The stability of benzoyl peroxide by isothermal microcalorimetry

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Abstract

Isothermal microcalorimetry may be used to determine kinetic and thermodynamic parameters for chemical reactions. This paper reports rate constants, determined as a function of temperature, and the activation enthalpy for the degradation of solid benzoyl peroxide as determined by isothermal microcalorimetry. Studies were conducted on aqueous suspension phase, solid benzoyl peroxide. In addition, supporting evidence is cited from work carried out in this laboratory on the solution phase degradation of benzoyl peroxide using UV-visible spectrophotometry. The activation energy obtained by microcalorimetry was $E_a = 137.8 \pm 6.6$ kJ mol^{-1} and the activation energy obtained from UV-visible spectrophotometry was $E_a = 112.7 \pm 4.2$ kJ mol^{-1}. © 2001 Elsevier Science B.V. All rights reserved.

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1. Background

Benzoyl peroxide (BPO) is a non-toxic, colourless, odourless and tasteless crystalline solid. It is used to treat acne and products containing it are available 'over the counter'. It is, therefore, of commercial importance to know the degradation rate of benzoyl peroxide as a raw material a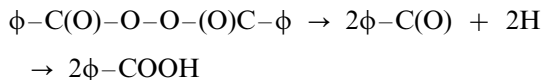nd in formulated products. This paper reports the microcalorimetric determination of the rate constants for the degradation of benzoyl peroxide under controlled conditions together with the associated value for the activation energy.

Pure (98%) benzoyl peroxide crystals are commercially available and extremely flammable and shock sensitive. Benzoyl peroxide is also available commercially as a 75% suspension of crystalline solid in water. These wet crystalline solids are less flammable and less shock sensitive than pure, dry crystals, allowing for safe shipment.

Benzoyl peroxide is very unstable and degrades to form benzoic acid in solution via a free-radical mechanism.

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$$\phi\text{–C(O)–O–O–(O)C–}\phi \rightarrow 2\phi\text{–C(O)} + 2H$$

$$\rightarrow 2\phi\text{–COOH}$$

This occurs because of the instability of the O–O bond (bond energy approximately 120 kJ mol^{-1}, compared with 143 kJ mol^{-1} for a O–O bond and 498 kJ mol^{-1} for O–O bond).

2. Introduction

Nearly all physical and chemical processes are accompanied by changes in enthalpy (there are very few thermoneutral reactions). Isothermal calorimeters have successfully been used for the prediction of long term stability of drugs and chemical compounds (Willson, 1995). Modern commercially available instruments are, in principle, able to monitor a reaction that has a first-order rate constant of 1×10^{-11} s^{-1} at 298 K. Such a reaction has a half-life of 2200 years and an annual degradation rate of 0.03% (Willson et al., 1996). Degradation rates for pharmaceutical compounds are usually determined using techniques such as HPLC, NMR and DSC, following long term storage of the compound, often at elevated temperatures to accelerate the rate of reaction. All these techniques have problems associated with the experimental procedure for the analysis of degradation products, and are only valid if the mechanism of the reaction remains the same over the entire temperature range of the experimental data and subsequent extrapolation. The greater detection limits of these methods leads to an increased time (months to years) period being required before analysis can be accurately performed. An isothermal microcalorimeter allows the study of reactions in one or multiple phases under specifically controlled conditions such as temperature, pressure, humidity and gas partial pressure. The sample environment may, therefore, be controlled and maintained at ambient storage conditions. Furthermore the low detection limit of modern microcalorimeters allows *direct* and *continuous* observation of a reaction rate. Quantitative degradation data can, therefore, be obtained within 50 h (Willson, 1995).

It is notable that the study of the degradation rate of benzoyl peroxide via classical means has necessarily been followed at elevated temperatures (Pryor, 1966). The rate constant determined at 100 °C is 3.84×10^{-4} s^{-1} and the derived activation energy from studies at temperatures around 100 °C is 125.5 kJ mol^{-1}.

Isothermal calorimetry is being used more frequently as an analytical tool for the prediction of the long-term stability of drugs and compounds manufactured in the pharmaceutical industry (Ford and Willson, 1999). In preformulation and formulation work, accelerated isothermal calorimetric studies are commonly used to predict drug stability properties (Wadso, 1997; Ford and Willson, 1999).

In a heat conduction microcalorimeter the recorded signal is of thermal power, dq/dt in μW ($= \mu$J s^{-1}) as a function of time. The thermal power is proportional to the rate of the reaction and the time integral of the signal is proportional to the heat change (q, J) evolved or absorbed during the process. The size of the monitored thermal power signal depends on factors such as the rate constant, the enthalpy change of the process (or processes, if more than one reaction occurs simultaneously) and the amount of reacting material. By increasing the temperature, the reaction rate will increase. If there are many simultaneous reactions and/or the reaction products degrade further, the enthalpy changes associated with these reactions will also contribute toward the thermal power and may complicate interpretation of the registered output signal. Gaisford et al. (1999) have, however, demonstrated that complex consecutive reactions (of the A→B→C→D type) can be successfully analysed via this calorimetric technique.

This paper reports the determination of the rate constants, enthalpy and activation energy for the degradation of benzoyl peroxide from study over the temperature range 20–45 °C. The results are comparable with those obtained at higher temperatures (Pryor, 1966) and extrapolated to 25 °C.

3. Theory

The background and theoretical development of the equations used to determine thermodynamic and kinetic parameters from isothermal heat conduction calorimetry have been discussed previously (Willson et al., 1996).

An estimate of the degradation rate at 20 °C can be obtained from the Arrhenius equation:

$$k = A\,\mathrm{e}^{-Ea}/_{RT} \tag{1}$$

In Eq. (1), A is the pre-exponential factor, E_a is the activation energy, R is the gas constant, and T is the absolute temperature.

4. Experimental

Hydrated benzoyl peroxide (75% crystalline benzoyl peroxide + 25% water) was supplied by Akzo Nobel. The calorimeter used in these studies was a Setaram MicroDSC III operated in the isothermal mode. Samples (0.5 g) were weighed into Hastalloy closed batch vessels using an inert reference system (here talc was chosen purely for convenience), and loaded in the MicroDSC III (Setaram, Caluire, France: the instrument was operated following the manufacturer's instructions). Baseline drift was determined with both cells loaded with talc and over a 24 h period was less than 0.1 mW. A 30 minute equilibration time was allowed before data was collected, using the dedicated SETSOFT software package operating under WINDOWS™.

Samples of 0.5 g benzoyl peroxide were analysed using the microcalorimeter operated in the isothermal mode at 20 °C, 25 °C, 30 °C, 40 °C and 45 °C. The calorimetric data were analysed as described in the experimental section (Willson et al., 1996).

Calorimetric runs were carried out for approximately 16 h before the experiment was terminated. The data collected using the SETSOFT software was then processed using the ORIGIN™ graphics package (MicroCal, Amherst, Mass., USA). This was used to calculate kinetic and thermodynamic parameters as described previously (Willson et al., 1996).

The UV-visible studies were carried out on a sample of 1.33 g of benzoyl peroxide in 100 ml deionised water and stirred in a thermostatted vessel at the required study temperatures. Samples were taken at specified time intervals, and filtered through a 0.22 μm membrane filter, to eliminate small particulates, and the UV-visible spectrum recorded (HP 8452 diode array spectrophotometer fitted with a Peltier heating/cooling facility). The production of benzoic acid was followed at 270 nm.

UV-visible studies showed that benzoyl peroxide had a negligible (i.e. could not be detected in solution from the diode array spectrophotometer used in these studies) solubility in water and the UV-visible spectrum of benzoyl peroxide was identical with that of benzoic acid (BA). This was further verified by carrying out starch–iodine tests to test for the presence of peroxides on filtered aqueous saturated solutions of benzoyl peroxide.

5. Results and discussion

5.1. Isothermal microcalorimetry

A linear plot of ln (power) vs. time yields the first order rate constant from the slope (linearity in these plot indicates first order behaviour (Willson et al., 1996)). The rate constants are displayed in Table 1 where it is apparent that the associated standard deviations are high. These determined rate constants (ca. $10^{-9}\,\mathrm{s}^{-1}$) indicate a half life of about 22 years. Given the heterogeneous nature of the experimental system (a 75% solid crystalline suspension, of variable particle size, in water) and the slow reaction rate this is, perhaps, not surprising. Confidence in the data can be improved by noting that the Arrhenius plot of ln k vs. $1/T$ is linear over the study temperature range (Fig. 1). The power–time curves for the benzoyl peroxide reaction as a function of temperature show the rate of reaction increases with increasing temperature. The Arrhenius plot constructed from the isothermal microcalorimetric data results in calculation of E_a and A as; $E_a = 137.8 \pm 6.6$ kJ mol^{-1} and $A = 4.7 \times 10^{15} \pm 13.7$ s^{-1}.

Table 1
The kinetic parameters for the degradation of benzoyl peroxide

T (°C)	k^a (s^{-1}) (Microcalorimetry)	k^b (s^{-1}) (UV)
20	$1.16 \times 10^{-9} \pm 3.74 \times 10^{-9}$	–
25	$4.33 \times 10^{-9} \pm 3.59 \times 10^{-9}$	–
30	$6.85 \times 10^{-9} \pm 1.33 \times 10^{-8}$	–
35	$2.00 \times 10^{-8} \pm 2.83 \times 10^{-8}$	–
40	$5.84 \times 10^{-8} \pm 2.53 \times 10^{-8}$	–
45	$1.07 \times 10^{-7} \pm 8.49 \times 10^{-9}$	–
55	–	$1.00 \times 10^{-5} \pm 1.50 \times 10^{-6}$
70	–	$7.00 \times 10^{-5} \pm 9.92 \times 10^{-6}$
90	–	$5.4 \times 10^{-4} \pm 6.00 \times 10^{-5}$

[a] Microcalorimetric rate constants obtained with experiments with 0.5 g benzoyl peroxide and talc reference.

[b] Rate constants obtained with experiments using 1.33 g of benzoyl peroxide in 100 ml water using UV-visible spectrophotometry.

A comparable rate constant for this reaction has also been reported by Willson (1995) for the isothermal degradation of benzoyl peroxide at room temperature. Willson also reports the enthalpy change associated with the degradation process as -19.2 ± 0.7 kJ mol^{-1}, which is in good agreement with the results found in this study (-18.7 ± 0.8 kJ mol^{-1}) and with the theoretical enthalpy change for the process (-20.5 kJ mol^{-1}), calculated from gas phase bond energies.

5.2. UV-visible spectrophotometry

The UV-visible studies of benzoyl peroxide in water, which monitored the rate of production of benzoic acid, showed rate profiles that did not go through the origin as expected. This was thought to be owing to the presence of a residual amount of benzoic acid in the original sample, inevitably formed as benzoyl peroxide is in the hydrated form.

It is therefore difficult because of the unquantifiable initial content of BA, but feasible to deduce the rate of degradation of benzoyl peroxide by studying the production of benzoic acid at higher temperatures (55 °C–90 °C) up to the limit of solubility of benzoic acid in water at these elevated temperatures. Rate data for the production of BA from BPO at 55, 70 and 90 °C are presented in Table 1.

The microcalorimetric results correlate well with data provided by the suppliers on the degradation of benzoyl peroxide in chlorobenzene solvent with $E_a = 122.4$ kJ mol^{-1} and $A = 6.9 \times 10^{13}$ s^{-1}. The activation energy obtained from UV-visible spectrophotometry on aqueous solutions at 55, 70 and 90 °C is $E_a = 112.7 \pm 4.2$ kJ mol^{-1} and $A = 9.2 \times 10^{12} \pm 1.7$ s^{-1}.

Fig. 1. Arrhenius plot for the degradation of solid benzoyl peroxide.

6. Conclusions

Isothermal heat conduction microcalorimetry can be used to evaluate benzoyl peroxide stability. It is also possible to determine the concentration of benzoic acid in a sample of benzoyl peroxide by UV-visible spectrophotometry to obtain higher temperature degradation data.

The capacity of the calorimeter to make rapid (16 h per experiment), real-time observations on an experimental system, which is closely related to the commercially produced material, is significant. Considerable savings in time and experi-
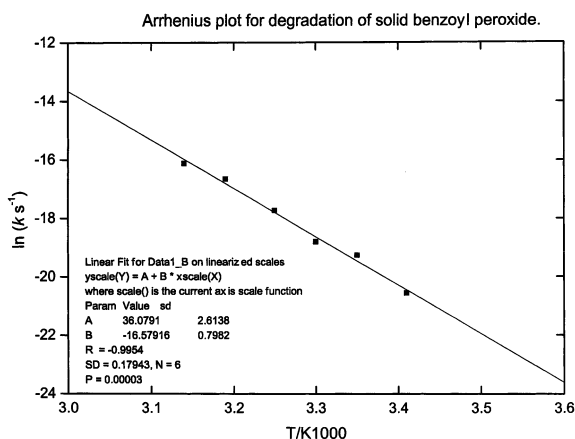
mental complexity are made through the use of the calorimetric technique. Such advantages may prove useful in industrial contexts.

The rate constants determined at temperatures appropriate for storage from the isothermal microcalorimetric studies compare favorably with those calculated from the high temperature UV study reported here, and from other high temperature data reported in the literature. We take this to mean that the benzoyl peroxide degradation reaction is reasonably well behaved over this wide temperature range and hence the Arrhenius equation satisfactorily estimates the values of the rate constant at significantly lower temperatures. Isothermal microcalorimetry is to be preferred, however, as direct non-invasive determination of the kinetic parameters under conditions appropriate for storage is on the hydrated crystalline material supplied. The natural extension of this study is that direct, non-invasive study of formulated preparations of benzoyl peroxide is now possible.

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