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Kinetic Data by Nonisothermal Reaction Calorimetry: A Model-Assisted Calorimetric Evaluation

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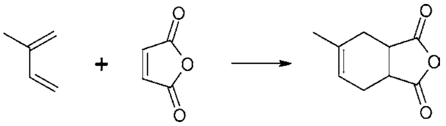
Abstract:

The use of a reaction calorimeter in combination with kinetic modeling software to obtain nonisothermal kinetic data is presented. The Diels−Alder reaction of maleic anhydride and isoprene in DMF was used as a model to demonstrate the feasibility of the method. The Arrhenius *A* factor and the activation energy could be achieved from a single experiment with a reaction calorimeter (Mettler RC1) by fitting the experimental heat generation curve to a second-order kinetic model using commercially available software packages. The use of fitting software revealed a discrepancy between the experimental reaction heat and the heat calculated from the rate parameters. This discrepancy could be resolved by reintegration of the heat generation curve using an adjusted baseline derived from the rate data. The methodology was applied by varying reaction conditions (starting concentrations, heat rate, temperature range), and the results appeared to be independent of these variations within the experimental errors ($E_a = 58.5 \pm 2.0$ kJ mol^{-1}, *A* factor 4.02×10^6 L mol^{-1} s^{-1}). It is shown by comparison with literature data that this fast method generates kinetic parameters with a sufficient reliability to be used with process-modeling tools for computer-supported scale-up.

Introduction

There is an increasing pressure on the Pharmaceutical Industries to reduce development times without putting safety and quality at risk. This is only achievable by making the best use of available tools. The use of reaction calorimeters has been tremendously successful in obtaining the required heat generation data for safe scale-up and has delivered valuable insights into the process.[1] Another tool that has largely benefited from developments in computer technology (hard- and software) is Kinetic Modeling and Simulation. This tool allows the calculation of chemical process variables as a function of time (concentrations, temperature, etc.) and therefore provides valuable help in process design decisions.[2] Kinetic Modeling and Simulation, however, requires a reasonable process chemistry description and a lot of numerical input, first of all kinetic data.

Scheme 1. **Reaction of isoprene and maleic acid anhydride (MAA)**



As reaction calorimetric experiments are run routinely to obtain the required safety information, it would be straightforward to derive kinetic data from the very same experiment. A large number of reports demonstrate the use of heat generation rates, obtained by reaction calorimetric measurements, to derive kinetic data; however, the vast majority of these measurements are isothermal experiments, which give only rate constants at a single temperature.[3] In order to obtain full temperature-dependent kinetics, these isothermal experiments have to be repeated at different temperatures, and the Arrhenius parameters may then be obtained in the classical way by a linear regression of a plot of ln *k* vs 1/*T*, which is time-consuming and hard to be done in a routine manner during process development. On the other hand, the use of nonisothermal experiments to obtain temperature-dependent kinetic parameters from heat-related data of a single experiment is a technique well-known in differential scanning calorimetry (DSC).[4]

The Reaction of Isoprene and Maleic Anhydride

This report describes a method to obtain the full Arrhenius data set by using temperature ramp experiments in a reaction calorimeter, thus combining the advantages of reaction calorimetry (process-like conditions with representative sample volumes) and the speed of DSC.

The present approach is shown by a model reaction, namely the Diels−Alder reaction of isoprene and maleic anhydride (MAA),[5] Scheme 1.

This reaction was chosen because Diels−Alder reactions are highly exothermic, which gives a good degree of operational freedom to study the effects of variations of concentration and heating rate. The reaction is kinetically

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[1] (a) LeBlond, C.; Wang, J.; Larsen, R. D.; Orella, C. J.; Forman, A. L.; Landau, R. N.; Laquidara, J.; Sowa, J. R.; Blackmond, D. G.; Sun, Y. -K. *Thermochim. Acta* **1996**, *289*, 189. (b) Hoffmann, W. *Chimia* **1989**, *43*, 62−67.

[2] (a) Wright, A.; Bramfitt, V. *Chem. Ind.* **1988**, *4*, 114. (b) Lobben, P. C.; Leung, S. S. -W.; Tummala, S. *Org. Process Res. Dev.* **2004**, *8(6)*, 1072−1075.

[3] Zogg, A.; Stoessel, F.; Fischer, U.; Hungerbuehler, K. *Thermochim. Acta* **2004**, *419*, 1−17.

[4] (a) Hugo, P.; Wagner, S.; Gnewikow, T. *Thermochim. Acta* **1993**, *225(2)*, 143−151.; b) Wagner, S.; Hugo, P.; Gnewikow, T. *Thermochim. Acta* **1993**, *225(2)*, 153−163.

[5] Rabijohn, N.; Drumm, M. F.; Elliot, R. L. *J. Am. Chem. Soc.* **1956**, *78*, 1631−1634.

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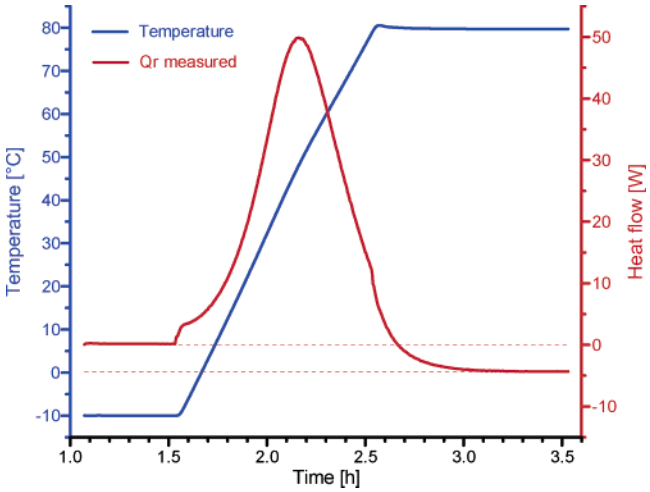

Figure 1. **Heat flow curve (Q_r, [W]) and temperature T_r [°C] from heating 0.80 mol MAA and 0.70 mol isoprene in DMF from −10 to 80 °C in 1 h.**

well characterized by Dewar,[6] and his data show that the reaction can be investigated in a temperature range easily accessible by reaction calorimeters; the reaction is simple with apparently no side reactions in the temperature range studied, and it is strictly second order. The materials are cheap and readily available, and the high volatility of isoprene makes it a good test case, as a pressurized reactor will be used to avoid boiling effects of the solvent and the reactants. Although not utilized by Dewar, DMF was used as a solvent because of its high boiling point, its good dissolution properties, and an only modest and nearly linear increase of its specific heat with temperature in the used temperature range studied.[7]

In a typical experiment, performed using a Mettler-Toledo reaction calorimeter (RC1) with an MP06 pressure reactor (covered with a thermostated lid), 78.5 g (0.80 mol) of MAA was dissolved in 300 mL of DMF and cooled down to −10 °C, followed by the addition of 47.7 g (0.70 mol) of precooled isoprene. The total volume of the resulting solution was 420 mL at ambient temperature. The reactor was pressurized with nitrogen to about 2.5 bar, and after calibration and cp (specific heat of reaction mixture) determination the temperature was linearly increased to 80 °C over 1 h period. The cover temperature was controlled to be 3−5 °C higher than the reaction temperature during the heat ramp, so that the heat losses or gains through the lid can be considered constant. The reaction was isothermally run to completion, and then a final calibration and cp determination were performed.

With the assumption of a temperature proportional change of the heat transfer coefficient and of cp (the standard evaluation procedure), the resulting heat flow curve was obtained (Figure 1).

It is a striking feature of such heat generation curves that despite a temperature-controlling cover there is a shift in the baseline levels before and after the reaction (dotted lines in Figure 1). To obtain the net heat generation curve, the baseline curve (Q_b) has to be subtracted from the measured (Q_r) curve. This is routinely done by assuming that the net heat generation rate is zero outside the integration limits, i.e., $Q_b = Q_r$, and, by the choice of the baseline, in between these integration limits. A baseline proportional to the reaction temperature T_r was preferred over a baseline proportional to conversion (the default in the Mettler software). In the first case the baseline shift is attributed to a change in temperature, whereas in the second case the baseline shift is attributed to a change of the physicochemical properties on going from starting materials to products. Here the principal decision was made to use a temperature proportional baseline, as a 90 °C temperature change is more likely to affect the physicochemical properties of the reaction mixture than a chemical conversion. The difference between these choices in the presented reaction is only about 2.5% in the calculated reaction heats [ΔH_r −142.7 kJ mol^{-1} ($\propto T_r$) vs −146.2 kJ mol^{-1} ($\propto$ conv)] but can be very significant when the values of the baseline shift and the maximum heat production are getting closer. ΔH_r values of −118.5 kJ mol^{-1} vs −35.2 kJ mol^{-1} were reported.[8] Another advantage of a temperature proportional baseline is the implicit correction of heat losses to the surrounding, which are temperature proportional and can be very significant at higher temperatures, so that otherwise a heat loss term must be added in the heat balance equation.

Kinetic Fitting. The kinetic analysis of the heat generation curves was carried out using the BatchCad software[9] package. The second-order rate law was numerically integrated as a function of the Arrhenius parameters (A and E_a), which were automatically adjusted to time, temperature, and heat data by the method of least-squares without any linearization to get the best fit. To allow for the correct integration of the model, the start time was chosen to be the real starting point of the reaction, i.e. when the isoprene was added and not the integration limit of the RC1 evaluation, which was about an hour later because of the required calibration and cp measurements.

The results of a typical fit are shown in Figure 2, where the best-fit graph is plotted together with the experimental data.

It should be pointed out that the reliability of the kinetic system description is of fundamental importance, as an accurately measured data set will not give a satisfying fit with an inappropriate model, so this well-known strictly second-order reaction should test the feasibility of the application of the kinetic fitting method to nonisothermal heat data sets.

In a package of experiments, the concentration of the starting materials, the heating rates, and the end temperature were varied, and each experimental data set was evaluated individually by the method described above.

The results are summarized in Table 1. The data in Table 1 show a good reproducibility and suggest that, within experimental error, the obtained kinetic results are randomly

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(6) Dewar, M. J. S.; Pyron, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 3098−3103.

(7) DIPPR (Design Institute for Physical Properties) database, accessed as part of Aspen BatchCAD, see ref 9.

(8) Hoffmann, W. Presentation at 4th International Conference on the Scale-up of Chemical Processes, Jersey, U.K., 2000.

(9) Aspen BatchCAD, version (13.3.0.73), Aspen Technology Inc., 2004.

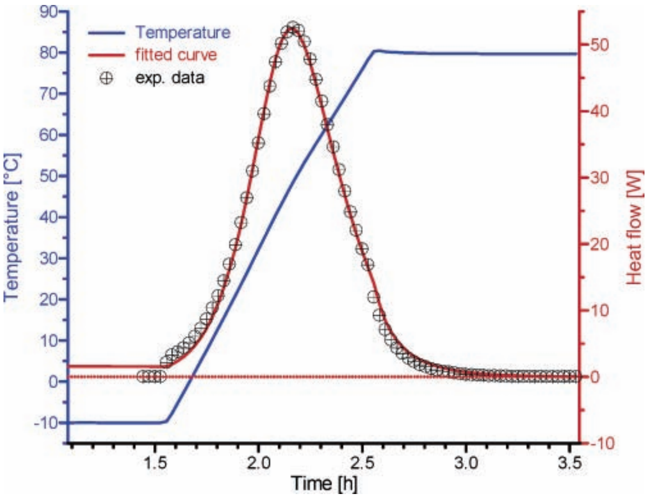

Figure 2. **Fit of experimental nonisothermal heat data of reaction of isoprene with maleic acid anhydride.**

Table 1. **Kinetic fitting results for calorimetric temperature ramp experiments of the reaction of isoprene and maleic acid anhydride**

	experimental data					fitted data	
entry	isoprene [mol]	MAA [mol]	vol [mL]	ramp range [°C]	ramp time [h]	A [10^6] [L mol^{-1} s^{-1}]	E_a [kJ mol^{-1}]
1	0.7	0.8	420	−5−80	1.5	4.74	59.4
2	0.7	0.8	420	−10−80	1	3.94	58.8
3	0.7	0.8	420	−10−80	2	7.50	60.3
4	0.7	0.8	420	−10−100	1.5	1.96	57.1
5[a]	0.7	0.8	420	−10−100	1.5	1.72	56.7
6	0.7	0.8	420	−10−100	2	6.81	55.0
7	0.5	0.57	384	−10−80	1	1.44	62.2
8	0.5	0.57	384	−10−80	1.5	7.64	60.4
9	0.5	0.75	398	−10−80	1.5	1.59	56.7
10	0.7	0.58	404	−10−80	1	2.92	58.0
11[b]	0.7	0.58	404	−10−80	1	4.74	59.4
						4.02 ± 2.5	58.5 ± 2.0

[a] Different cover temperature from entry 4. [b] Prolonged time from addition of isoprene till start of temperature ramp than entry 10.

scattered and there is no significant dependence from variations of concentrations and heat ramps.

Discussion

These data should now be compared with Dewar's results[6] (Table 2) obtained by the classical method of measuring isothermal rate constants with a graphical linearization method and then obtaining the activation parameters by a linear regression.

The comparison with Dewar's data shows that the Arrhenius factor appears to be high and the activation energy is the second highest in the series. However, when comparing rate constants at selected temperatures, the rates are not much different from Dewar's data, as the higher Arrhenius factor and the higher activation energy have a compensating effect.

A general source of error in this kind of measurement is caused by the volume change with temperature and with conversion. It is a well-known phenomenon that Diels−Alder reactions proceed with volume contraction, which has been used to obtain kinetic data.[10] On the other hand, the density of the reaction mixture decreases with temperature, so that the reaction volume is a complex function of temperature. This volume profile can be estimated by a kinetic simulation, given the densities of the solvent and the pure components as a function of temperature. The result is shown in Figure 3.

It is shown in Figure 3 that the volume change is of the order of 5% of the total volume, and it should be pointed out that the fitting of the kinetic parameters does consider these changes within the accuracy of the applied model.

However, there are sources of errors associated with the general method of data evaluation by an RC1 calorimeter. The heat generation data (Q_r) were calculated from the measured temperature-based data (T_j, T_{rr}, and dT_r/dt) by using the general heat balance eq 1.

$$Q_r = Q_{flow} + Q_{accu} = AU(t)(T_r - T_j) + \frac{dT_r}{dt}[m\,cp(t) + Cp_i] \quad (1)$$

The total heat transfer (AU) and the specific heat (cp) were measured at the reaction start temperature and at the end of the reaction and as a first approximation it was assumed, that these two parameters change linearly with temperature. The heat capacity of the inserts (Cp_i) is small compared to the heat capacity of the reaction mass (Cp_r), (100 J/K vs around 800 J/K), and its temperature dependence was ignored (all metal inserts).

Database values for cp of DMF are nearly linear ranging from 2.05 J g^{-1} K^{-1} @ 0 °C to 2.23 J g^{-1} K^{-1} @ 100 °C.[7]

The validity of the assumption that the total heat transfer AU is linear between the calibration points at the lower temperature before the ramp starts and the high temperature after the ramp has finished has been tested by stepwise heating up and cooling down 300 mL of DMF in the temperature range of −10 to 100 °C and calibrating isothermally at every 10 °C. The results are shown in Figure 4.

It is concluded that the assumption of a linear increase in AU with temperature is justified. It should be pointed out that in contrast to isothermal experiments the contribution of Q_{flow} to the overall Q_r (eq 1) is reduced, as a considerable amount of energy is used to heat up the reaction mixture, and therefore less heat has to be withdrawn by jacket cooling, so that errors in UA have a less striking effect on the overall heat, in particular in reactions with a large temperature ramp (see Table 3). The results of the heat evaluation are summarized in Table 3.

Integrations of $Q_r - Q_{baseline}$ between the arbitrary set integration limits give larger fluctuations in the experimental ΔH as expected, although the error is still in an acceptable range for this kind of measurements. A remarkable difference, however, is the calculated reaction enthalpy from the fitted curve. Here the exothermic reaction heat is significantly larger. The reason for this discrepancy is the assumption that the heat generation outside the integration limits is negligibly small. A calculation for the heat generation of the standard run immediately after the addition of the isoprene at −10 °C with the kinetic parameters of Table 2 and the experi-

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(10) Roth, W. R.; Biermann, M.; Dekka, H.; Jochems, R.; Mosselman, C.; Hermann, H. *Chem. Ber.* **1978**, *11*, 3892−3903.

Table 2. **Kinetic parameters for the reaction between maleic anhydride and isoprene by Dewar**

solvent	temp range (°C)	temp data points	A [10^5] (L mol^{-1} s^{-1})	E_a (kJ mol^{-1})[a]	k [10^{-3}] at 60 °C (L mol^{-1} s^{-1})
benzene	0−100	4	1.2	51.5	1.0
anisole	0−100	4	3.07	52.7	1.7
isopropyl ether	30−100	3	8.70	59.4	0.42
veratrole	30−90	3	4.40	53.1	2.1
chlorobenzene	0−100	4	2.86	52.7	1.5
m-dichlorobenzene	30−90	3	3.43	52.3	2.1
o-dichlorobenzene	0−90	5	2.12	49.4	14
benzonitrile	0−90	4	8.03	54.4	2.4
nitrobenzene	0−100	4	3.41	51.5	2.8
nitromethane	0−100	4	4.60	51.5	3.8
dimethylformamide[b]	**−10−100**	**continuous**	**40**	**58.5**	**2.7**

[a] Dewar's values given in kcal mol^{-1} were multiplied by 4.184 J cal^{-1} and rounded to the first digit. [b] Our data.

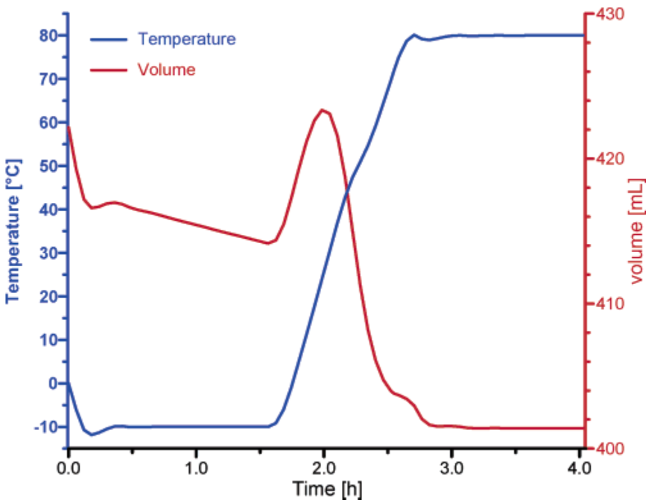

Figure 3. **Simulation of volume as a function of temperature and conversion.**

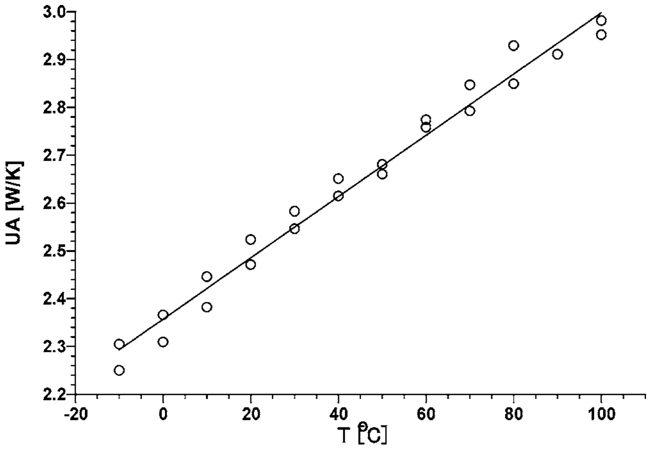

Figure 4. **Total heat transfer UA as a function of temperature for DMF solvent.**

Table 3. **Experimental reaction heats and BatchCad fitted heats**

entry	Δ***H*** flow [kJ mol^{-1}]	Δ***H*** accu [kJ mol^{-1}]	Δ***H*** exp [kJ mol^{-1}	Δ***H*** fitted [kJ mol^{-1}]
1	−25.1	−111.5	−136.6	−148.6
2	−29.0	−117.2	−146.2	−158.0
3	−25.9	−117.9	−143.9	−152.7
4	−2.9	−144.9	−147.9	−159.3
5	−1.8	−145.1	−146.9	−161.5
6	11.9	−144.2	−132.2	−141.6
7	12.4	−146.5	−134.1	−140.4
8	10.9	−151.5	−140.5	−147.8
9	9.0	−158.3	−149.3	−163.3
10	−12.2	−136.9	−149.1	−159.1
MEAN			−142.7 ± 6.4	−153.2 ± 8.3

mental heat of ΔH = −142.7 kJ mol^{-1} gives a value of 1.86 W. Taking into account that the temperature increased during the calibration to about −4 °C, there is an estimated 8 kJ (11−12 kJ mol^{-1}) heat generated in the time before the integration interval is selected, and this value even rises, when the time from start of the reaction to the start time of the integration is getting longer. In experiment 11 (Table 1) this time was about 4 h, and consequently the integration gave a low result not included in Table 3 (ΔH_r = −127.6 kJ mol^{-1}). A major improvement of Table 3 thus would be a re-integration of the Q_r data with a manually set baseline to account for the heat generation at the time of mixing. This will significantly change the first part of the baseline-corrected data, but has only a small effect on the mid and actually no effect on the later part of data. Applying the same treatment to the standard reaction changed the measured heat from ΔH = −136.6 kJ mol^{-1} to ΔH = −160.8 kJ mol^{-1}, so that the experimental reaction heat and the heat data obtained by fitting are now in agreement. The difference between the measured heat and the heat calculated from the fitted Q_r with the measured temperatures including the temperature increase during calibration can therefore be accounted for. Remarkably, this significant correction of the measured reaction heat does not have a similar effect on the obtained Arrhenius parameters. The kinetic parameters fitted with the corrected heat generation curve (A factor 3.06 × 10^6 mol L^{-1} s^{-1}, E_a = 58.2 kJ mol^{-1}) changed only within the given errors (3.94 × 10^6 mol L^{-1} s^{-1} and E_a = 58.8 kJ mol^{-1} before the heat correction).

Other factors to be considered are the differences in the data weightings due to the logarithmic transformation when comparing Arrhenius parameters obtained by a linearization method and by a direct kinetic fitting. This has already been discussed in detail by Cvetanovic.[11]

Conclusion

The method of nonisothermal reaction calorimetry with a kinetic model assisted evaluation is a rapid tool to get Arrhenius parameters for kinetic simulation supported process development. The baseline selection for the net heat generation curve to account for the shift in the baseline level, and the temperature-dependent parameters (cp and UA) are the critical parameters for the activation parameters; for good reaction heat data it is important to consider the heat output at the starting point of the reaction and to integrate from this point.

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(11) Cvetanovic, R. J.; Singleton, D. L.; Paraskevopoulos, G. *J. Phys. Chem.* **1979**, *83*, 50−60.