

Thermodynamic and kinetic analysis of isothermal microcalorimetric data: applications to consecutive reaction schemes

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Abstract

Recent developments have led to a general procedure that allows the analysis of isothermal microcalorimetric data to determine both kinetic and thermodynamic information. Such an analysis means that isothermal microcalorimetry is a powerful technique with which to gain information on a wide range of reactions. Previously, the method of analysis has, principally, been applied to simple, two-state, solution phase reactions. It is the purpose of the data presented here to show how such an analysis may be applied to solution phase reactions that follow more complex, consecutive reaction pathways using, as a model and example, the acid catalyzed hydrolysis of potassium hydroxylamine trisulfonate. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

In this work we show how it is possible to analyze microcalorimetric data using modified kinetic equations. The equations presented herein apply to solution phase, consecutive reaction schemes. The analysis of data deriving from other reaction schemes will be discussed in a future publication. Solution phase reactions have been well characterized and often follow specific reaction pathways. More often than not, it is possible to express such pathways using relatively simple kinetic expressions (see,

for example [1]). Knowledge of the rate constant allows the prediction of a shelf-life if the reaction order is known.

The output from a heat conduction, isothermal microcalorimeter is power versus time, and it follows that analysis of these data allows information to be obtained on both the kinetics and thermodynamics of the reaction under investigation. In the absence of data obtained via other chemical assay techniques (for example, HPLC), thermodynamic data do not allow molecular interpretation, but kinetic data form the basis of mechanistic investigations. Many systems that are of interest pharmaceutically, including solid-state or heterogeneous reactions and biological processes, are complex, and analyses of such data often present considerable difficulties. The general nature of the microcalorimetric technique may offer

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some advantages for the study of these complex reactions, without the need for further analytical investigation.

Previous work from our group has resulted in a general method of analysis of microcalorimetric data that allows the recovery of both kinetic and thermodynamic parameters [2]. The method involves writing a kinetic equation that describes the reaction under study, converting it to a calorimetric form and then fitting the calorimetric data using a process of iteration. It has been shown previously how such an analysis may be applied to reactions that are perceived as being fast to medium term in duration [2,3], and to reactions that occur in the solid state [4]. It is the purpose of this paper to show how the analysis may be extended to allow the study of solution phase reactions that follow consecutive pathways, using both real and simulated data. For this work, we chose to study the acid catalyzed hydrolysis of potassium hydroxylamine trisulfonate, a reaction that proceeds via a three-step, consecutive first-order mechanism. We show how the calorimetric data recorded can be fitted to a suitable model to determine values for the rate constants and enthalpies for this reaction, and since the reaction has been the subject of previous investigations [5,6], compare our values with literature data. We also present a general protocol that should be adopted when using the Willson [2] method to fit calorimetric data.

2. Materials

Potassium hydroxylamine trisulfonate is readily prepared from potassium hydroxylamine-NN-disulfonate [5,6]. Potassium hydroxylamine-NN-disulfonate is not, however, commercially available, and was prepared by the method outlined by Palmer [7].

3. Experimental

Stock solutions of potassium hydroxylamine trisulfonate (0.01 M) and perchloric acid (0.2 M) were prepared in deionized water, and were stored at 25°C. Mixtures were prepared for experiments by dilution of the stock solutions with deionized

water. Sample mixtures were prepared by mixing aliquots of the potassium hydroxylamine trisulfonate and perchloric acid standards. The time of mixing the solutions was noted. Reference mixtures were prepared using an equivalent quantity of perchloric acid, as present in the sample, diluted in deionized water.

The calorimeter employed for these studies was an LKB 2277 Thermal Activity Monitor (TAM, Thermometric AB, Järfälla, Sweden), which was housed in a temperature controlled environment ($21 \pm 0.1^\circ\text{C}$), allowing a baseline stability of $\pm 0.1 \mu\text{W}$ over 24 h to be attained. The calorimeter was calibrated periodically using an electrical substitution method. Experiments were performed at 25°C, 30°C and 35°C, in glass ampoules. Ampoules were sealed with crimped aluminum caps, the caps being fitted with rubber sealing disks. All solutions used were pre-equilibrated at the temperature of the particular experiment, and ampoules were allowed to equilibrate in the TAM for 5 min prior to the onset of data capture. Such a short equilibration time, while not being ideal, was necessary to ensure that the maximum number of data were collected, the reaction occurring relatively quickly. The heat-flow in, or out, of the sample ampoule was recorded using the dedicated Digitam 4.1 software. Data analysis was performed using the software package ORIGINTM (Microcal Software, MA, USA) and the mathematical worksheet package Mathcad 6.0 (Mathsoft Europe, UK).

4. Results

Integration of the heat-flow (power, dq/dt (Φ), in Watts) versus time (t , in seconds) plot obtained from an isothermal microcalorimeter gives the heat output (q , in Joules) for a particular reaction. If a suitable kinetic equation can be written that describes the reaction under investigation, then if either power is plotted versus time or q is plotted versus power, it is possible, using a suitable graphics software package, to determine the constants of the kinetic expression by a process of iteration [2–4].

The calorimetric equations that describe two-step, three-step and four-step first-order reaction schemes are given by the following equations, respectively:

$$\frac{dq_{\text{obs}}}{dt} = k_1 \cdot \Delta H_1 \cdot A_0 \cdot e^{-k_1 \cdot t} + k_1 \cdot k_2 \cdot \Delta H_2 \cdot A_0 \frac{e^{-k_1 \cdot t} - e^{-k_2 \cdot t}}{k_2 - k_1}, \quad (1)$$

$$\begin{aligned} \frac{dq_{\text{obs}}}{dt} = & k_1 \cdot \Delta H_1 \cdot A_0 \cdot e^{-k_1 \cdot t} + k_1 \cdot k_2 \cdot \Delta H_2 \cdot A_0 \frac{e^{-k_1 \cdot t} - e^{-k_2 \cdot t}}{k_2 - k_1} \\ & + \Delta H_3 \left(A_0 \cdot k_1 \cdot e^{-k_1 \cdot t} - \frac{A_0 \cdot k_1}{k_2 - k_1} (-k_1 \cdot e^{-k_1 \cdot t} + k_2 \cdot e^{-k_2 \cdot t}) + \frac{k_2^2 \cdot k_1 \cdot A_0 \cdot e^{-k_2 \cdot t}}{-k_1 \cdot k_2 - k_3 \cdot k_2 + k_2^2 + k_3 \cdot k_1} \right. \\ & + \frac{k_2 \cdot k_1^2 \cdot A_0 \cdot e^{-k_1 \cdot t}}{-k_1 \cdot k_2 + k_3 \cdot k_2 - k_3 \cdot k_1 + k_1^2} - \frac{k_2 \cdot k_1 \cdot A_0 \cdot k_3}{-k_1 \cdot k_2 - k_3 \cdot k_2 + k_2^2 + k_3 \cdot k_1} \\ & \left. - \frac{k_2 \cdot k_1 \cdot A_0 \cdot k_3 \cdot e^{-k_3 \cdot t}}{-k_1 \cdot k_2 + k_3 \cdot k_2 - k_3 \cdot k_1 + k_1^2} \right), \quad (2) \end{aligned}$$

$$\begin{aligned} \frac{dq_{\text{obs}}}{dt} = & k_1 \cdot \Delta H_1 \cdot A_0 \cdot e^{-k_1 \cdot t} + k_1 \cdot k_2 \cdot \Delta H_2 \cdot A_0 \frac{e^{-k_1 \cdot t} - e^{-k_2 \cdot t}}{k_2 - k_1} \\ & + \Delta H_3 \left(A_0 \cdot k_1 \cdot e^{-k_1 \cdot t} - \frac{A_0 \cdot k_1}{k_2 - k_1} (-k_1 \cdot e^{-k_1 \cdot t} + k_2 \cdot e^{-k_2 \cdot t}) + \frac{k_2^2 \cdot k_1 \cdot A_0 \cdot e^{-k_2 \cdot t}}{-k_1 \cdot k_2 - k_3 \cdot k_2 + k_2^2 + k_3 \cdot k_1} \right. \\ & + \frac{k_2 \cdot k_1^2 \cdot A_0 \cdot e^{-k_1 \cdot t}}{-k_1 \cdot k_2 + k_3 \cdot k_2 - k_3 \cdot k_1 + k_1^2} - \frac{k_2 \cdot k_1 \cdot A_0 \cdot k_3}{-k_1 \cdot k_2 - k_3 \cdot k_2 + k_2^2 + k_3 \cdot k_1} \\ & \left. - \frac{k_2 \cdot k_1 \cdot A_0 \cdot k_3 \cdot e^{-k_3 \cdot t}}{-k_1 \cdot k_2 + k_3 \cdot k_2 - k_3 \cdot k_1 + k_1^2} \right) + H_4 \left[A_0 \cdot k_1 \cdot e^{-k_1 \cdot t} - A_0 \frac{k_1}{k_2 - k_1} (-k_1 \cdot e^{-k_1 \cdot t} + k_2 \cdot e^{-k_2 \cdot t}) \right. \\ & + \frac{k_2^2 \cdot k_1 \cdot A_0 \cdot e^{-k_2 \cdot t}}{-k_2 \cdot k_1 - k_3 \cdot k_2 + k_2^2 + k_3 \cdot k_1} + \frac{k_2 \cdot k_1^2 \cdot A_0 \cdot e^{-k_1 \cdot t}}{-k_2 \cdot k_1 + k_3 \cdot k_2 - k_3 \cdot k_1 + k_1^2} - \frac{k_2 \cdot k_1 \cdot A_0 \cdot k_3 \cdot e^{-k_3 \cdot t}}{-k_2 \cdot k_1 - k_3 \cdot k_2 + k_2^2 + k_3 \cdot k_1} \\ & - \frac{k_2 \cdot k_1 \cdot A_0 \cdot k_3 \cdot e^{-k_3 \cdot t}}{-k_2 \cdot k_1 + k_3 \cdot k_2 + k_1^2 - k_3 \cdot k_1} \\ & - \frac{k_2 \cdot k_1 \cdot k_3^2 \cdot A_0 \cdot e^{-k_3 \cdot t} \cdot (k_1 - k_2)^2}{-k_1 \cdot k_4 \cdot k_2 + k_1 \cdot k_4 \cdot k_3 - k_1 \cdot k_3^2 + k_2 \cdot k_1 \cdot k_3 - k_3^2 \cdot k_2 + k_3^2 + k_4 \cdot k_3 \cdot k_2 - k_4 \cdot k_3^2} \\ & + \frac{k_2^2 \cdot k_1 \cdot k_3 \cdot A_0 \cdot e^{-k_2 \cdot t} \cdot (k_1 - k_2)}{-k_3 \cdot k_2 - k_4 \cdot k_2 + k_4 \cdot k_3 + k_2^2} - \frac{k_2 \cdot k_1^2 \cdot k_3 \cdot A_0 \cdot e^{-k_1 \cdot t} \cdot (k_1 - k_2)}{k_1^2 - k_3 \cdot k_1 - k_1 \cdot k_4 + k_4 \cdot k_3} \\ & - \frac{k_2 \cdot k_1 \cdot k_3 \cdot A_0 \cdot k_4 \cdot e^{-k_4 \cdot t} \cdot (k_1 - k_2)}{-k_3 \cdot k_2 - k_4 \cdot k_2 + k_4 \cdot k_3 + k_2^2} \\ & + \frac{k_1 \cdot k_2 \cdot k_3 \cdot k_4 \cdot A_0 \cdot e^{-k_4 \cdot t} \cdot (k_1 - k_2)^2}{-k_1 \cdot k_4 \cdot k_2 + k_1 \cdot k_4 \cdot k_3 - k_1 \cdot k_3^2 + k_2 \cdot k_1 \cdot k_3 - k_3^2 \cdot k_2 + k_3^2 + k_4 \cdot k_3 \cdot k_2 - k_4 \cdot k_3^2} \\ & \left. + \frac{k_1 \cdot k_2 \cdot k_3 \cdot k_4 \cdot A_0 \cdot e^{-k_4 \cdot t} \cdot (k_1 - k_2)}{k_1^2 - k_3 \cdot k_1 - k_1 \cdot k_4 + k_4 \cdot k_3} \right], \quad (3) \end{aligned}$$

where A_0 is the number of moles of reactant available for reaction, k_1 , k_2 and k_3 are the rate constants and ΔH_1 , ΔH_2 and ΔH_3 are the enthalpies of the successive reaction steps, respectively.

The equations shown above may be used to generate power–time data using a mathematical worksheet. The ability to construct power–time data leads to many

advantages. Firstly, it is possible to study the effects of the values of the reaction parameters on the shape of power–time trace obtained. In this way, it is possible to study, for example, the effects of the rate constant on a particular scheme while holding the value of the reaction enthalpy constant, or to investigate the difference in the values of the rate constants for a multi-

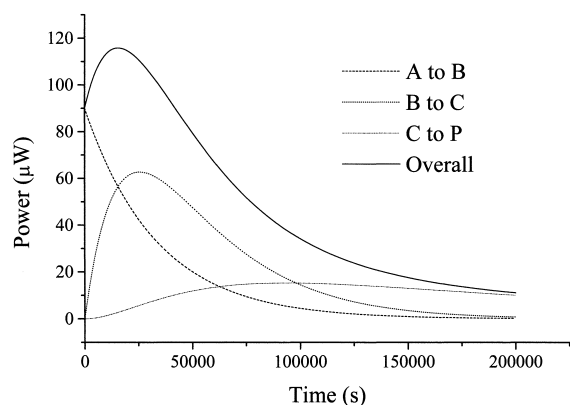
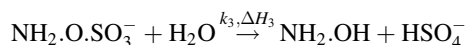
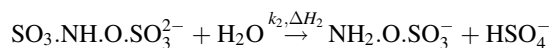
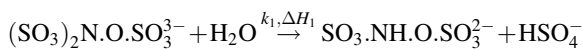


Fig. 1. Power-time data for a three-step, consecutive, first-order reaction scheme constructed using Mathcad™ having entered the following reaction parameters: $A=0.00001$ moles, $k_1=3\times 10^{-5} \text{ s}^{-1}$, $k_2=5\times 10^{-5} \text{ s}^{-1}$, $k_3=6\times 10^{-6} \text{ s}^{-1}$, $\Delta H_1=30 \text{ kJ mol}^{-1}$, $\Delta H_2=45 \text{ kJ mol}^{-1}$, and $\Delta H_3=40 \text{ kJ mol}^{-1}$. The power-time data for each of the three reaction steps are shown, as well as the overall power-time data that would be observed calorimetrically.

step reaction that is required to allow the separation of the trace into its component parts. It is also possible to model the power-time data for each of the individual steps of a particular scheme, as well as to investigate the overall power-time data that would be observed for a reaction.

Some simulated data for a three-step consecutive reaction are shown in Fig. 1. These data were created using the mathematical worksheet, having entered the values shown for the constants. Data are shown for the reaction steps $A\rightarrow B$, $B\rightarrow C$ and $C\rightarrow P$, as well as for the overall signal that would be observed calorimetrically. These data may then be exported into a mathematical fitting program, and treated as if they were real data. It is possible to fit the data to a suitable model and recover the values of the reaction parameters. Since the values of the parameters are known absolutely, because they were used to construct the original data, it is possible to know precisely if the fitting procedure is accurate. In this way, it is possible to gain experience in the techniques of fitting and to understand how a particular model behaves.

To apply the models to real data, we chose to study the acid catalyzed hydrolysis of potassium hydroxylamine trisulfonate, which reacts according to the following model:



The reaction has been studied previously using a titration method [5,6], and a number of kinetic data are available. The hydrolysis of the trisulfonate ion is the fastest of the three steps, and produces the relatively stable hydroxylamine-NO-disulfonate ion. Potassium hydroxylamine-NO-disulfonate is stable enough to be recrystallized from dilute acid solution. The disulfonate is hydrolyzed slowly in dilute acid solution forming the hydroxylamine-O-sulfonate ion and, eventually, hydroxylamine and hydrogen sulfate. The published kinetic studies were based on titration, using ^{35}S labeled compounds. The first hydrolytic step was observed to proceed at a much faster rate than the second and third hydrolyses, the final two hydrolyses proceeding at similar, slow, rates. Kinetic data for the three steps are represented in Table 1.

It is notable that the authors of the above work were not able to conduct the assay titrations at 25°C for the second hydrolytic step, since the rate of reaction was too slow, and that a very high concentration of acid was required to enable the third hydrolytic step to be studied at 25°C ; that is, the reaction conditions had to be varied extensively to allow the investigation of the second and third hydrolytic steps. Using the microcalorimeter, it was possible to study the reaction directly at 25°C , 30°C and 35°C .

The microcalorimetric data were fitted to (2), in order to recover the values of the reaction parameters. The study reaction undergoes both endo- and exother-

Table 1
Kinetic data for the acid catalyzed hydrolysis of potassium hydroxylamine trisulfonate

Reaction	Temperature ($^\circ\text{C}$)	$[\text{HClO}_4]$ (M)	$10^4 k$ (s^{-1})	I (M)
Step 1 ^b	25.0	0.0005	0.089	0.0011 ^a
Step 2 ^b	75.0	0.025	1.80	0.025
Step 3 ^c	45.0	0.0708	0.042	1.00
Step 3 ^c	25.0	1.01	0.085	1.05

^aIonic strength adjusted using NaClO_4 .

^bData reproduced from [5]: $[\text{trisulfonate}]=0.01 \text{ M}$.

^cData reproduced from [6]: $[\text{monosulfonate}]=0.04 \text{ M}$.

mic processes and, consequently, the reaction parameters must include both positive and negative ΔH values. Since there are no data available in the literature for these constants, the initial estimates for the enthalpy values entered into the fitting package were all positive, and the iterative process determined the signs of the final constants. The value of A_0 was calculated to equal 3×10^{-6} moles, and was set as a constant. It was observed that the model gave an excellent fit to the data.

Values for the reaction parameters returned from the fitting process for each data set are represented in Tables 2 and 3. Note that, in all cases, the iterative procedure returned values for ΔH_1 that were positive and values for ΔH_3 that were negative, but the sign of ΔH_2 varied with temperature. For reactions studied under identical conditions, the fitting process returned values that were generally reproducible (the one exception is the values returned for ΔH_1 at 30°C).

Table 2

ΔH values for the acid catalyzed hydrolysis of potassium hydroxylamine trisulfonate (0.001 M), determined by fitting power–time data to Eq. (2) (reactions were conducted using an acid concentration of 0.0005 M)

Temperature (°C)	ΔH_1 (kJ mol ⁻¹)	ΔH_2 (kJ mol ⁻¹)	ΔH_3 (kJ mol ⁻¹)
35	134.0	104.8	-167.7
35	147.0	141.0	-82.36
35 (Average)	140.5	122.9	-125.0
30	135.3	-31.75	-37.44
30	56.37	-35.21	-36.23
30 (Average)	95.84	-33.48	-36.84
25	28.30	-82.23	-47.39

Table 3

Rate constant values for the acid catalyzed hydrolysis of potassium hydroxylamine trisulfonate (0.001 M), determined by fitting power–time data to Eq. (2) (reactions were conducted using an acid concentration of 0.0005 M)

Temperature (°C)	k_1 (s ⁻¹)	k_2 (s ⁻¹)	k_3 (s ⁻¹)
35	5.5×10^{-4}	4.3×10^{-5}	2.6×10^{-4}
35	4.7×10^{-4}	5.0×10^{-5}	2.1×10^{-4}
35 (Average)	5.1×10^{-4}	4.8×10^{-5}	2.3×10^{-4}
30	4.4×10^{-4}	2.9×10^{-5}	5.8×10^{-5}
30	4.4×10^{-4}	2.6×10^{-5}	6.6×10^{-5}
30 (Average)	4.4×10^{-4}	2.8×10^{-5}	6.2×10^{-5}
25	4.2×10^{-4}	4.6×10^{-6}	6.7×10^{-6}

It should be borne in mind that, when fitting data to an equation which is quite complex, it is possible to obtain a large number of answer sets, each of which appears to be equally valid. It was observed that, when fitting the power–time data from each of the study reactions, many answer sets were obtained, each giving what appeared to be an excellent fit line to the data. The values of the enthalpy parameters varied widely in each answer set, and it was necessary to choose the answer set giving the lowest χ^2 (the program's statistical measure of fit) value. This problem has been noted previously [7,8] for consecutive reaction schemes. It follows that, if any literature values for any of the enthalpy parameters were available, it would be possible to compare the answer sets with these values, to aid the fitting process, but this was not possible.

However, Candlin and Wilkins [5,6] did publish values for the rate constants for the individual hydrolytic steps, and although the published data were not recorded under the same conditions as the experimental data presented above, some comparisons can be made. At 25°C, the published value for k_1 is $8.9 \times 10^{-6} \text{ s}^{-1}$, compared with the value determined from the fitting procedure of $4.2 \times 10^{-4} \text{ s}^{-1}$, a 100-fold difference in reaction rate. The only other value determined at 25°C is k_3 , determined to equal 8.5×10^{-6} by Candlin and Wilkins [5,6] and $6.7 \times 10^{-6} \text{ s}^{-1}$ by fitting microcalorimetric data. However, the published value was determined with an added acid concentration of 1.01 M, far in excess of the 0.0005 M acid used in the calorimetric experiment.

It was noted above that, when choosing an equation to which to fit some microcalorimetric data, the equation with the fewer or fewest variables, but which gives an acceptable fit line, should be selected. This applies to reactions where the exact mechanism of reaction is unknown. In the case of the hydrolysis of potassium hydroxylamine trisulfonate it is known that the reaction follows a three-step consecutive reaction scheme, and that was the model chosen for fitting. However, it might seem reasonable to assume that, at such a low added concentration of acid, the third hydrolytic step might not occur during the lifetime of the experiment. If that were the case, then the reaction would follow a two-step consecutive reaction scheme, and following the advice given above, should be fitted to a model with fewer variables. Eq. (1)

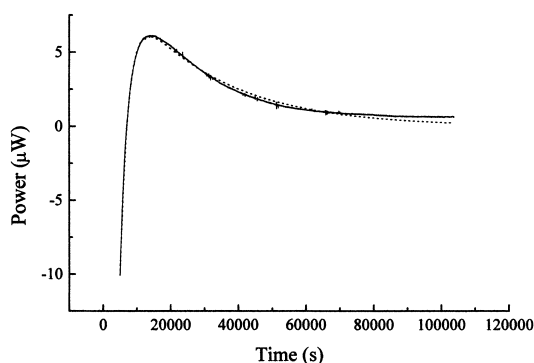


Fig. 2. Power–time data for the hydrolysis of potassium hydroxylamine trisulfonate (0.001 M) at 35°C, with 0.0005 M acid added, and the fit line (dotted) obtained after the data were fitted to Eq. (1).

describes power–time data for a reaction undergoing a two-step consecutive mechanism and this was used to fit the microcalorimetric data. A typical fit line is shown in Fig. 2. It can be seen that, using the two-step consecutive model, it was not possible to obtain a good fit line to the microcalorimetric data. The fit is good over the initial section of data, which is to be expected since, over this region, the first two reaction steps predominate and the reaction is essentially a two-step process. As the reaction progresses, the third step begins to contribute to the observed signal, and the model no longer describes the overall reaction. This is a good evidence that the data observed derive from a three-step process, and that Eq. (2) was the best choice model for fitting the data.

Since the microcalorimetric data were recorded at three temperatures, it is possible to plot $\ln k$ versus $1/T$ and obtain estimates for the values of the activation energies for each step. These values are listed in Table 4. It can be seen from the values given in Table 4 that the activation energy of the first step is considerably lower than those of the second and third steps.

An additional benefit of using the mathematical worksheet is that, using the data presented in Tables 2 and 3, it is possible to deconvolute the power–time curves for the individual reactions. The process is, essentially, the reverse of the way microcalorimetric data were simulated earlier. The reaction parameters, obtained from the fitting process, are entered into the worksheet and the power–time curves for the three

Table 4

Activation energies determined via an Arrhenius analysis for the three reaction steps of the hydrolysis of potassium hydroxylamine trisulfonate (0.001 M)

Concentration of acid (M)	Activation energy (kJ mol^{-1})		
	Step 1	Step 2	Step 3
0.0005	14.74	179.3	270.7

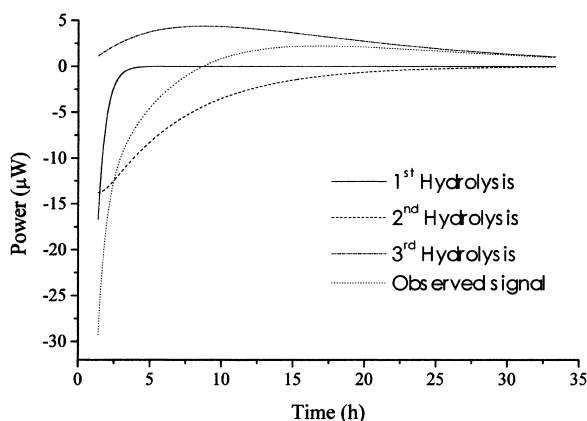


Fig. 3. Deconvolution of the observed power–time data obtained for the hydrolysis of potassium hydroxylamine trisulfonate (0.001 M) at 30°C using the mathematical worksheet.

individual hydrolytic steps are constructed. An example is shown in Fig. 3. The ability to separate complex microcalorimetric signals into their component parts using specific models is a significant advance in the analysis of microcalorimetric data and, in a future publication, we will show how more complex parallel, consecutive/parallel and higher order reaction schemes may be analyzed in a similar way.

5. Summary

The Willson method [4] is based on fitting calorimetric data to a specific model. The work presented here shows how such an analysis may be extended to allow the analysis of calorimetric data derived from reactions undergoing consecutive, solution phase reactions. The use of simulated data and the ability to model accurately specific reaction schemes have

many advantages. It is now possible to model many complex reactions, and to explore the behavior of those reactions, without the need to obtain real microcalorimetric data. In this way, it is possible to examine the effects of varying the reaction parameters, such as the rate constants or reaction enthalpy, on the power–time signal that would be obtained, and to learn how a reaction behaves before starting a series of experiments. Having constructed some data, it is possible to import those data into a mathematical fitting program, and treat them as if they are real microcalorimetric data. It is then possible to learn how to fit those data to a model. It is possible to explore the effects of fitting different equations to the data, to see if the mechanism of reaction can be deduced on the basis of the fit lines obtained.

The study of the hydrolysis of potassium hydroxylamine trisulfonate has proved the ability to fit microcalorimetric data, derived from a reaction undergoing a complex reaction mechanism, to a model, and to use the reaction parameters obtained to deconvolute those data.

It follows that it is possible to follow a protocol for analyzing microcalorimetric data for reactions where the mechanism is unknown. The data should be fitted to a series of models based on rate equations to determine which scheme gives the best fit. Using the parameters obtained, it is possible to determine at what time, following initiation of the reaction, any

reaction intermediates will be present at maximum concentration and a chemical assay technique, such as HPLC, can be employed. In this way, it is possible to gain both mechanistic and molecular information. This is a significant step forward in the analysis of microcalorimetric data.

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