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Thermochimica Acta 412 (2004) 33–37

thermochimica acta

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Thermodynamic study of ibuprofen by adiabatic calorimetry and thermal analysis

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Received 17 February 2003; received in revised form 28 August 2003; accepted 29 August 2003

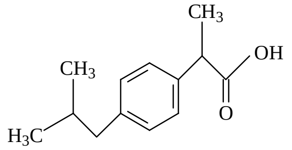
Abstract

Molar heat capacities of ibuprofen were precisely measured with a small sample precision automated adiabatic calorimeter over the temperature range from 80 to 400 K. The polynomial functions of $C_{p,m}$ ($\mathrm{J\,K^{-1}\,mol^{-1}}$) versus T were established on the heat capacity measurements by means of the least fitting square method. The functions are as follows: for solid ibuprofen, at the temperature range of $79.105\,\mathrm{K} \le T \le 333.297\,\mathrm{K}$, $C_{p,m} = 144.27 + 77.046X + 3.5171X^2 + 10.925X^3 + 11.224X^4$, where $X = (T - 206.201)/127.096$; for liquid ibuprofen, at the temperature range of $353.406\,\mathrm{K} \le \mathrm{T} \le 378.785\,\mathrm{K}$, $C_{p,m} = 325.79 + 8.9696X - 1.6073X^2 - 1.5145X^3$, where $X = (T - 366.095)/12.690$. A fusion transition at $T = 348.02\,\mathrm{K}$ was found from the C_p–T curve. The molar enthalpy and entropy of the fusion transition were determined to be $26.65\,\mathrm{kJ\,mol^{-1}}$ and $76.58\,\mathrm{J\,mol^{-1}\,K^{-1}}$, respectively. The thermodynamic functions on the base of the reference temperature of 298.15 K, $(H_T - H_{298.15})$ and $(S_T - S_{298.15})$, were derived. Thermal characteristic of ibuprofen was studied by thermo-gravimetric analysis (TG–DTG) and differential scanning calorimeter (DSC). The temperature of fusion, the molar enthalpy and entropy of fusion obtained by DSC were well consistent with those obtained by adiabatic calorimeter. The evaporation process of ibuprofen was investigated further by TG and DTG, and the activation energy of the evaporation process was determined to be $80.3 \pm 1.4\,\mathrm{kJ\,mol^{-1}}$.

Keywords: Ibuprofen; Adiabatic calorimeter; Heat capacity; Thermodynamic function; DSC; TG–DTG

1. Introduction

Ibuprofen, chemically named as 2-(4-isobutylphenyl)-propionic acid (molar mass: $206.28\,\mathrm{g\,mol^{-1}}$), a white crystal and non-steroidal anti-inflammatory drug having analgesic and antipyretic activities, shows a melting process at 75–77 °C [1] and will evaporate in an open container. Its structure is as follows:



The earlier investigation [2] has indicated that the evaporation of ibuprofen was a zero-order process. The activation energy and enthalpy of vaporization were found to be 81.8–87.0 and $42.7–46.1\,\mathrm{kJ\,mol^{-1}}$, respectively. Lerdkanchanaporn and coworkers [3–5] have studied thermal characteristics of mixtures of ibuprofen and/or starch/stearic acid by using simultaneous TG–DTA. Romero and Rhodes [6] have studied thermodynamic properties of ibuprofen enantiomers.

The thermodynamic properties of ibuprofen are significant for producing the drug and clinical application. To our best knowledge, there is no report on molar heat capacity measurement by adiabatic calorimetry. Therefore, the thermodynamic properties of ibuprofen including activation energy, melting point, the enthalpy and entropy of fusion, molar heat capacity have been determined by thermal analysis (TG–DTG and DSC) and adiabatic calorimetry.

2. Experimental

2.1. Material

Ibuprofen (CAS 15687-27-1) was supplied by Hunan Institute of Drug Detection, PR China, and was a racemic

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doi:10.1016/j.tca.2003.08.021

compound. FTIR and C13 NMR determined its structure. Quantitative analysis of ibuprofen was performed by titration according to Chinese pharmacopoeia (2000) and its purity is 99.0%.

2.2. Adiabatic calorimeter

The heat capacity measurements were carried out by means of a high-precision automatic adiabatic calorimeter over the temperature range of 78–400 K. The principle and structure of the adiabatic calorimeter were described in detail elsewhere [7–10]. Briefly, the calorimeter mainly comprises a sample cell, a platinum resistance thermometer, an electric heater, an inner and outer adiabatic shield, and two sets of differential thermocouples and a high vacuum can. The samples were cooled by liquid nitrogen, and the sample cell was made of gold-plated copper and had an internal volume of about 6 cm^3. Four gold-plated copper vanes of 0.2 mm thickness were put into the cell to promote heat distribution between the sample and the cell. The platinum resistance thermometer was inserted into the copper sheath, which was soldered at the bottom of the sample cell. The heater wire was wound on the side surface of the cell. The lid of the cell with a copper capillary was sealed to the sample cell with adhesive, after the sample was loaded in it. The air on the cell was evacuated and a small amount of helium gas (0.1 MPa) was introduced into it to enhance the heat transfer within the cell. The temperature differences between the sample cell and the inner shield, and between the inner and outer shields were monitored by two sets of six-junction chromel–copel (Ni: 55%, and Cu: 45%) thermocouples, and controlled by two sets of DWT-702 precision temperature controller (manufactured by Shanghai No. 6 Automated Instrumentation Works). The electrical energy introduced into the sample cell and the equilibrium temperature of the cell after the energy input were automatically picked up by use of the Data Acquisition/Switch Unit (Model 34970A, Agilent, USA), and processed on line by a computer. To verify the reliability of the calorimeter, the heat-capacity measurements of the reference standard material (α-Al_2O_3) were made over the same temperature range as that of the measurement of ibuprofen sample. The deviation of our experimental results from the recommended value [11] of the former National Bureau of Standards lies within ±0.2%, in the whole experimental temperature range.

2.3. Thermal analysis

A thermo-gravimetric analyzer (Setsys 16/18 from Setaram Company, France) was used for TG measurements of ibuprofen under the atmosphere of nitrogen. The heating rate was 10 °C min^{-1} and the flow rate of nitrogen was 30 ml min^{-1}. The sample mass varied from 7.1 to 10.8 mg. Two Al_2O_3 crucibles were used (capacity: 100 μl). The reference crucible was filled with α-Al_2O_3. TG–DTG equipment was calibrated by $CaC_2O_4 \cdot H_2O$.

A differential scanning calorimeter (DSC 141 from Setaram Company, France) was used to perform the thermal analysis of ibuprofen with a heating rate of 10 °C min^{-1}. Liquid nitrogen was used as the cooling medium. Dry nitrogen was used as a purge gas at a flow rate of 50 ml min^{-1}. Two opened aluminum crucibles were used (capacity 30 μl) and the reference crucible was empty. The calibration of DSC-141 equipment was carried out with various standard materials including Sn (99.9995%), Zn (99.999%), Al (99.999%), Pb (99.999%), Hg (99.999%) and Ni (99.999%).

3. Results and discussion

3.1. Heat capacities and thermodynamic properties of ibuprofen

Fig. 1 shows a plot of experimental molar heat capacities of ibuprofen versus the temperatures obtained by the adiabatic calorimeter over the temperature range from 80 to 390 K. The mass of sample used for the experiment was 1.7408 g. The temperature increment for each experimental point was about 3 K in the whole temperature range. The experimental molar heat capacities of ibuprofen and calculated thermodynamic properties (relative to 298.15 K) are listed in Tables 1 and 2, where $C_{p,m}$ ($J\,K^{-1}\,mol^{-1}$) were calculated according to following Eqs. (1) and (2). $H_T - H_{298.15}$ and $S_T - S_{298.15}$ were derived from heat capacity data according to the following equations:

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

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

The molar heat capacities of the solid sample were fitted to the following polynomial of heat capacities versus reduced temperature (X) by means of the least square fitting, in the light of the method described in literature [10,12].

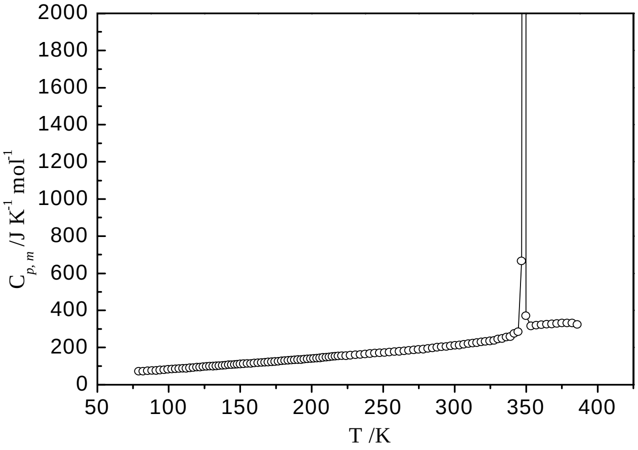

Fig. 1. Molar heat capacities of ibuprofen.

Table 1
The experimental molar heat capacity of ibuprofen ($M = 206.28\,\mathrm{g\,mol^{-1}}$)

T (K)	$C_{p,m}$ ($\mathrm{J\,K^{-1}\,mol^{-1}}$)	T (K)	$C_{p,m}$ ($\mathrm{J\,K^{-1}\,mol^{-1}}$)	T (K)	$C_{p,m}$ ($\mathrm{J\,K^{-1}\,mol^{-1}}$)	T (K)	$C_{p,m}$ ($\mathrm{J\,K^{-1}\,mol^{-1}}$)
79.105	70.862	152.486	111.84	221.149	154.05	318.598	229.96
82.196	71.886	154.995	113.6	224.025	155.17	321.544	232.02
85.25	73.86	157.494	113.91	227.187	158.55	324.596	235.58
88.26	74.606	159.977	116.2	230.628	160.23	327.529	237.9
91.183	76.459	162.441	116.86	234.016	161.51	330.432	245.23
94.034	78.021	164.882	118.39	237.384	163.96	333.297	248.78
96.815	79.726	167.29	119.91	240.751	167.52	336.147	254.81
99.533	81.59	169.669	122.02	244.091	169.65	338.974	258.57
102.198	83.109	172.037	123.52	247.503	170.89	341.765	275.74
104.81	84.416	174.393	124.52	250.991	172.68	344.435	285.04
107.374	86.048	176.728	125.76	254.456	174.86	346.73	664.6
109.895	87.008	179.039	127.118	257.899	177.32	347.747	7290.4
112.375	88.093	181.338	128.75	261.319	179.53	347.9	20910
114.816	89.604	183.629	129.73	264.715	181.33	347.95	32554
117.221	90.994	185.902	131.51	268.085	183.53	347.981	44338
119.592	93.164	188.157	132.78	271.432	185.76	347.999	70392
121.933	94.139	190.393	134.41	274.753	188.62	348.014	86020
124.241	95.539	192.625	135.16	278.052	191.27	348.024	115951
126.524	97.024	194.862	136.97	281.323	193.8	349.791	369.86
128.783	98.065	197.087	137.72	284.568	196.43	353.406	316.66
131.017	99.249	199.293	139.18	287.779	201.51	357.111	319.28
133.229	100.62	201.475	140.43	290.957	203.41	360.791	321.88
135.416	102.37	203.654	142.1	294.097	205.05	364.441	324.53
137.583	103.32	205.834	143.91	297.229	208.08	368.069	326.95
139.726	104.47	208.002	145.84	300.348	211.13	371.671	329.49
141.852	105.98	210.16	147.41	303.444	213.65	375.241	330.82
143.962	106.89	212.302	148.92	306.514	216.69	378.785	331.6
146.055	108.05	214.432	151.01	309.563	220.23		
148.132	109.42	216.551	151.7	312.593	222.94		
150.194	110.83	218.657	153.04	315.605	226.28		

$$C_{p,m} = 144.27 + 77.046X + 3.5171X^2 + 10.925X^3 + 11.224X^4 \qquad (1)$$

where $X = (T - 206.201)/127.096$, T the absolute temperature. The correlation coefficient of the fitting is $R^2 = 0.9997$. This equation is valid in the temperature range from 79.105 to 333.297 K. The standard deviation of the experimental points from the smoothed values in this temperature region is within ±0.5%.

The molar heat capacities of the liquid sample were fitted to the following polynomial:

$$C_{p,m} = 325.79 + 8.9696X - 1.6073X^2 - 1.5145X^3 \qquad (2)$$

where $X = (T - 366.095)/12.690$. This equation is valid in the temperature range from 353.406 to 378.785 K and correlation coefficient $R^2 = 0.9996$. The standard deviation is within ±0.04%.

The melting point of ibuprofen (T_m) obtained is 348.02 K from Fig. 1. The molar enthalpy of fusion ΔH_m was determined to be 26.65 $\mathrm{kJ\,mol^{-1}}$ based on the following formula:

$$\Delta H_\mathrm{m} = \frac{1}{n}\left[Q - n\int_{T_\mathrm{i}}^{T_\mathrm{m}} C_{\mathrm{p(S)}}\,\mathrm{d}T - n\int_{T_\mathrm{m}}^{T_\mathrm{f}} C_{\mathrm{p(L)}}\,\mathrm{d}T - \int_{T_\mathrm{i}}^{T_\mathrm{f}} H_0\,\mathrm{d}T\right]$$

where T_i is the temperature which is slightly lower than the initial melting temperature; T_m the melting temperature; T_f the temperature slightly higher than the final melting temperature; n the molar number of the sample; Q the total energy introduced into the sample and cell from T_i to T_f; $C_{p(\mathrm{S})}$ the heat capacity of the sample in solid phase from T_i to T_m; $C_{p(\mathrm{L})}$ the heat capacity of sample in liquid phase from T_m to T_f; and H_0 the capacity of sample cell from T_i to T_f. The molar entropy of fusion ΔS_m was calculated to be 76.58 $\mathrm{J\,mol^{-1}\,K^{-1}}$ from the formula: $\Delta S_\mathrm{m} = \Delta H_\mathrm{m}/T_\mathrm{m}$.

3.2. The results of DSC of ibuprofen

The DSC curve of ibuprofen is shown in Fig. 2. Two obvious endothermic peaks appear in DSC curve; the first endothermic peak corresponds to the melting of ibuprofen with a peak temperature of 351.25 ± 0.21 K. The melting point, molar enthalpy and entropy of fusion were determined as 348.35 ± 0.11 K, 25.04 ± 0.10 $\mathrm{kJ\,mol^{-1}}$ and 71.88 ± 0.28 $\mathrm{J\,mol^{-1}\,K^{-1}}$, respectively. These values are the mean of three times of repeat measurements. It is obvious that T_m, ΔH_m and ΔS_m obtained by DSC are consistent with those obtained by adiabatic calorimetry. These data are also in good agreement with [6]. The literature reported that T_m, ΔH_m and ΔS_m were 349 K, 25.5 $\mathrm{kJ\,mol^{-1}}$ and 73.2 $\mathrm{J\,mol^{-1}\,K^{-1}}$, respectively. The second peak occurred

Table 2
Calculated thermodynamic function data of ibuprofen

T (K)	$C_{p,\mathrm{m}}$ ($\mathrm{J\,K^{-1}\,mol^{-1}}$)	$H_T - H_{298.15}$ ($\mathrm{kJ\,mol^{-1}}$)	$S_T - S_{298.15}$ ($\mathrm{J\,K^{-1}\,mol^{-1}}$)
80	71.45	−29.45	−159.2
90	76.262	−28.71	−150.6
100	81.444	−27.92	−142.3
110	86.914	−27.08	−134.2
120	92.6	−26.19	−126.4
130	98.437	−25.23	−118.7
140	104.38	−24.22	−111.2
150	110.37	−23.14	−103.8
160	116.4	−22.01	−96.51
170	122.43	−20.81	−89.29
180	128.46	−19.56	−82.14
190	134.49	−18.25	−75.05
200	140.52	−16.87	−68.01
210	146.58	−15.43	−61
220	152.69	−13.94	−54.03
230	158.91	−12.38	−47.09
240	165.27	−10.76	−40.18
250	171.84	−9.075	−33.28
260	178.7	−7.322	−26.39
270	185.93	−5.499	−19.51
280	193.61	−3.602	−12.61
290	201.85	−1.625	−5.681
300	210.77	0.437	1.295
310	220.48	2.593	8.345
320	231.13	4.85	15.5
330	242.85	7.219	22.79
Phase transition (solid–liquid) at 348.02 K			
360	321.27	36.73	107.7
370	328.34	39.98	116.6
380	331.53	42.62	123.7

in the part of mass-loss of TG–DTG curve. So, it was caused from the endothermic evaporation of ibuprofen.

3.3. The results of TG and thermodynamic study for ibuprofen

The TG–DTG measurements were carried out under the atmosphere of high-purity N_2. The results in the above condition are presented in Fig. 3. The TG curve shows that the evaporation starts at about 460 K, ends at 550 K and maximum differential mass-loss percentage obtained from DTG curve is 50% at 528 K; the residue is about 0.8% at the end of evaporation, in the above condition.

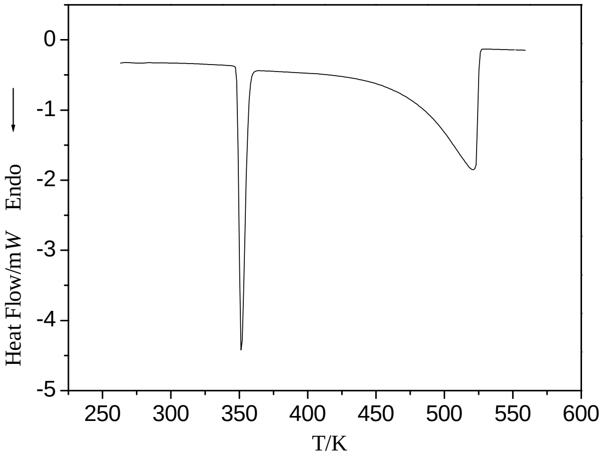

Fig. 2. DSC curve of ibuprofen.

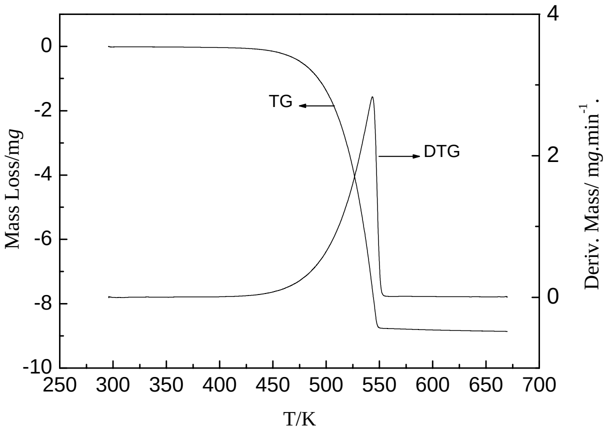

Fig. 3. TG and DTG curves of ibuprofen.

Lerdkanchanaporn and coworkers [3,5] have studied evaporation process of ibuprofen in detail, and found its evaporation process is characteristic of a zero-order. And at any specified temperature, the rate of evaporation from a uniform surface will be a constant value for the zero-order process. This process can be described as follows:

$$\frac{\mathrm{d}M}{\mathrm{d}t} = \frac{\mathrm{d}\beta M}{\mathrm{d}T} = k_T \tag{3}$$

where M is the mass of material in milligrams; t the time in minutes; $\mathrm{d}M/\mathrm{d}t$ represents the mass-loss rate of the liquid into the gaseous phase at each temperature T; k_T the rate coefficient of evaporation at the abstract temperature T in Kelvin and β the heating rate in $\mathrm{K\,min^{-1}}$. So, k_T can be determined directly from DTG signal. The process can be kinetically related to the temperature by the Arrhenius

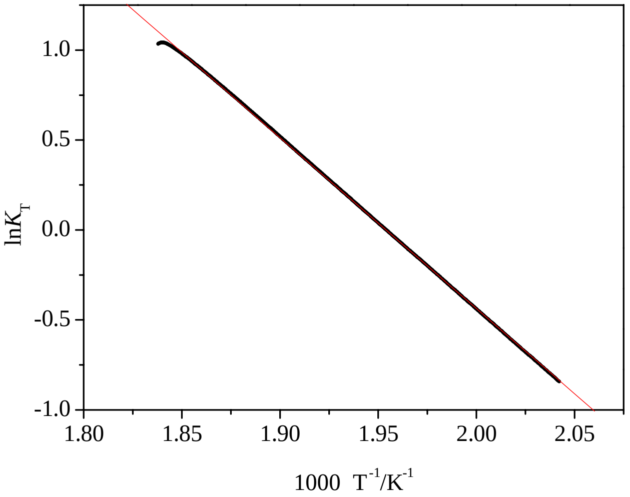

Fig. 4. A plot of $\ln k_T$ vs. $1/T$ of ibuprofen.

equation:

$$\ln k_T = \ln A - \frac{E_{\mathrm{act}}}{RT} \tag{4}$$

where A is pre-exponential factor; E_{act}, activation energy; and R the gas constant. Hence, $\ln A$ and E_{act} can be calculated from the above equation.

A plot of $\ln k_T$ versus $1/T$ according to Eq. (4) for the evaporation process of ibuprofen was given in Fig. 4. E_{act} can be calculated from the slope of this plot, and the intercept is equal to $\ln A$. So, E_{act} and $\ln A$ were obtained to be $80.33 \pm 1.44\,\mathrm{kJ\,mol^{-1}}$and 20.49 ± 1.24, respectively, by four repeat measurements. These results are in good agreement with [2] which reported E_{act} and $\ln A$ were $81.9\,\mathrm{kJ\,mol^{-1}}$ and 20.7, respectively.

Acknowledgements

The authors gratefully acknowledge the National Natural Science Foundation of China for financial support to this work under Grant NSFC no. 20073047.

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