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The imidazole catalysed hydrolysis of triacetin: an inter- and intra-laboratory development of a test reaction for isothermal heat conduction microcalorimeters used for determination of both thermodynamic and kinetic parameters

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Abstract

This paper reports the outcomes of an inter- and intra-laboratory microcalorimetric investigation of the triacetin hydrolysis reaction in an imidazole/acetic acid buffer system. The purpose was to establish whether this reaction would be an appropriate test reaction system for validation of isothermal heat conduction microcalorimeters used to determine both thermodynamic and kinetic data. To be acceptable for this purpose a reaction should be simple to perform, robust in operation, undemanding with respect to sources of chemicals, operators, calorimeters and their operating procedures (within defined limits). The reaction system studied is shown to fulfil these criteria. For this second-order reaction, performed at 298 K the recommended

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values for the reaction rate constant, k, and the enthalpy change, $\Delta_R H$, are: $k = 2.80 \pm 0.10 \times 10^{-6}$ dm^3 mol^{-1} s^{-1}; $\Delta_R H = -91.7 \pm 3.0$ kJ mol^{-1}.

Keywords: Microcalorimetry; Test reaction; Thermodynamics; Kinetics; Triacetin

1. Introduction

In 1998, a Workshop was held in Torino, Italy under the auspices of the Commission on Thermodynamics (1.2) of IUPAC on the topic "Calibration of Calorimeters". One of the authors of this paper (AEB) was a member of the organising Committee and the proceedings of this Workshop have been published [1]. In 1998, AEB was charged by the (US) Calorimetry Conference with investigating potential reactions for use in test procedures for isothermal heat conduction microcalorimeters. In 2001 Wadsö (Physical Chemistry 1, University of Lund, Sweden), as Chairman of a sub-Committee on Standards and Calibration in Calorimetry (AEB and Buckton were also members of this sub-Committee), will present a final report to the IUPAC Commission on Thermodynamics (1.2) for acceptance. Interest in this area currently appears to be high and establishing test procedures for calorimeters is perceived as essential [2].

Suitable reactions for such test procedures have to satisfy clear criteria and be of obvious and significant use to calorimetrists.

Firstly, regulatory authorities require that experimental data be obtained from validated instruments, i.e. that an appropriate test system yielding established results can be performed successfully. Secondly, any subsequent experimental data recorded on that same instrument can be traced to the establishment of performance in that instrument for a defined test system.

Therefore, any test system must be robust, simple to perform, require commonly available materials which require no significant preparation prior to use (triacetin is a common pharmaceutical excipient and the other materials are available in analytical grade quality), applicable to a range of commercially available microcalorimeters.

Further uses of such a test reaction will be: training of new operators in the operation of microcalorimeters and the analysis of experimental data, "trouble-shooting" the causes of poor/imprecise instrument performance (a further paper on this topic has been accepted for publication in this Journal), judging appropriate locations for the laboratory siting of microcalorimeters (judged against manufacturer's performance specifications).

To examine these criteria and to establish its utility an intra- and inter-laboratory trial of the imidazole catalysed hydrolysis of triacetin was undertaken. The results of this investigation are reported in this paper. This reaction has been proposed previously [3] as "a test and calibration process for microcalorimeters used as thermal power meters". The report lists the time-dependent thermal power outputs expected from this system under defined reaction conditions without specifying values for the reaction rate constant or for the reaction enthalpy change. A more recent paper [4] analysed calorimetric output data for this reaction using the iterative procedure noted below and identified values for k and for $\Delta_R H$. These experiments were performed using a slightly different protocol to that described in this paper. The results were, therefore, not part of the inter- and intra-laboratory trials reported here.

To facilitate this study a protocol was established at the University of Greenwich and subsequently circulated to all the participating laboratories — a mix of academic and industrial collaborators.

The interest in such test reactions for isothermal heat conduction microcalorimeters arises, in part, from the recently demonstrated capacity of these instruments to allow both thermodynamic and kinetic parameters to be determined [5]. The details of this early approach to the analysis of calorimetric data output have been given [5,6] as have outlines of their application to, for example, problems associated with the determination of long-term stability in pharmaceuticals, compounds and industrial materials ([4] and references therein). The advantages cited are: direct, non-destructive, non-invasive observation on the sample; control of environmental conditions; speed of procedures.

These earlier methods [5,6] required the assumption that all the material loaded into the calorimeter would react. This is obviously a severe constraint on the utility and application of the methods. Furthermore,

the determination of values for the reaction rate constant, k, and the reaction enthalpy change, $\Delta_R H$ (hereafter H for simplicity) involved an iterative procedure. Recent developments [7] now allow direct calculation of all the required parameters without the need for prior assumptions. Thus, it is now possible to determine values for reaction order, n; reaction rate constant, k; reaction enthalpy change, H; equilibrium constant, K, for those reactions which do not go to completion; the Gibb's function value, G; the entropy change, S. The new procedures require that the system under investigation be studied over a range of temperature (most usefully at around ambient/storage conditions). Thus, it is possible to determine, in addition, the activation energy, E_a. The collaborators in this study have used a variety of commercially available calorimeters requiring different operating procedures. Experiments have been performed over the temperature range 20–80°C. The results reported here refer to data using the final protocol. Some of the authors of this paper (RJW; TCH & JB; MAP & RAW; EAS; LDH; MKP) contributed to the development of this protocol by examining earlier versions. For consistency and brevity of presentation their results are not reported here but they are entirely consistent with the values of k and H established.

2. The protocol

Temperature 298 K (controlled, for example, at the set temperature in the Thermometric TAM to $\pm 10^{-4}$ K).

Buffer: 1.6 g acetic acid, 2.72 g imidazole made up to 10 ml with de-ionised water.

Reaction: weigh 0.267 g triacetin, to this add buffer making up to 5 ml. Ensure thorough mixing as triacetin is not readily soluble. Note the time of addition of buffer to triacetin — this is time = 0. Pipette a suitable volume of this solution into a calorimetric ampoule (3 ml for a Thermometric AB, Järfälla, Sweden, thermal activity monitor (TAM). For other instrument volumes used see below. These instructions and the subsequent data analysis refer only to experiments performed in the batch or ampoule mode. A further paper will describe the application of this test reaction system to flow microcalorimeters). Place the triacetin sample into the calorimeter for the appropriate equilibration time using as the reference an ampoule loaded with, for the TAM example, 3 ml of buffer solution. Glass, stainless steel and Hastalloy ampoules have been used successfully in this trial. In the ampoule mode no stirring is used. After equilibration commence data recording (thermal power, time) noting the time after buffer addition. It is recommended that one data point be recorded every 2 min and that recording be continued for 4 days. Import the data into a suitable graphics fitting programme such as Origin (Microcal, Amherst, MA, USA) and fit to the following equation:

$$\frac{dq}{dt} = -HVk\left(\frac{[A_0]}{1 + [A_0]kt}\right)^2$$

where dq/dt is the thermal power, k the reaction rate constant, H the reaction enthalpy change, $[A_0]$ the initial concentration of triacetin, t the time and V is the volume of solution placed into ampoule.

In the fitting procedure the order of reaction is fixed as 2, as is the initial concentration (see below for comment on this requirement) and volume of the triacetin solution. The values of k and H are allowed to vary to obtain a good fit (lowest value of χ^2) to the experimental data.

The rate of reaction is dependent upon buffer composition (this, and its temperature dependence will be the subject of a further publication) and hence study of buffers containing 2.5, 2.6 and 2.8 g imidazole would be useful.

3. Results

The hydrolysis of this tri-ester evidently is well described by a second order kinetic equation over the whole lifetime so far studied (100 days) of the process. There appears therefore, no steric control over the rate of reaction.

The empirical results described by Chen and Wadsö [3] can be analysed for values of k and H following an assumption about the volume of solution employed (weight of solution is specified in the paper not volume: a density of 1 g ml^{-1} was assumed). Their results approximate to those reported here, i.e. the values of k and H reported in this paper give a satisfactory fit to their published thermal power — time data.

Beezer et al. [7] demonstrate that a test for complete reaction (i.e. the absence of a detectable equilibrium in the reaction) is the enthalpy change, when normalised

to mass or moles of reaction, for the study reaction should be independent of temperature. (Provided the reaction mechanism is constant over the temperature range considered and that H does not vary with temperature. See [7] for discussion of this point.) This condition was met with the triacetin reaction over the temperature range 20–80°C (data to be published in a further paper. There is some evidence that, at temperatures in excess of 80°C this condition does not hold.) It is, therefore, appropriate to apply the equation above to the analysis of output data for this reaction and the results from the collaborating laboratories are listed below. A Thermometric TAM was used unless otherwise specified.

Experiment	$[A_0]$ (mol dm^{-3})	V (dm^3)	H (kJ mol^{-1})	k (dm^3 mol^{-1} s^{-1})
Hills (University of Kent)				
1	0.245	0.003	−89.39	2.98×10^{-6}
2	0.245	0.003	−96.20	2.61×10^{-6}
3	0.245	0.003	−91.40	2.83×10^{-6}
Lane, Gaisford and Buckton (London School of Pharmacy)				
1	0.245	0.003	−95.76	2.73×10^{-6}
2	0.245	0.003	−87.74	2.96×10^{-6}
3	0.245	0.003	−92.18	2.85×10^{-6}
4	0.245	0.003	−89.76	2.92×10^{-6}
O'Sullivan (AstraZeneca, UK)				
1	0.245	0.003	−108.46	3.16×10^{-6}
2	0.245	0.003	−120.51	2.64×10^{-6}
Wolf and Baitalow (Institute of Physical Chemistry, Freiberg, Germany) Setaram Micro DSC III				
1	0.245	0.009	−89.6	2.81×10^{-6}
2	0.245	0.009	−90.9	2.84×10^{-6}
3	0.245	0.009	−97.3	2.62×10^{-6}
4	0.245	0.009	−86.8	2.95×10^{-6}
Setaram DSC C-80				
1	0.245	0.01	−93.7	2.76×10^{-6}
DAK				
1	0.245	0.005	−91.8	2.89×10^{-6}
2	0.245	0.005	−93.1	2.78×10^{-6}
Kierstan (Medway Sciences, University of Greenwich)				
1	0.245	0.003	−90.03	2.8×10^{-6}
2	0.245	0.003	−92.41	2.78×10^{-6}
3	0.245	0.003	−95.53	2.69×10^{-6}
4	0.247	0.003	−88.47	2.77×10^{-6}
O'Neill (Medway Sciences, University of Greenwich)				
1	0.245	0.003	−91.11	2.79×10^{-6}
2	0.246	0.003	−94.03	2.75×10^{-6}
3	0.244	0.003	−85.87	2.82×10^{-6}
4	0.245	0.003	−91.89	2.78×10^{-6}
Morris (Medway Sciences, University of Greenwich)				
1	0.245	0.003	94.31	2.71×10^{-6}

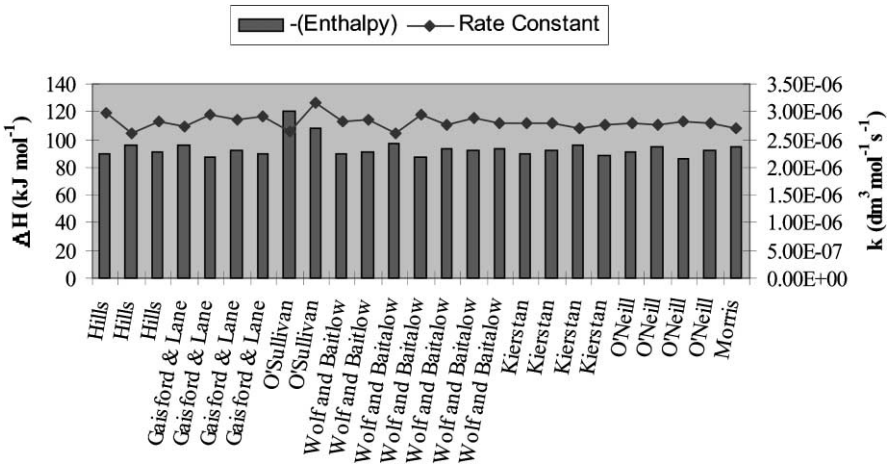

Fig. 1.

Fig. 1 shows the collected data in bar diagram format where the excellent consistency is apparent. One set of data shows good agreement with all other sets for the values of k but shows somewhat higher values for H. The availability of a test reaction allows the exploration of possible reasons for these observations and these will be described in a subsequent paper which has been accepted for publication in this Journal and which will appear shortly.

4. Conclusions

The triacetin reaction satisfies all the criteria outlined in the Section 1. It appears well suited to the role of a test reaction and the applications described in the Section 1 for such a system.

The recommended ''best'' values are simply the means of all the reported values (excluding the data set that shows the high H values) and are: reaction rate constant, $k = 2.80 \pm 0.10 \times 10^{-6}\,\mathrm{dm^3\,mol^{-1}\,s^{-1}}$; reaction enthalpy change, $H = -91.7 \pm 3.0\,\mathrm{kJ\,mol^{-1}}$.

Therefore, for a given calorimeter, it will be possible to trace data for other reacting systems to this test reaction system and hence validate values for k and H. Furthermore the capacity to make experimental determinations of H for long slow reactions indicates that a new, direct and experimentally based thermochemistry is now accessible.

As noted above a further paper on the imidazole concentration dependence and temperature dependence of this reaction is in preparation.

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