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ADIABATIC CALORIMETRY AND THERMAL ANALYSIS ON ACETAMINOPHEN

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Molar heat capacities of acetaminophen were precisely measured with a small sample precision automated adiabatic calorimeter over the temperature range from 80 to 330 K. A solid–solid transition at 149.96 K was found from the $C_{p,m}$–T curve. The polynomial functions of $C_{p,m}$(J K^{-1} mol^{-1}) *vs.* T were established on the heat capacity measurements by means of the least square fitting method.

Thermal decomposition processes of acetaminophen have been studied by thermogravimetry. And the thermal decomposition kinetics parameters, such as activation energy E, pre-exponential factor A and reaction order n, were calculated by TG-DTG techniques with the Freeman–Carroll method, Kissinger method and Ozawa method. Accordingly the thermal decomposition kinetics equation of acetaminophen is expressed as: $d\alpha/dt=2.67\cdot10^{7}e^{-89630/RT}(1-\alpha)^{0.23}$.

The process of fusion has been investigated through DSC. The melting point, molar enthalpy and entropy of fusion are to be (441.89±0.04) K, 26.49±0.44 kJ mol^{-1} and 59.80±1.01 J K^{-1} mol^{-1}, respectively.

Keywords: *acetaminophen, adiabatic calorimetry, DSC, TG-DTG, thermokinetics*

Introduction

Acetaminophen (PAPA) is a kind of antipyretic drug that is similar to aspirin. But its toxicity is lower than aspirin. Recently, it is recommended as preferred drug of defervescence for children.

Acetaminophen (CAS: 103-90-2) shows a melting process at 168–172°C [1]. It exists in three polymorphic forms, but only two of which can be readily isolated. Form I (monoclinic) is the commercially marketed version. Form II (orthorhombic), however, has distinct advantages in its tableting properties due to its plasticity, which enables direct compression without binders [2]. Sacchetti [3] determined heat capacities, melting point (T_m) and fusion enthalpy (ΔH_f) for Form I and Form II of acetaminophen in the temperature range from –60~200°C by means of DSC. Results show the T_m (168.6±0.2°C) and ΔH_f (28.1±2.2 kJ mol^{-1}) of Form I are higher than Form II [T_m as (156.4±0.2°C and ΔH_f as (27.6±1.2 kJ mol^{-1})].

Thermal analysis (TA) is one technique used in the pre-formulation and development of drugs. It has attracted attentions of many researchers [4, 5]. Thermal property of medicine plays an important role in the qualification and quantification of pharmaceutical materials and ensuring production quality. Literature [3, 6, 7] reported thermal analysis for acetaminophen.

We have studied the thermodynamic properties of berberine sulphate by using thermal analysis and adiabatic calorimetry [8]. In this article, thermokinetics and thermal properties of acetaminophen are studied using thermogravimetry (TG-DTG) and differential scanning calorimetry (DSC).

Experimental

Material

Acetaminophen was supplied by Hunan Institute of Drug Detection, P. R. China. Quantitative analysis was performed using spectrophotometer [1] and its purity was 99.0%.

Adiabatic calorimetry

The heat capacity measurements were carried out by a high-precision automatic calorimeter over the temperature range of 80–370 K. The principle and structure of the adiabatic calorimeter were described in detail elsewhere [9, 10].

Thermal analysis

A thermogravimetric analyzer (Setsys 16/18 from Setaram Company, France) was used for TG-DTG measurements of acetaminophen under the atmosphere of nitrogen. Heating rates were 5, 10, 15, 20, 25 K min^{-1}. Dry nitrogen was used at a flow rate of

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30 mL min^{-1} as a purge gas. Two Al_2O_3 crucibles were used (capacity 100 μL) and reference crucible was filled with α-Al_2O_3.

A differential scanning calorimetry (DSC 141 from Setaram Company, France) was used to perform the thermal analysis of acetaminophen. Heating rate was also 10 K min^{-1}. A flow of dry nitrogen was 50 mL min^{-1}. Two opened aluminum crucibles were used (capacity 30 μL) and reference crucible was empty.

Results and discussion

Heat capacities and thermodynamic properties of acetaminophen

Figure 1 shows a plot of experimental molar heat capacities of acetaminophen *vs*. the temperature obtained by the adiabatic calorimeter over the temperature range from 80 to 330 K. The results indicate that there is a small transition at 149.96 K. According to literature [3], the acetaminophen exists in two polymorphic forms (Form I and Form II) and the transition temperature between the two polymorphs was estimated to be less than –120°C/153 K. Therefore, the small transition is caused by solid–solid transition at 149.96 K. Figure 2 is the results obtained by experimental is compared with literature [3]. Figure 2 shows there is Form II before 149.96 K and Form I after 149.96 K for the acetaminophen.

At temperature range from 80 to 149 K, the experimental molar heat capacities are fitted to the following linear relation in temperature (T), by means of the least square fitting:

$$C_{p,m}\ [\mathrm{J\,K^{-1}mol^{-1}}] = 30.144+0.4446T\ (R^2= 0.9981) \quad (1)$$

At temperature range from 150 to 330 K, the experimental molar heat capacities are linearity with temperature (T):

$$C_{p,m}\ [\mathrm{J\,K^{-1}mol^{-1}}]=17.645+0.5226T\ (R^2= 0.9980) \quad (2)$$

Table 1 lists thermodynamic properties of acetaminophen, where $C_{p,m}$ [J K^{-1} mol^{-1}] are calculated according to Eqs (1) and (2), H_T–$H_{298.15}$ and S_T–$S_{298.15}$ are derived from capacity data according to the following equation:

$$H_T - H_{298.15} = \int_{298.15}^{T} C_{p,m}\,dT \quad (3)$$

$$S_T - S_{298.15} = \int_{298.15}^{T} \frac{C_{p,m}}{T}\,dT \quad (4)$$

Calculation method of thermal kinetics

In the present study, three calculation methods were used to obtain thermal kinetic parameters.

Firstly, differential expressions of kinetics function [$f(\alpha)$] was supposed as $f(\alpha)=(1-\alpha)^n$. According to the Freeman–Carroll method [11], we can write:

$$\frac{\Delta \lg(d\alpha/dt)}{\Delta \lg(1-\alpha)} = -\frac{E}{2.3R}\left[\frac{\Delta(1/T)}{\Delta \lg(1-\alpha)}\right] + n \text{ (to answer } E, n)$$

and

$$\ln\left(\frac{d\alpha}{dt}\right) + \frac{E}{RT} =$$
$$= \ln[A(1-\alpha)^n] =$$
$$= \ln A + n\ln(1-\alpha) \text{ (to answer } A, n)$$

where α is conversion of reaction; E/J mol^{-1} is activation energy; A is pre-exponential factor; n is reaction order; T/K is absolute temperature and R/J K^{-1} mol^{-1} is gas constant as 8.314.

Making a linear plot of [Δlg(dα/dt)]/[Δlg(1–α)] *vs*. [Δ(1/T)]/[Δlg(1–α)], the activation energy (E) was derived from slope of the above curve; reaction order (n) was obtained from its intercept.

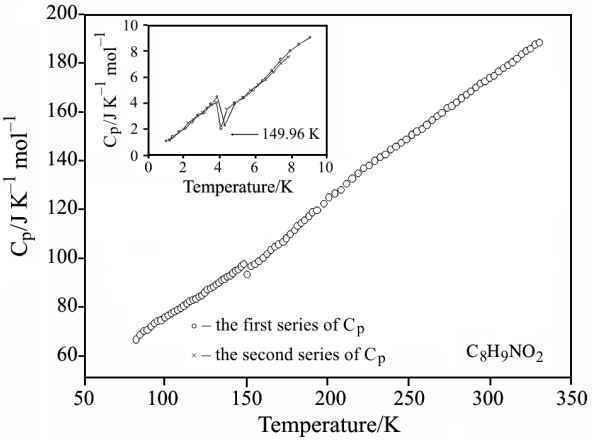

Fig. 1 Experimental molar heat capacities of acetaminophen determined by adiabatic calorimetry

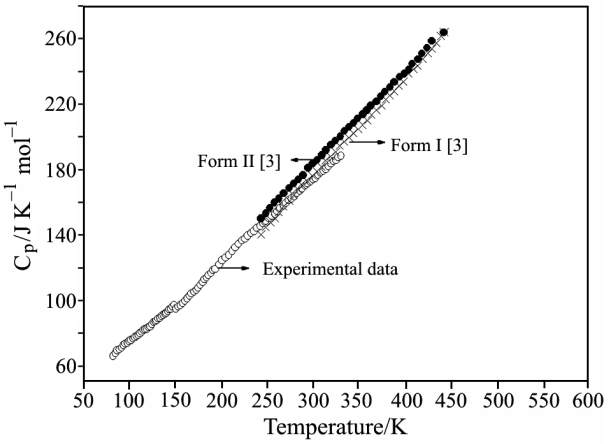

Fig. 2 The experimental C_p is compared with literature data

Table 1 Calculated thermodynamic function data of acetaminophen

Temperature/ K	C_p/ J mol^{-1} K^{-1}	H_T–$H_{298.15}$/ J mol^{-1}	S_T–$S_{298.15}$/ J mol^{-1} K^{-1}	Temperature/ K	C_p/ J mol^{-1} K^{-1}	H_T–$H_{298.15}$/ J mol^{-1}	S_T–$S_{298.15}$/ J mol^{-1} K^{-1}
			Form II				
80	65.712	–24.914	–18.159	85	67.935	–24.580	–15.185
90	70.158	–24.235	–12.331	95	72.381	–23.878	–9.5968
100	74.604	–23.511	–6.9828	105	76.827	–23.132	–4.4888
110	79.05	–22.743	–2.1148	115	81.273	–22.342	0.13919
120	83.496	–21.930	2.2732	125	85.719	–21.507	4.2872
130	87.942	–21.073	6.1812	135	90.165	–20.628	7.9552
140	92.388	–20.171	9.6092	145	94.611	–19.704	11.143
149	96.389	–19.322	12.284				
			Solid–solid transition (149.96 K)				
			Form I				
150	96.035	–19.963	–89.490	155	98.648	–19.476	–86.368
160	101.26	–18.976	–83.253	165	103.87	–18.463	–80.142
170	106.49	–17.938	–77.038	175	109.10	–17.398	–73.939
180	111.71	–16.846	–70.847	185	114.33	–16.281	–67.761
190	116.94	–15.703	–64.682	195	119.55	–15.112	–61.609
200	122.16	–14.508	–58.543	205	124.78	–13.890	–55.484
210	127.39	–13.260	–52.432	215	130.00	–12.616	–49.388
220	132.62	–11.960	–46.351	225	135.23	–11.290	–43.322
230	137.84	–10.608	–40.300	235	140.46	–9.9118	–37.287
240	143.07	–9.2030	–34.282	245	145.68	–8.4811	–31.286
250	148.30	–7.7462	–28.298	255	150.91	–6.9982	–25.319
260	153.52	–6.2371	–22.349	265	156.13	–5.4629	–19.388
270	158.75	–4.6758	–16.436	275	161.36	–3.8755	–13.494
280	163.97	–3.0622	–10.561	285	166.59	–2.2358	–7.6387
290	169.20	–1.3963	–4.7259	295	171.81	–0.54380	–1.8233
298.15	173.46	0	0	300	174.42	0.32179	1.0689
305	177.04	1.2004	3.9506	310	179.65	2.0921	6.8216
315	182.26	2.9970	9.6818	320	184.88	3.9148	12.531
325	187.49	4.8457	15.369	330	190.10	5.7897	18.195

Plotting a curve of $\ln[A(1-\alpha)^n]$ *vs*. $\ln(1-\alpha)$, A and n were derived.

Secondly, in the light of the Kissinger method [12], we can get:

$$\ln\left(\frac{\beta}{T_p^2}\right) = \ln\left(\frac{AR}{E}\right) + \ln\left[\frac{-df(\alpha)}{d\alpha}\right]_{\alpha_p} - \frac{E}{RT_p}$$

where β is heating rate and T_p is peak temperature of DTG.

T_p was obtained from several DTG curves of different heating rate. E was also obtained by plotting $\ln(\beta / T_p^2)$ *vs*. $1/T_p$.

Finally, equation of $d(\lg\beta)/d(1/T) = -0.4567E/R$ was obtained by the Ozawa method [13]. For the same relative mass losses (α), the plot of the logarithm of the heating rate, $\lg\beta$, as a function of the reciprocal temperature, $1/T$, is a line, whose slope is proportional to the activation energy. So, E was also derived.

Thermal decomposition kinetics of acetaminophen

TG-DTG curves of acetaminophen are shown in Figs 3 and 4. Figure 3 shows the thermogravimetric measurements shift to higher temperature. But the amounts of mass loss are not changed basically. The results are presented in Table 2.

Figure 5 is a plot of $[\Delta\lg(d\alpha/dt)]/[\Delta\lg(1-\alpha)]$ *vs.* $[\Delta(1/T)]/[\Delta\lg(1-\alpha)]$ according to the Freeman–Carroll method. The activation energy E was calculated from the slope and the reaction order n was gotten from the intercept (Table 3).

Table 2 The situation of mass loss at different heat rates

Heating rate, β/K min^{-1}	5	10	15	20	25
Range of temperature for mass loss/K	460–630	483–654	490–657	510–678	511–680
Rate of mass loss/%	98	99	99	97	97

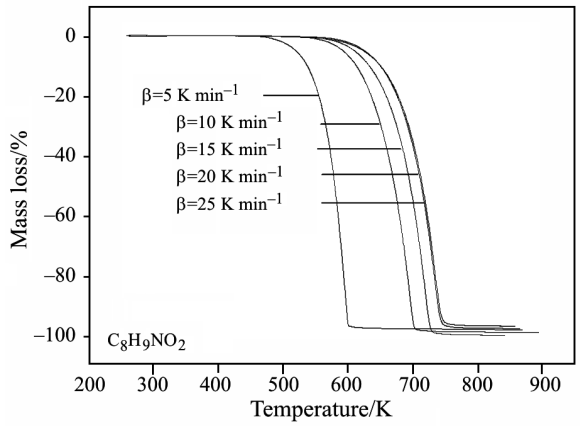

Fig. 3 TG curves of acetaminophen at different heating rates

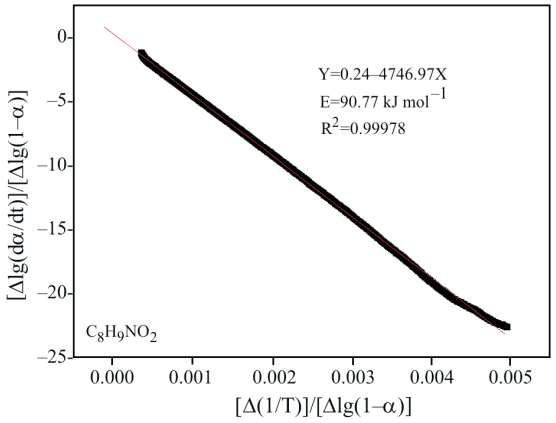

Fig. 5 A plot of [Δlg(dα/d*t*)]/[Δlg(1–α)] *vs.* [Δ(1/*T*)]/[Δlg(1–α)]

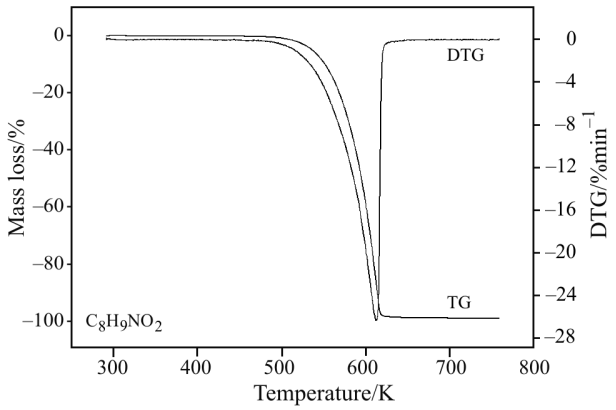

Fig. 4 TG-DTG curves of acetaminophen at β=10 K min^{-1}

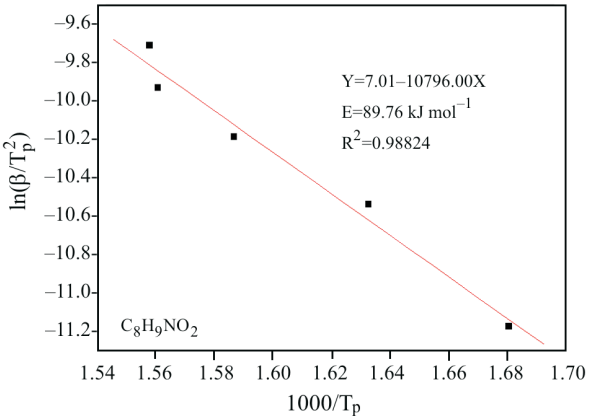

Fig. 6 A plot of ln(β/T_p^2) *vs.* 1/T_p

The ln*A* is obtained through plotting ln[$A(1–\alpha)^n$] *vs*. ln(1–α) as 17.1. The reaction order (*n*) is also obtained as 0.22.

According to the Kissinger method, a curve of ln(β / T_p^2) *vs.* 1/T_p was plotted (Fig. 6). *E* is derived from the slope to be 89.76 kJ mol^{-1}.

With the Ozawa method, the advantage is taken of the fact that thermogravimetric measurements shift to higher temperatures, with increasing heating rate. For each relative mass loss (α=0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8), the plot of the logarithm of different heating rates (lgβ) at 5, 10, 15, 20, 25 K min^{-1} *vs*. the reciprocal temperature, 1/*T*, is drawn. The value of activation energy *E* under different α can be derived from different slopes. These results are listed in Table 4.

When α changes from 0.20 to 0.80, the calculated values of activation energy *E* range are between 84.61~90.11 kJ mol^{-1} by using the Ozawa method. It seems that the activation energies do not change considerably during the whole decomposition process. Moreover, these values from the Ozawa method are close to those obtained by using the Freeman–Carroll and the Kissinger methods. This means that the simple reaction function, $f(\alpha)=(1–\alpha)^n$, for fitting of acetaminophen thermal decomposition, is reasonable.

Table 3 Activation energy (*E*) and reaction order (*n*) for acetaminophen decomposition

β/K min^{-1}	*E*/kJ mol^{-1}	*n*	R^2
10	90.77	0.24	0.9997
	92.51	0.25	0.9999
	92.44	0.25	1
	87.26	0.24	0.9996
5	91.82	0.18	0.9967
15	90.19	0.25	0.9959
	90.83±1.98[a]	0.24±0.027[a]	

[a]Standard deviation.

Table 4 Activation energy obtained from the Ozawa method under different α

α	0.2	0.3	0.4	0.5	0.6	0.7	0.8
E/kJ mol^{-1}	84.61	85.97	86.76	87.15	88.14	98.16	90.11

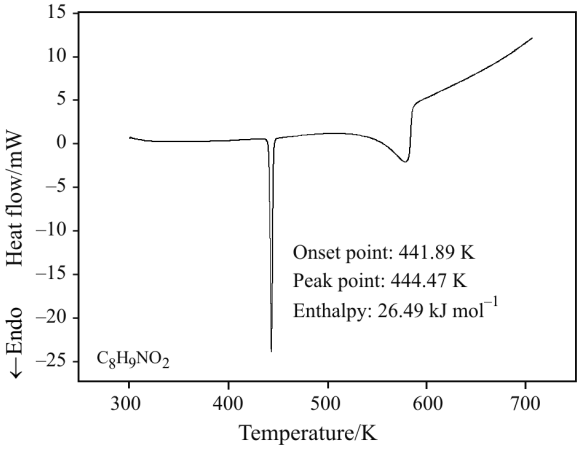

Fig. 7 DSC curve of acetaminophen

Kinetics equation of thermal decomposition of acetaminophen is expressed as:

$$\frac{d\alpha}{dt} = 2.67 \cdot 10^7 e^{-\frac{89630}{RT}} (1-\alpha)^{0.23}$$

Differential scanning calorimetry for acetaminophen

The DSC curve of acetaminophen is given in Fig. 7. Two obvious endothermic peaks appear in the DSC curve. The first endothermic peak appears before the mass loss happens as shown in Fig. 4, and it corresponds to the melting of acetaminophen with a peak temperature of (444.47±0.11) K. The melting point, molar enthalpy and entropy of fusion were determined to be (441.89±0.04) K, (26.49±0.44) kJ mol^{-1} and (59.80±1.01) J K^{-1} min^{-1}, respectively. These results are based on the four repeated measurements. The melting point is well in agreement with that reported in literature [3]. Therefore, the acetaminophen studied in this article is Form I. The second endothermic peak appears during the mass loss happens in Fig. 4 and it is caused by the thermal decomposition of acetaminophen.

Conclusions

The molar heat capacities of acetaminophen were precisely measured with a small sample precision automated adiabatic calorimeter over the temperature range from 80 to 330 K while Sacchetti [3] determined its heat capacities in the temperature range from –60~200°C by DSC. A solid–solid transition at 149.96 K was found from the $C_{p,m}$–T curve. The polynomial functions of $C_{p,m}$(J K^{-1} min^{-1}) *vs.* T were established in the light of the heat capacity measurements by the least square fitting method.

The thermal decomposition kinetics parameters, such as activation energy E, pre-exponential factor A and reaction order n, were calculated by TG-DTG techniques with the Freeman–Carroll method, Kissinger method and Ozawa method of acetaminophen. The thermal decomposition kinetics equation of acetaminophen is established. The process of fusion has been investigated through DSC. The melting point, molar enthalpy and entropy of fusion are determined.

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