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Kinetic study of the drug acetazolamide using thermogravimetry

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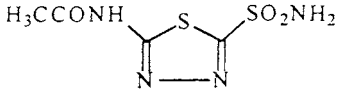
Abstract

The drug acetazolamide ($C_4H_6N_4O_3S_2$) was studied using a simultaneous thermogravimetric–differential thermal analysis (TG–DTA) unit. The study covered the temperature range of ambient to 600 °C. The DTA showed a melting point of 258.5 °C followed by a three-stage decomposition. The TG–DTG plots clearly show the decomposition when subjected to heat treatment in a nitrogen atmosphere. A kinetic analysis of all stages was attempted, where a zero-order process appeared to be the best fit mechanism and plots of ln k versus T^{-1} show this. The values of E_{act} are shown to vary throughout each stage as the reaction progressed.

1. Introduction

Acetazolamide has the formula $C_4H_6N_4O_3S_2$ and its structural formula is given in the following figure. It finds use in the treatment of epilepsy and glaucoma. It is an unsubstituted sulfonamide. All unsubstituted sulfonamides inhibit the enzyme carbonic anhydrase. No other class of compounds approaches these in activity [1]. It is a white crystalline powder. The melting point is reported to be 258–259 °C and at this temperature it begins to decompose [1].



The present thermal analysis study utilized TG–DTA with various supportive data. From the thermal analysis data obtained, the melting point is 277.2 °C, which must be compared with the melting point reported.

2. Materials and methods

Scanning electron microscopy (SEM) studies, using JOEL JSM-6100 scanning electron microscope, indicated a range of rectangular shaped particles (Fig. 1).

Thermal analysis was completed using a simultaneous TG–DTA instrument from TA Instruments. It is a model 2960 TG–DTA with a Thermal-Analyst 2000 workstation, using a TA operating system version 2.3C. The experiments were carried out using platinum crucibles with approximately 7–8 mg of the sample. An empty crucible was used as a reference. The experiments were completed in an atmosphere of dry nitrogen at a flow rate of 100 ml min^{-1}. These were performed using a rising temperature program from ambient to 600 °C at a heating rate of 10 °C min^{-1}. The flow rate was regulated using an electronic flow meter from J. and W. Scientific.

3. Results and discussion

Fig. 2 shows the TG–DTG plot for the drug acetazolamide. The plots show a three-stage process when

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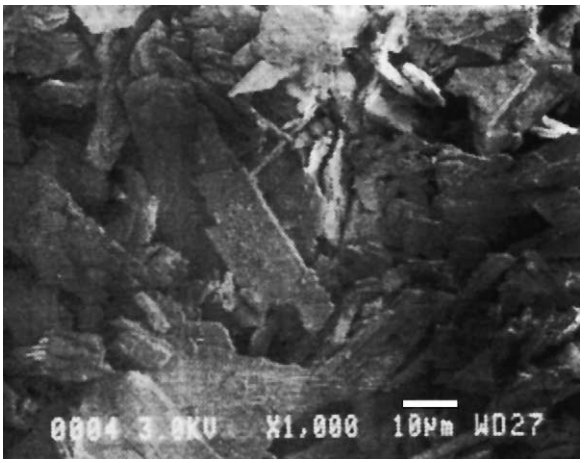

Fig. 1. A scanning electron microscopy study of acetazolamide.

the material is subjected to an atmosphere of nitrogen and heated at a uniform heating rate.

Fig. 3 shows the DTA plot of the decomposition. It is clear, the melting point is 276 °C due to the sharp endothermic peak at that temperature. There is also another peak and a somewhat indeterminate peak associated with the decomposition.

Fig. 4 shows a temperature versus time plot. These plots are useful in determining if the heating rate is constant and gives information when a process is occurring by a perturbation at that point. This confirms that the run obtained was indeed at a heating rate of 9.9–10.1 °C min^{-1} with perturbations at the melting point. Previous studies show that the perturbation is of a kind that is associated with endothermic processes [2].

There was some black carbonaceous residue left in the crucible at the end of the experiment. This was

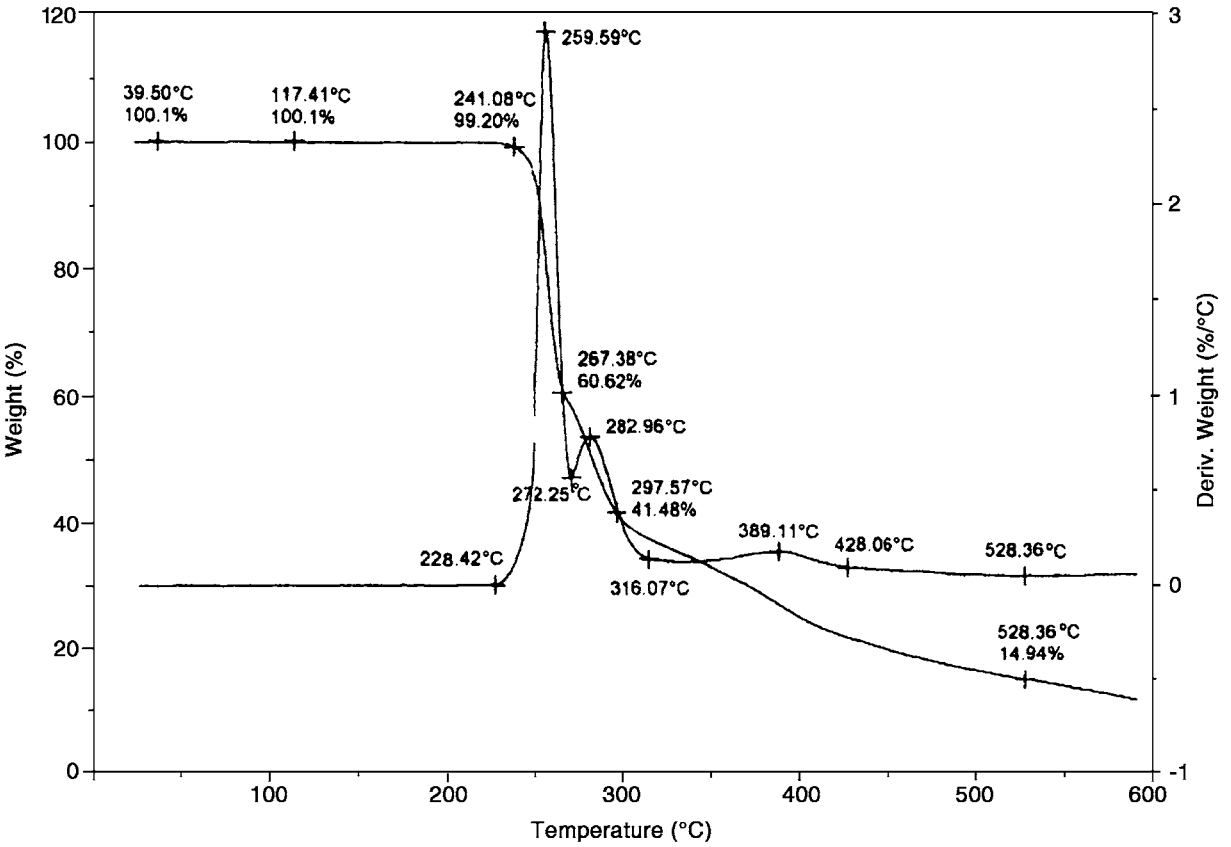

Fig. 2. A typical TG–DTG plot of percentage mass loss vs. temperature for the decomposition of acetazolamide.

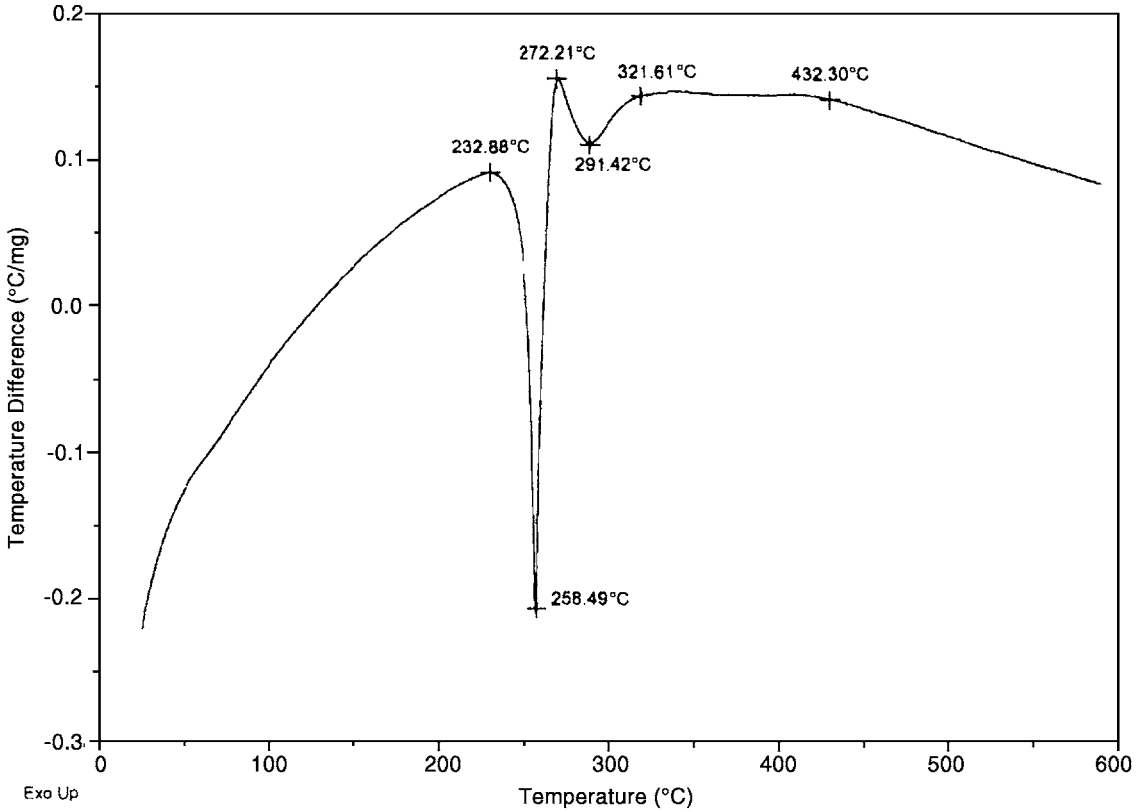

Fig. 3. A typical DTA plot of temperature difference vs. temperature for the decomposition of acetazolamide.

formed from the liquid state being that the melting point had occurred at 276 °C and the decomposition was noted in the temperature range of 303–460 °C.

4. Kinetics

The kinetics of the reaction can be determined from the information given in a TG–DTG plot. For general homogeneous reactions of the type:

$$\mathrm{A} \rightarrow \mathrm{B} + \mathrm{C} \tag{1}$$

the rate is determined from the following equation:

$$\text{rate} = k(F(\text{concentration of reactants and products}))_{T_{\text{constant}}} \tag{2}$$

The Arrhenius equation:

$$k = A\mathrm{e}^{-E_{\text{act}}/RT} \tag{3}$$

describes the vaporization of the specific reaction rate with temperature. In the above equation k is the reaction rate and varies with temperature, E_{act} the activation energy and A the pre-exponential term. The terms E_{act} and A can then be calculated [3]. In a solid-state reaction, then [4]:

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = k(T)f(\alpha) \tag{4}$$

where α is the fraction decomposed at time t, $\mathrm{d}\alpha/\mathrm{d}t$ the rate of the reaction, $k(T)$ the reaction rate at temperature T, and $f(\alpha)$ is some function α. The term α has to be used in solid-state chemistry as concentration terms are meaningless in such circumstances. It is a term used by almost every worker studying the degradation of systems involving the solid-state. Then, if:

$$T = T_0 + \beta t \tag{5}$$

where T is temperature at time t, T_0 the starting temperature, and β the heating rate. The equations

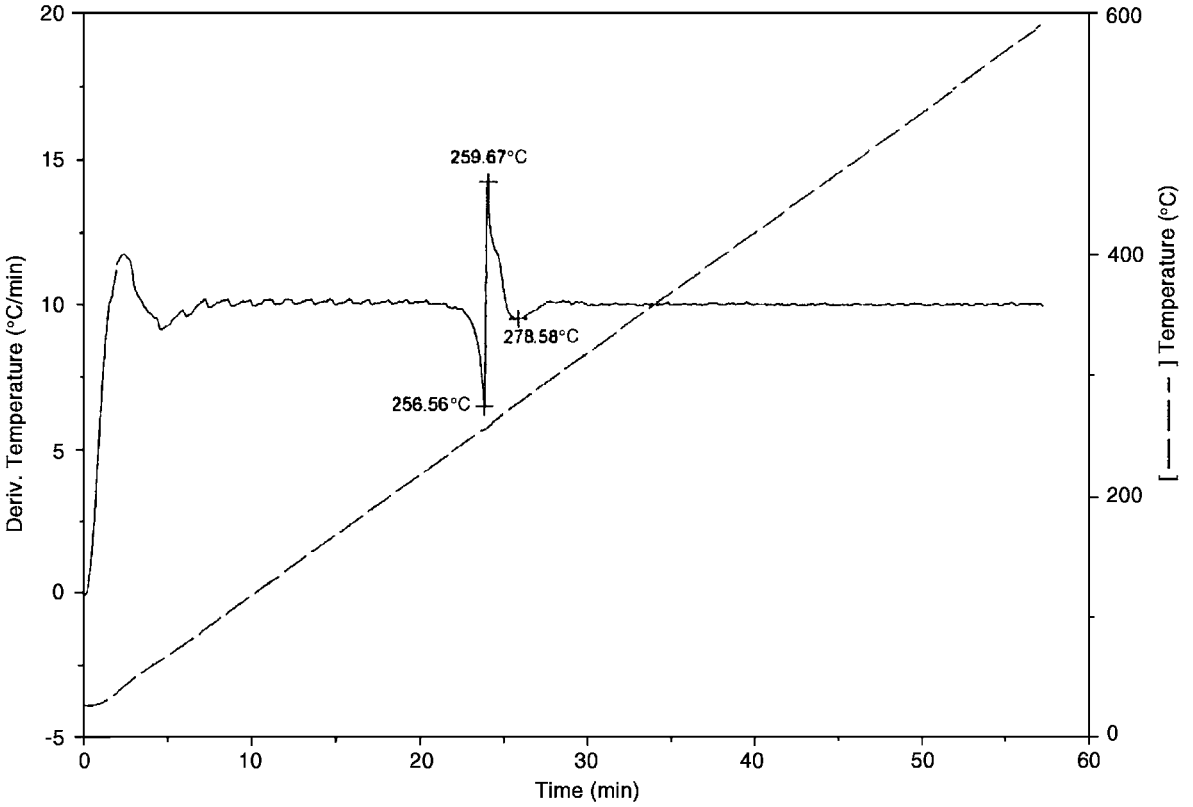

Fig. 4. A typical time vs. temperature plot and its first derivative for acetazolamide.

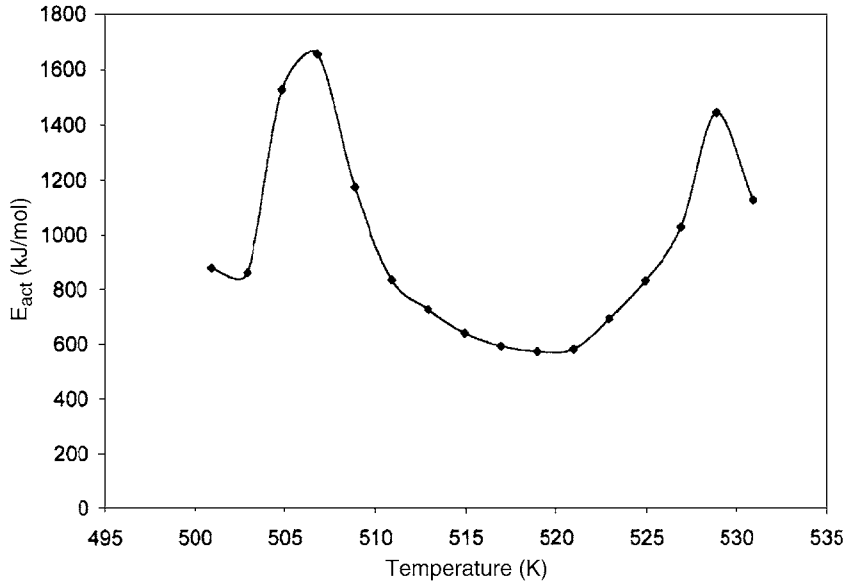

Fig. 5. A typical E_{act} vs. temperature plot for the first stage of the decomposition of acetazolamide.

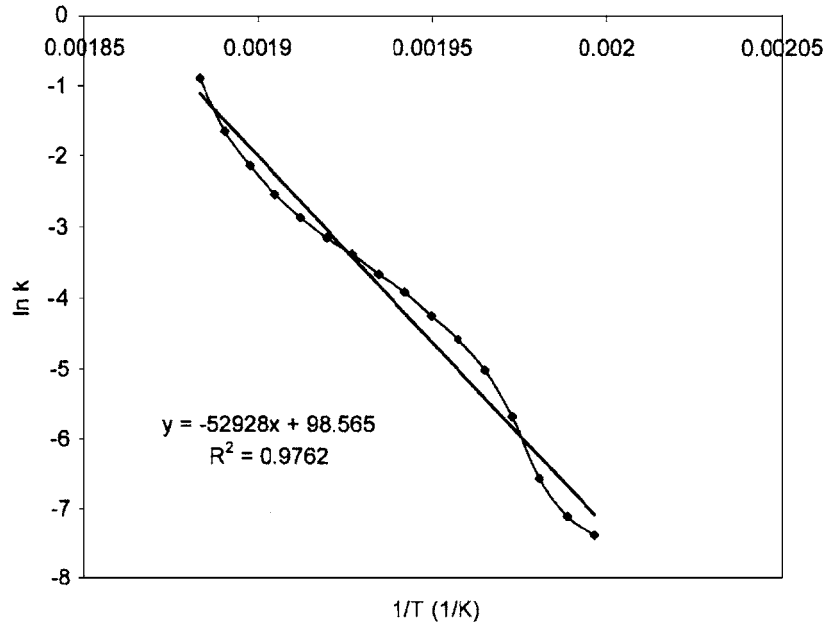

Fig. 6. A typical ln k vs. T^{-1} for the first stage of the decomposition of acetazolamide.

can be rearranged and combined to give the following:

$$k(T) = \frac{(\mathrm{d}\alpha/\mathrm{d}t)\,\beta}{f(\alpha)} \tag{6}$$

For a first-order reaction the equation for k is as follows:

$$k = \frac{\mathrm{d}\alpha/\mathrm{d}t}{1-\alpha} \tag{7}$$

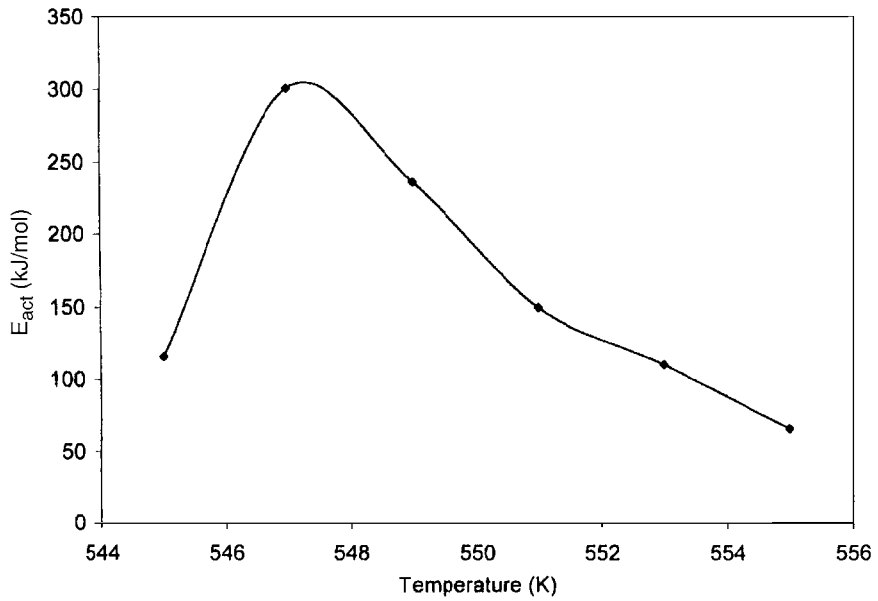

Fig. 7. A typical E_{act} vs. temperature plot for the second stage of the decomposition of acetazolamide.

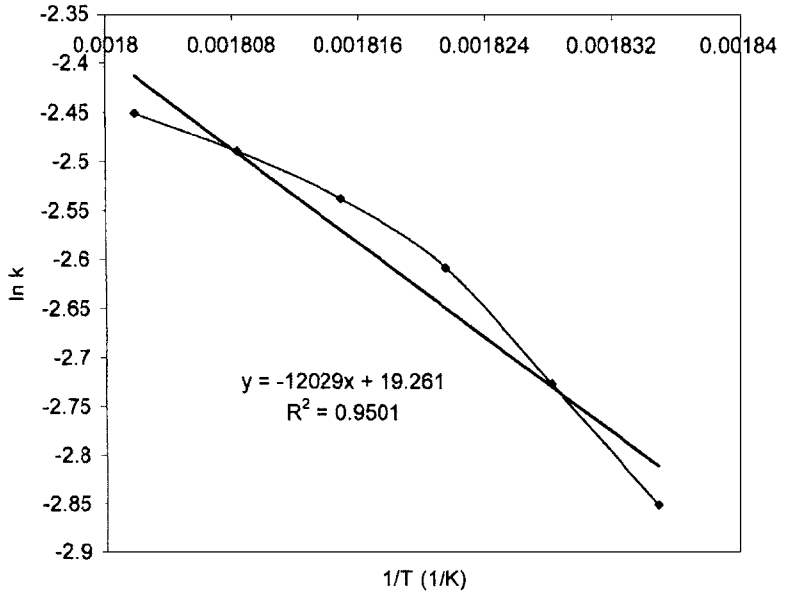

Fig. 8. A typical ln k vs. T^{-1} for the second stage of the decomposition of acetazolamide.

By taking the natural log of the Arrhenius equation:

$$\ln k = \ln A - \frac{E_{act}}{RT} \tag{8}$$

and then combining the two equations the following is obtained:

$$\ln\left(\frac{d\alpha/dt}{1-\alpha}\right) = \ln A - \frac{E_{act}}{RT} \tag{9}$$

From the plot obtained, the activation energy can be calculated from the slope of the line.

Fig. 5 shows that from 500 to 531 K the E_{act} calculated was in the region of 200–250 kJ mol^{-1} for this first stage of decomposition, shown in Fig. 2. The energy of activation can be calculated from the plot of ln k versus T^{-1} for this stage (Fig. 6). The data in Fig. 6 allowed for the calculation of E_{act}, and it had a value of 111.0 kJ mol^{-1}. This demonstrates that reasonably large variations in E_{act} calculated by the ''general chemistry method'' only shows up as small deviations for the linear plot of ln k versus T^{-1}. For the second stage over the temperature range 569–585 K the activation energy varied from around 50–90 kJ mol^{-1} (Fig. 6). Again the large variation in Fig. 7 shows up as relatively minor departures from the calculated value of E_{act} using the plots of ln k versus T^{-1} (Fig. 8). However it should be noted that the variation around the linear lines drawn in the plots of ln k versus T^{-1} are systematic and not random, which indicates that the variation of E_{act} is also apparent on the Arrhenius plots. The third stage was omitted from the investigation due to the fact that such a small peak occurred for the reaction.

5. Conclusion

It is concluded that in a system where a material is degrading by a series of reaction mechanisms, the rate controlling mechanism varies in different temperature regions. The difference method provided in most general chemistry textbooks, when taken over small temperature increments is sufficiently precise to demonstrate the allocation in the energy of activation as the reaction proceeds. This is illustrated by the detailed analysis on acetazolamide. It is further shown that the use of plots of ln k versus T^{-1} over wide ranges of temperature show small systematic variations from the ''best'' straight line, which can be explained by the basis of this ''general chemistry method'' approach.

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