcal/mol **1**)	adiabatic ΔT (°C)
1	VAZO add/reaction	−35.1	22
2	VAZO add/reaction	−35.7	19

[a] Note: sign convention for ΔH (−) exothermic (+) endothermic.

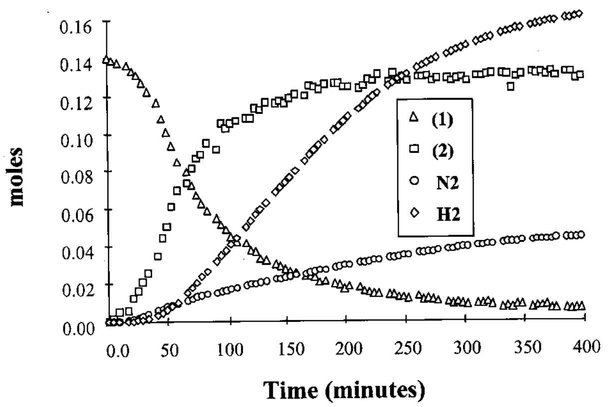

Figure 4. **Mol−time data from the liquid and gas analyses for run 2.**

This chemistry was successfully run at a 100-gal pilot-plant scale, and the pilot-plant results were well predicted by the proposed kinetic model, as shown in Figure 5.

The first-order rate of decomposition of VAZO 52 initiator was compared with literature predictions. The integrated rate expression can be written as:

$$-\ln[\mathrm{I}]/[\mathrm{I}_o] = kt \qquad (11)$$

Since the decomposition is first-order,[11] the rate of free radical formation can be controlled by regulating the temperature. The decomposition rates are essentially independent of the solvent, and for VAZO 52 the half-life, $t_{1/2}$ is reported to be:[12]

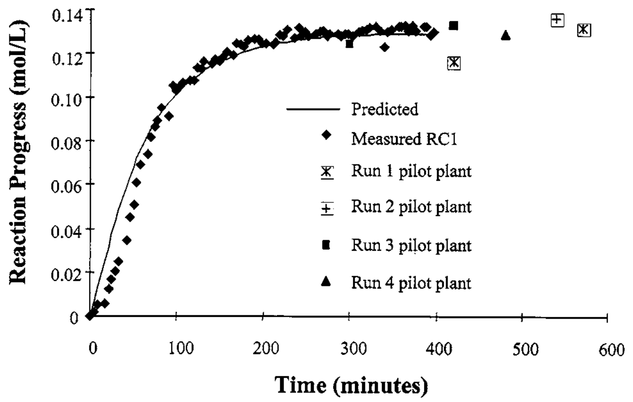

Figure 5. **Predicted and measured rates of formation of 2.**

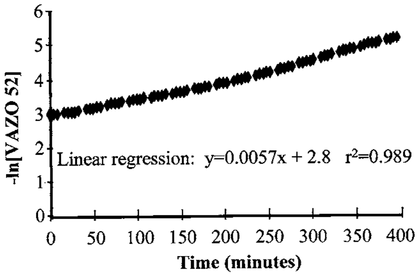

Figure 6. **Measured rate of decomposition of VAZO 52 initiator.**

$$\text{VAZO 52:}\quad \log_{10}(t_{1/2}) = 6767(1/T) - 18.037T \text{ in °C}, \quad t \text{ in min} \qquad (12)$$

The activation energy of the decomposition is reported to be about 31 kcal/mol.[12] From eq 12, the theoretical value for the rate constant at 55 °C is calculated to be 1.8×10^{-3} min^{-1}. The measured rate is plotted in Figure 6. The measured rate constant was determined from the slope of the ln[I] versus time curve, where the concentration [I] was calculated from the mass spectrometric measurement of evolved nitrogen, using eq 4. From linear regression, $k_{\text{meas}} = 5.7 \times 10^{-3}$ min^{-1}. The agreement is qualitatively good, considering there were no corrections for vapor−liquid equilibria or dilution in the headspace volume.

Conclusions

A third-order analyzer consisting of an integrated Mettler RC1 calorimeter, Applied systems, Inc. ReactIR, and Hewlett-Packard 5971A mass selective detector was successfully utilized to study the conversion of **1** to **2**. The utility of the analyzer was demonstrated for reactive chemical hazard evaluation, environmental emissions determination, and information regarding reaction kinetics.

In situ mass spectrometry and FTIR analysis techniques for monitoring the concentrations of **1**, **2**, hydrogen, and nitrogen were demonstrated. A reaction mechanism and rate expression were developed for the conversion of **1** to **2**. The reaction was then run in the integrated RC1/MSD/ReactIR system, and the experimentally measured concentrations of

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(11) Hammond, G. S. et al., Abstracts 137th ACS Meeting, Cleveland, Ohio, April 1960, American Chemical Society: Washington, DC, 1960; *J. Am. Chem. Soc.* **1960**, *82*, 5394.

(12) *VAZO Polymerization Initiators*; DuPont Product Literature.

2 were compared with those predicted from integration of the rate expression. The data showed generally good agreement with the predicted rate, although there was evidence of an initial induction period which was not predicted.

According to the proposed rate expression, the stannylation reaction is half-order dependent on the initiator concentration, pseudo-first-order dependent on the tin hydride concentration, and pseudo-zero- to first-order dependent on the concentration of **1**. The proposed reaction mechanism predicts that there is a mol of hydrogen evolved per mol of **1** and that there is a mol of nitrogen evolved per mol of VAZO 52 initiator. The in situ MS data confirmed these predictions. The in situ technique for measuring the rate of decomposition of VAZO 52 initiator was also demonstrated. The heat of reaction and adiabatic temperature rise for the conversion of **1** to **2** were measured using RC1 calorimetry. The calculated heat of reaction was ∼−36 kcal/mol of **1** (exothermic), and the adiabatic temperature rise was ∼20 °C.

The in situ analyzer[3] has been shown to perform many operations better than off-line techniques and can be used to obtain data that cannot be obtained by other techniques. In addition to the application described in this report, the analyzer[3] has been used to study highly reactive processes, cryogenic reactions, corrosive or hazardous processes, and multiphase systems. Transient intermediates have been observed and identified and the data used to improve mechanistic information. Similar *n*th-order analyzers have been used by other research groups.[13,14]

Higher-order analyzers than described here have been employed in the Custom and Fine Chemicals Process Development Laboratory at Dow. In addition to the capabilities described above, pH measurements as well as percent solids content or crystallization measurements have been made on-line for reactive processes. Finally, in the event that a product candidate is commercialized and on-line analyzers are required for feedback control of the large-scale manufacturing process, the data generated in early stages of the development process using the analyzer^n can aid in the determination of the most appropriate analyzer.

Experimental Section

General Procedures. All reagents were obtained from commercial sources and were used as received without additional purification. Cytidine, 2′-deoxy-2′-[fluoro(phenylsulfonyl)methylene]-3′,5′-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-,(2′Z), compound **1**, can be prepared according to published literature procedures.[15] HPLC analyses were performed using two Zorbax Rx-C8 (5 μm) cartridge columns (4.0 mm × 80 mm) with a Zorbax Rx-C8 (4 mm × 12.5 mm) guard column. Gradient elution conditions were employed; ramping from 70/30 acetonitrile/water to 100% acetonitrile during 13 min followed by a 17-min hold. The eluent flow rate was 1.5 mL/min and UV detection at 235 nm.

Preparation of Cytidine, 2′-Deoxy-2′-[fluoro(tributylstannyl)methylene]-3′,5′-*O*-[1,1,3,3-tetrakis (1-methylethyl)-1,3-disiloxanediyl]-,(2′Z): Compound 2. VAZO 52 (12.5 g, 0.050 mol) and the vinyl sulfone **1** (90 g, 0.14 mol) in cyclohexane (473 g) were charged to the RC1 calorimeter. To the stirred solution was added tri(*n*-butyl)tin hydride (174.9 g, 0.601 mol). The resulting reaction mixture was heated to about 55 °C. Reaction aliquots were periodically removed for HPLC analysis. Upon reaction completion the contents were cooled to room temperature.

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[14] Karet, G. *Drug Discovery Dev.* **2001**, *4* (10), 26.

[15] Matthews, D. P.; Perscochetti, R. A.; Sabol, J. S.; Stewart, K. T.; McCarthy, J. R. *Nucleosides Nucleotides* **1993**, *12* (2), 115.