Calculation of the vapor pressure–temperature relationship using thermogravimetry for the drug allopurinol

Lori Burnham, David Dollimore[†], Kenneth Alexander[*]

Department of Chemistry and College of Pharmacy, University of Toledo, 2801 W Bancroft St., Toledo, OH 43606-3390, USA

Abstract

Allopurinol sublimates when subjected to thermogravimetry in a nitrogen atmosphere. The process is zero order and plots of ln k versus reciprocal temperature (K) give a value of 132.64 kJ mol^{-1} for the activation energy. On the basis that equilibrium is achieved at all temperatures the data is used to establish a plot of the vapor pressure curve versus temperature from which a Clausius–Clapeyron relationship can be used to establish the ΔH for sublimation. The method requires that the equipment is calibrated and data for p-aminobenzoic acid is used for this purpose. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Allopurinol; Vapor pressure; Thermogravimetry

1. Introduction

The drug allopurinol is used pharmaceutically as an antiurolithic in the treatment of hyperuricemia and chronic gout. It is reported to have a melting point above 350°C. There does not appear to be any thermal analysis data reported for this drug. The formula for allopurinol is $C_5H_4N_4O$ and it has the structure:
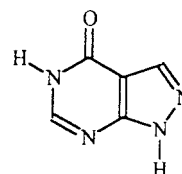
Mass spectra data has been reported using a low-resolution electron impact unit and showed the following assignments [1]:

m/e 136 $[M-NH_2]^+$ m/e 120   m/e 109
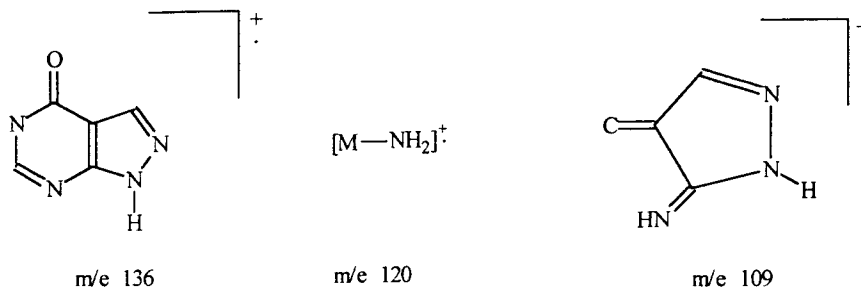
[*] Corresponding author.
E-mail address: kalexan@uoftø2.utoledo.edu (K. Alexander).
[†] Deceased.

In the present study, a thermal analysis investigation in nitrogen on allopurinol is reported using a simultaneous TG–DTA unit.
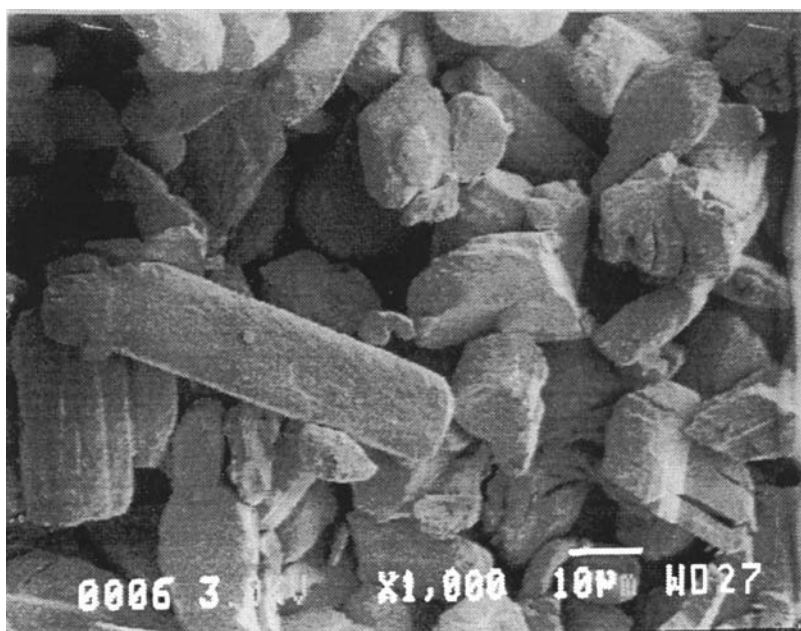
Fig. 1. Scanning electron microscopy of the drug allopurinol.

2. Materials

The allopurinol used in this study was obtained from the Sigma Chemical (lot No. 40H3501). Scanning electron microscopy (SEM) studies, using JOEL JSM-6100 scanning electron microscope, indicated a range of different size and shaped particles (see Fig. 1).

The thermal analysis system used was a simultaneous TG–DTA unit from TA Instruments, Model No. 2960, used with the Thermal Analyst 2000 workstation using a TA Operating System Version 2.3C. The runs were carried out using platinum crucibles with approximately 10–11 mg of the sample. An empty crucible was used as a reference. The runs were completed in an atmosphere of dry nitrogen at a flow rate of 100 ml min^{-1}. This was completed over the temperature range of ambient to 500°C at a heating rate of 10°C min^{-1}. The flow rate was regulated using an electronic flow meter from J&W Scientific.

The X-ray powder diffraction pattern was obtained using a Scintag XRD 200 X-ray powder diffractometer (Fig. 2, Table 1).

Table 1
X-ray powder diffraction data for the drug allopurinol

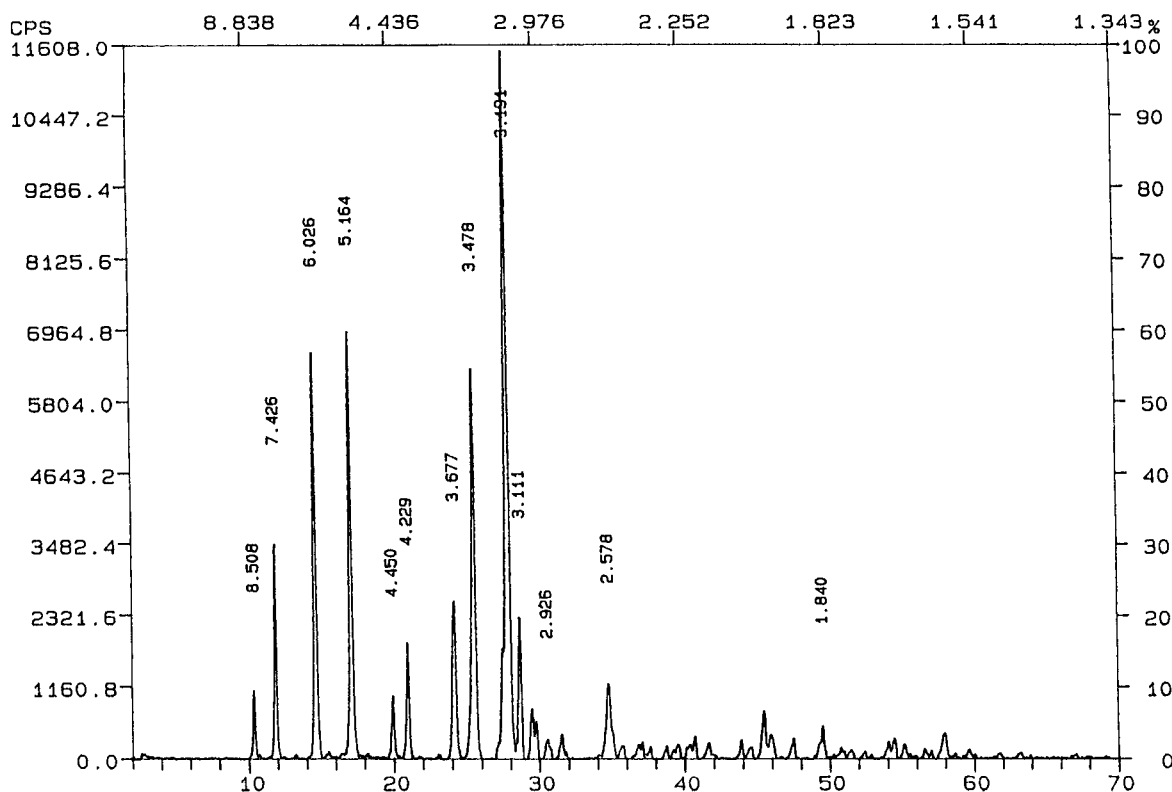| 2Θ	D-spacing	Intensity
10.3897	8.50756	9
11.9078	7.42613	30
14.6875	6.02635	56
17.1572	5.16405	59
19.9344	4.45043	8
20.9916	4.22863	16
24.1847	3.67706	22
25.5900	3.47823	55
27.9338	3.19149	100
28.6734	3.11081	20
29.4781	3.02770	6
29.7616	2.99951	5
31.5116	2.83681	3
34.7653	2.57839	10
40.6759	2.21633	3
45.4325	1.99473	6
45.9134	1.97495	3
49.4922	1.84019	4
57.9125	1.59106	3

Fig. 2. X-ray powder diffraction data for the drug allopurinol.

3. Results and discussion

Fig. 3 shows the endothermic process of sublimation of allopurinol. The TG plot shows sublimation in dry nitrogen atmosphere. In other TG experiments, the heating rate was varied from 2 to $12°C\ min^{-1}$ every $2°C$. Table 2 shows the effect of the heating rate on the sublimation of allopurinol. The DTG curve shows the typical sublimation plot (Fig. 3). In the DTA curve, the

temperature at which sublimation occurs is seen by the endothermic peak (Fig. 4). In the time–temperature plot, a perturbation is noted at the sublimation temperature (Fig. 5) and the heating rate seems to be a consistent $10°C\ min^{-1}$.

It must be stressed that the process observed is one of a solid in equilibrium with its vapor, i.e.
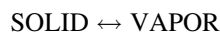
$$SOLID \leftrightarrow VAPOR$$

Table 2
The effect of heating rate on the sublimation of allopurinol

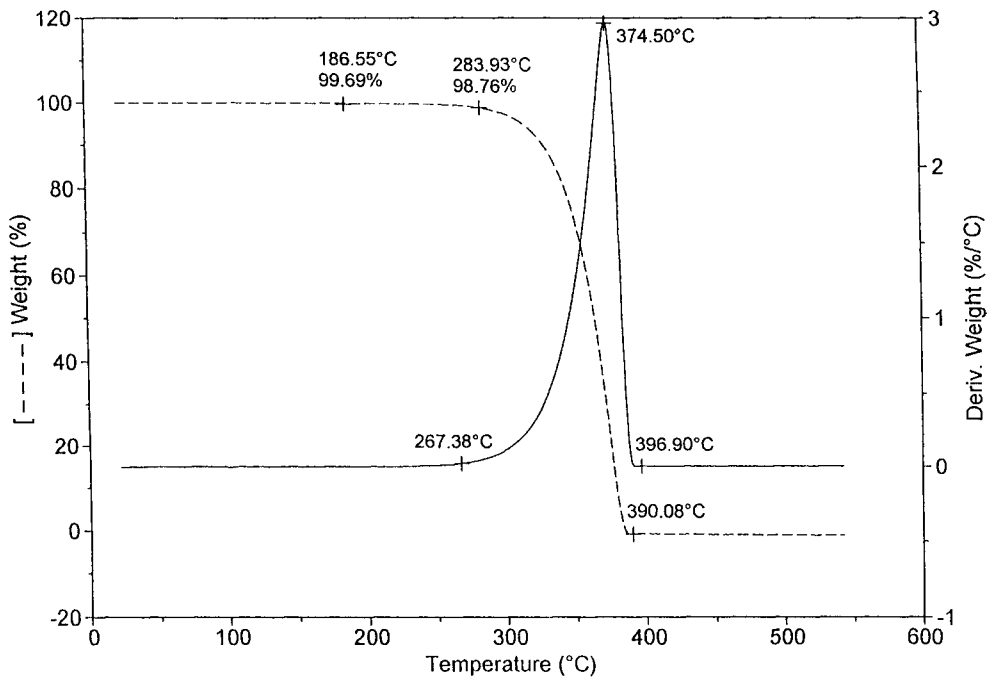| Heating rate ($°C\ min^{-1}$)	Mass of material (mg)	T_i (from DTG) ($°C$)	T_f (from DTG) ($°C$)	T_p (from DTG) ($°C$)	E_{act} ($kJ\ mol^{-1}$)
2	10.0298	245.95	355.02	337.49	133.20
4	10.5777	263.48	372.55	337.49	134.60
6	10.3914	264.46	384.24	362.81	133.49
8	10.3785	268.35	389.11	372.55	133.70
10	10.6675	267.38	396.90	374.50	132.64
12	10.9481	267.38	395.92	382.29	132.54

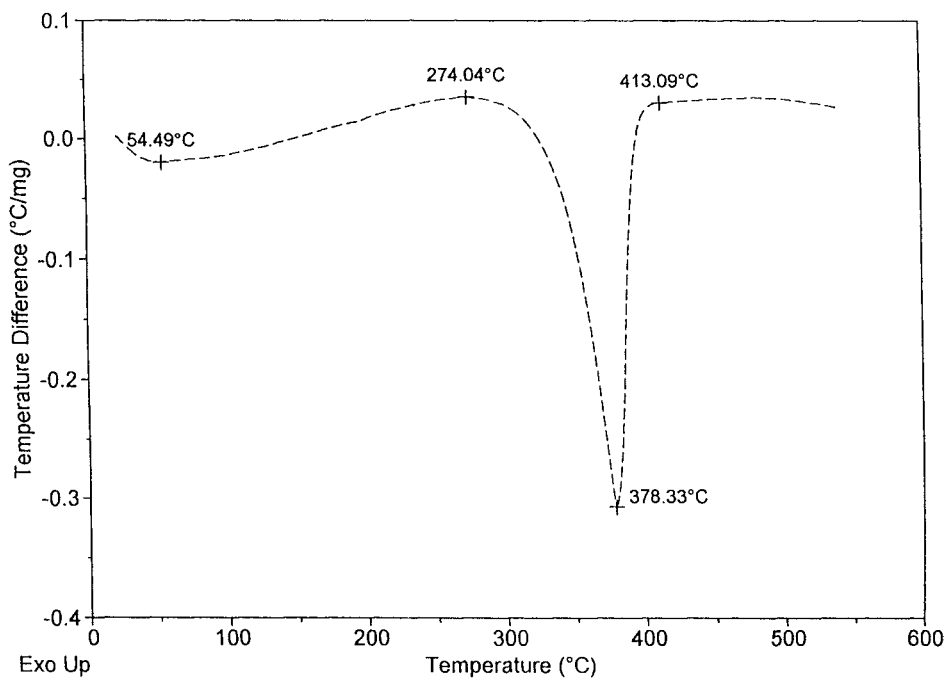Fig. 3. The TG–DTG curve for the drug allopurinol.
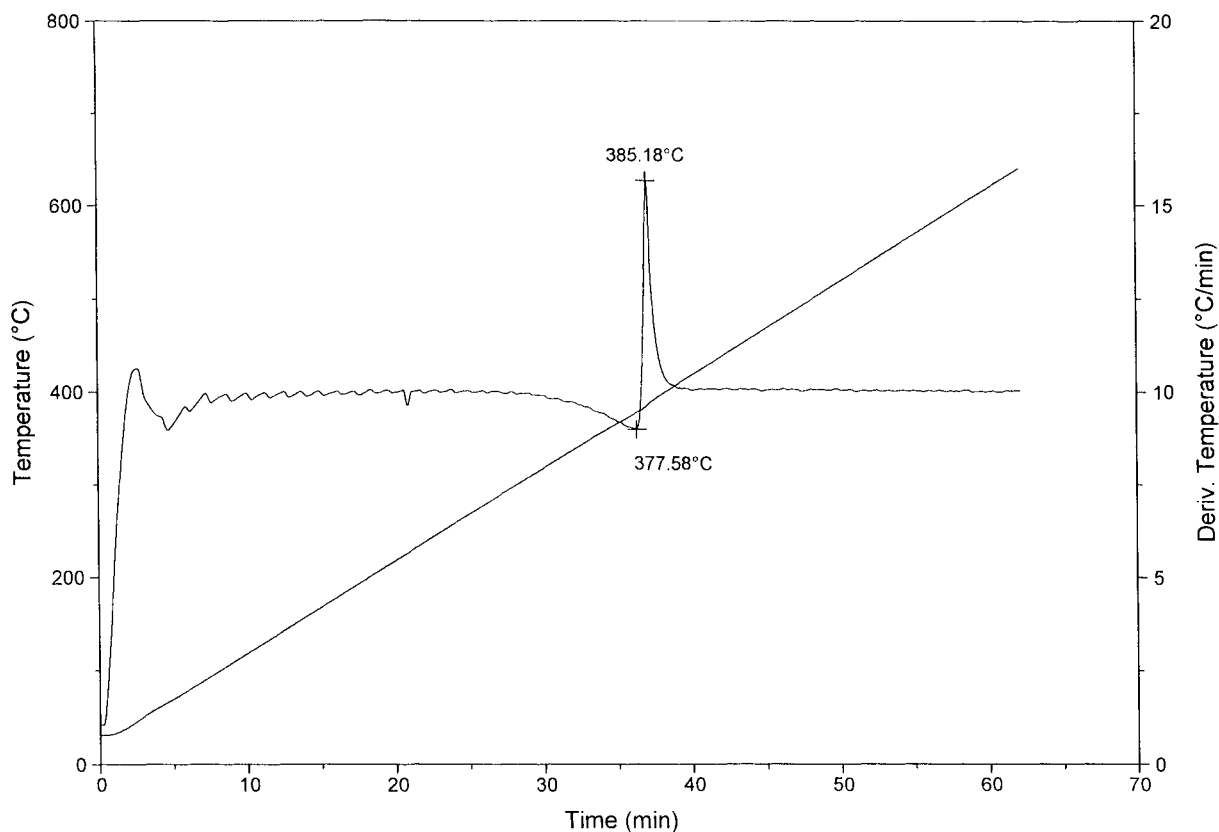

Fig. 4. The DTA curve for the drug allopurinol.

Fig. 5. Time–temperature plot for the drug allopurinol.

and not a liquid in equilibrium with its vapor, i.e.

LIQUID $\leftrightarrow$ VAPOR

There is a possibility here that such a process of sublimation might not be an overall zero kinetic-order process as the interface between the solid crystals may alter significantly as the material sublimes, however, as can be seen below, the kinetics observed were zero order.

4. Kinetics of sublimation

For the zero-order process, the rate constant was determined in the temperature range from 540.4 to 647.5 K using 2°C intervals in the following manner. The expression for k is given by

$$k = \frac{d\alpha}{dt} \tag{1}$$

where $d\alpha/dt$ is the derivative of the fraction decomposed with respect to time and k the rate of decomposition. By using this equation, k was calculated using every 2°C. α is defined by

$$\alpha = \frac{(\%w_i - \%w_t)}{(\%w_i - \%w_f)} \tag{2}$$

where $\%w_i$ is the initial percent weight, $\%w_t$ the percent weight at time t, and $\%w_f$ the final percent weight.

At any temperature T, the Arrhenius expression is

$$\ln k = \ln A - \frac{E_{act}}{RT} \tag{3}$$

So at any temperature T_{n-1} of a rising temperature reaction, the Arrhenius expression gives

$$\ln k_{T_{n-1}} = \ln A - \frac{E_{act}}{RT} \tag{4}$$

Then at any temperature T_{n+1}

$$\ln k_{T_{n+1}} = \ln A - \frac{E_{act}}{RT} \tag{5}$$

Based on these assumptions, we obtain the expression

$$\ln\left(\frac{k_{T_{n-1}}}{k_{T_{n+1}}}\right) = -\frac{E_{act}}{RT_{n-1}} + \frac{E_{act}}{RT_{n+1}} = \frac{E_{act}}{R(T_{n+1} - T_{n-1})} \tag{6}$$

Simplifying this then gives

$$\ln\left(\frac{k_{T_{n-1}}}{k_{T_{n+1}}}\right) = \frac{-2E_{act}}{R(T_{n+1})(T_{n-1})} \tag{7}$$

It can be assumed that

$$T_n^2 = (T_{n+1})(T_{n-1}) \tag{8}$$

which then gives

$$\ln\left(\frac{k_{T_{n-1}}}{k_{T_{n+1}}}\right) = \frac{-2E_{act}}{RT_n^2} \tag{9}$$

This then allows us to calculate the activation energy using the expression [2]

$$E_{act} = -\frac{1}{2}\ln\left(\frac{k_{T_{n-1}}}{K_{T_{n+1}}}\right)RT_n^2 \tag{10}$$

It can be seen that the value of E_{act} calculated in this manner varies between 115 and 155 kJ mol^{-1} on the basis of this plot, which demonstrates the scatter of experimental values. Over this range of temperature an Arrhenius plot of $\ln k$ versus T^{-1} is a linear plot

from which E_{act} can be calculated as 132.64 kJ mol^{-1} (Fig. 6).

The value of E_{act} for the sublimation process lies in the range for the $\Delta H_{sublimation}$. The enthalpy for sublimation at the melting point if the material (taken here as 378.3°C) will be the sum of the solid–liquid phase change ($\Delta H_{melting}$) and the liquid–vapor phase change ($\Delta H_{vaporization}$), i.e.

$$\Delta H_{sublimation} = \Delta H_{melting} + \Delta H_{vaporization} \tag{11}$$

In other words, $\Delta H_{sublimation}$ should be greater than $\Delta H_{vaporization}$ by an amount equal to the enthalpy of melting.

In the previous publications it has been shown that the energy of activation for a transition to the vapor state is equal to the enthalpy of the transition [3], in this case $\Delta H_{sublimation}$.

On this basis we write

$$E_{act} = \Delta H_{sublimation} = 132.64 \text{ kJ mol}^{-1} \tag{12}$$

The value for $\Delta H_{vaporization}$ might be judged from the use of Trouton's Rule if the boiling point was known [4], i.e.

$$\frac{\Delta H_{vaporization}}{T} = \Delta S_{vaporization} \tag{13}$$

Speculating on this point, the melting point temperature, if it could be obtained, would be above 400°C or 673 K. At this temperature

$$\Delta S_{sublimation} = \frac{132.640}{673} \text{ J K}^{-1} \text{ mol}^{-1} \tag{14}$$

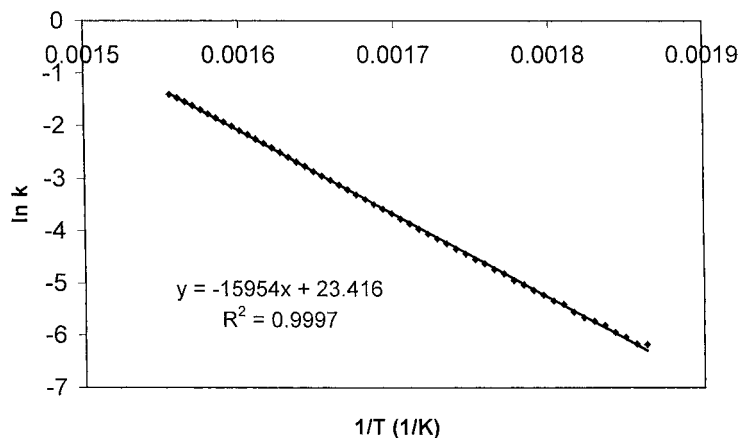

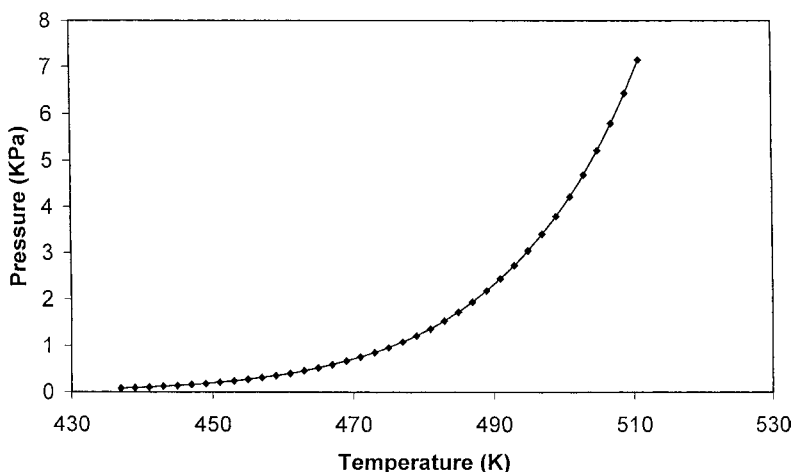Fig. 6. The Arrhenius plot of $\ln k$ versus T^{-1} for the drug allopurinol.

Fig. 7. The vapor pressure curve plot of P versus T for p-aminobenzoic acid.

therefore at temperatures above 673 K

$$\Delta S_{\text{sublimation}} \leq 197.1\,\text{J}\,\text{K}^{-1}\,\text{mol}^{-1} \tag{15}$$

which would seem to be the right order of magnitude for organic compounds but cannot be verified directly.

Langmuir treatment of the solid–vapor transition would then be as follows. First we use p-aminobenzoic acid. Using the Antoine equation [5]:

$$\log P = A - \frac{B}{C + T} \tag{16}$$

where P is the pressure, A, B, and C are Antoine constants and T the temperature in kelvin. A vapor pressure curve can then be established by plotting P versus T (Fig. 7). Then using the pressures obtained from the Antoine equation, we then apply them to the Langmuir equation [6]:

$$P = \left[\left(\frac{\text{d}m}{\text{d}t}\right)\left(\frac{T}{M}\right)^{1/2}\right]\left[\frac{(2\pi R)^{1/2}}{\alpha_1}\right] \tag{17}$$

where P is the pressure in kPa, $\text{d}m/\text{d}t$ the derivative of the mass with respect to time per unit area, T the temperature, M the molecular weight of the compound, R the gas constant and α_1 the modified fraction decomposed [7] which is just simply:
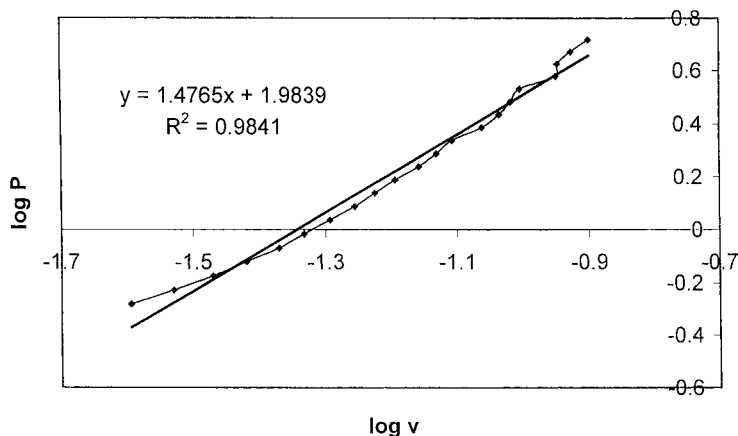
$$P = vk \tag{18}$$

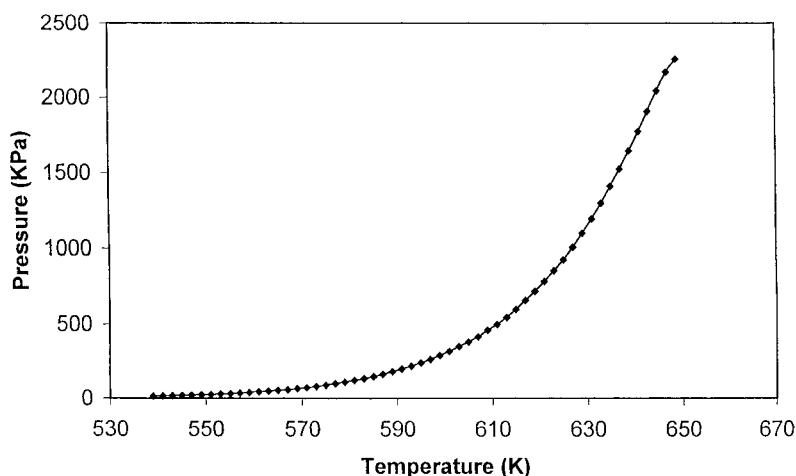Fig. 8. The log P versus log v plot for p-aminobenzoic acid.

Fig. 9. The vapor pressure curve of *P* versus *T* for the drug allopurinol.

where $v = [(dm/dt)(T/M)^{1/2}]$ and is dependent on the material and $k = [(2\pi R)^{1/2}/\alpha_1]$ is independent of the material. By plotting $\log P$ versus $\log v$ the intercept would then be equal to $\log k$ (Fig. 8). Using this k-value obtained from the intercept we can then construct a spreadsheet to calculate the pressures for the drug allopurinol. When the pressures have been calculated for allopurinol, one can then construct a vapor pressure curve for allopurinol (Fig. 9).

5. Conclusion

It has been shown that the drug allopurinol sublimates in a zero-order process. The DTG curve indicates this sublimation and the DTA curve shows a sublimation peak, i.e. solid going directly to vapor. The activation energy was calculated using zero-order kinetics. An Arrhenius plot showed a calculation of 132.6 kJ mol^{-1} for this process. Calibration of the equipment with *p*-aminobenzoic acid allowed the constant k in the Langmuir equation to be calculated and thus in turn allowed the construction of a vapor pressure curve for this sublimation process for allopurinol.

References

[1] S.A. Benezra, T.R. Bennett, in: K. Florey (Ed.), Analytical Profiles of Drug Substances, Vol. 7, Academic Press, New York, 1978, pp. 1–17.
[2] K. Whitten, K. Gailey, R. Davis, General Chemistry, 4th Edition, Saunders, New York, 1992.
[3] S. Lerdkanchanporn, D. Dollimore, An investigation of the evaporation of stearic acid using a simultaneous TG–DTA unit, Thermochim. Acta 324 (1998) 15–23.
[4] P.W. Atkins, Physical Chemistry, 5th Edition, Freeman, New York, 1994.
[5] C.L. Yaws, Handbook of Vapor Pressure, Vol. 3, Gulf Publishing Company, Texas, 1994.
[6] P.W. Atkins, Physical Chemistry, 4th Edition, Freeman, New York, 1990.
[7] D.M. Price, M. Hawkins, Thermochim. Acta 325 (1998) 19.