Low Temperature Heat Capacity of (*S*)-ibuprofen*

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Abstract Molar heat capacities of (*S*)-ibuprofen were precisely measured with a small sample precision automated adiabatic calorimeter over the temperature range from 80 to 370 K. Experimental heat capacities were fitted into a polynomial equation of heat capacities ($C_{p,m}$) with reduced temperature (X), [$X = f(T)$]. The polynomial equations for (*S*)-ibuprofen were $C_{p,m(S)} = -39.483X^4 - 66.649X^3 + 95.196X^2 + 210.84X + 172.98$ in solid state and $C_{p,m(L)} = 7.191X^3 + 4.2774X^2 + 56.365X + 498.5$ in liquid state. The thermodynamic functions relative to the reference temperature of 298.15 K, $H_T - H_{298.15}$ and $S_T - S_{298.15}$, were derived for the (*S*)-ibuprofen. A fusion transition at $T_m = (324.15 \pm 0.02)$ K was found from the $C_p - T$ curve. The molar enthalpy and entropy of the fusion transition were determined to be (18.05 ± 0.31) kJ·mol^{-1} and (55.71 ± 0.95) J·mol^{-1}·K^{-1}, respectively. The purity of the (*S*)-ibuprofen was determined to be 99.44% on the basis of the heat capacity measurement. Finally, the heat capacities of (*S*)-ibuprofen and racemic ibuprofen were compared.

Keywords: (*S*)-ibuprofen, Adiabatic calorimetry, Heat capacity

Ibuprofen has a chiral carbonaceous atom. It is generally recognized that (*S*)-ibuprofen is the enantiomer of ibuprofen. The (*S*)-ibuprofen, a white crystal powder and nonsteroidal anti-inflammatory drug having analgesic and antipyretic activities, shows a melting process over the temperature range from 51 to 53 ℃[1]. Clinic study showed that the (S)-ibuprofen possesses a pharmacological effect 160 times higher than that of 2-(4-isobutylphenyl)-*R*(-)-propionic acid[2]. The doses of 150 mg and 300 mg of the (*S*)-ibuprofen are biologically equivalent to those of 200 mg and 400 mg of racemic ibuprofen, respectively. The (*S*)-ibuprofen has the superiority to racemic ibuprofen in safety and pharmacological effect[3-4]. It is the most active species pharmaceutically from both the clinical and biopharmaceutical points of view. Methods used for preparing (*S*)-ibuprofen, such as chiral separation by chiral chromatography or chiral HPLC, chemical splitting method, biological catalysis and hydrolysis, have been presented in iterature[5-6].

The thermodynamic properties of drugs, e. g. heat capacities, are significant for the drug production and clinical applications. As far as the determination of heat capacities of drugs is concerned, there are many publications which used different methods such as modulated temperature differential scanning calorimetry (DSC)[7-8], standard differential scanning calorimetry[9-10]. As one knows, adiabatic calorimetry is a very accurate method for heat capacity determination. However, only very few papers[11-12] reported the heat capacity measurements of drugs by the adiabatic calorimetry.

The literature reported that the melting point, melting enthalpy and entropy of the (*S*)-ibuprofen were 327 K, 17.9 kJ·mol^{-1} and 54.8 J·mol^{-1}·K^{-1}, respectively[13]. In the present work, low-temperature heat capacities of the (*S*)-ibuprofen were studied in detail by a small sample precision automated adiabatic calorimeter. The purity of ibuprofen was determined in the light of the heat capacity measurements.

1 Experimental

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1.1 Sample

(*S*)-Ibuprofen (CAS 51146-56-6, its content is higher than 99.0%) was supplied by Hunan Institute of Drug Detection, P. R. China. It was separated by chiral HPLC. The separated product was further recrystallized three times with alcohol (A. R.). FTIR and C13 NMR were used to determine its structure. Qualitative analysis was carried out by polarimeter, and quantitative analysis was performed using titration.

1.2 Adiabatic calorimetry

Heat capacity measurement was carried out using a small sample precision automated adiabatic calorimeter over the temperature range from 80 to 390 K. The construction and principle of the calorimeter have been described previously in detail elsewhere[14-17]. Briefly, the calorimeter was based on Nernst step heating method[18]. A temperature increment ΔT is caused by supplying a known quantity of electric energy ΔE. The electrical energy introduced into the sample cell and the equilibrium temperature of the cell after the energy input were automatically picked up by using of the Data Acquisition/Switch Unit (Model 34970A, Agilent, USA), and processed on line by a computer. The total heat capacity (C) of the cell containing sample is given as the ratio of the supplied electric energy to the temperature increment, namely as $C = \Delta E/\Delta T$. Heat capacity of the (*S*)-ibuprofen sample is derived by subtracting the heat capacity of the empty calorimeter cell determined in an experiment using empty cell without sample from the total heat capacity.

To verify the reliability of the calorimeter, the molar heat capacities of sapphire (α-Al_2O_3, Standard Reference Material 720, the National Institute of Standards and Technology) were measured over the same temperature range. The deviations of our experimental results from those of the smoothed curve obtained by least square fitting of heat capacities data of sapphire were within ±0.2 %, while the inaccuracies lie within ±0.5 %, as compared with the heat-capacity values of sapphire recommended by Donald Archer for ITS-90[19] over the investigated temperature range.

The mass of the sample filled in sample cell of the adiabatic calorimeter was 1.5088 g, which was equivalent to 7.3143 mmol based on its molar mass of 206.28 g·mol^{-1}.

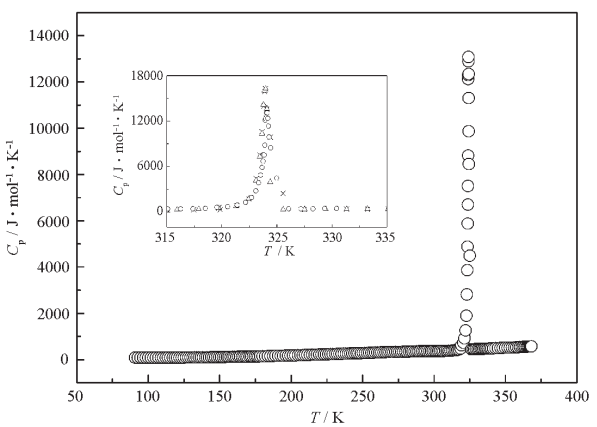

Fig. 1 Relation curve of heat capacities *vs* temperature ($C_{p,m} \sim T$) of (*S*)-ibuprofen obtained by adiabatic calorimetry

(o), (Δ) and (×) represent the first, second and third series of heat capacity measurements, respectively

2 Results and discussion

2.1 Heat capacity

Fig. 1 shows a plot of experimental molar heat capacities of (*S*)-ibuprofen *vs* temperature obtained by the adiabatic calorimeter over the temperature range from 88 to 370 K. The temperature increment for each experimental point was about 3 K in the whole temperature range. The smooth molar heat capacities of (*S*)-ibuprofen and other thermodynamic properties(relative to 298.15 K) are listed in Table 1, where

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

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

The molar heat capacities of the sample in solid state were fitted to the following polynomial of heat capacities *vs* reduced temperature(X) by means of the least square fitting

$$C_{p,m(S)} = -39.483X^4 - 66.649X^3 + 95.196X^2 + 210.84X + 172.98 \quad (1)$$

where $X = \{T - [(T_{max} + T_{min})/2]/[(T_{max} - T_{min})/2]\}$, when $T_{max} = 312$ K and $T_{min} = 88$ K, $X = (T - 200)/112$, T is the absolute temperature, the correlation coefficient of the fitting, $R^2 = 0.9999$. This equation is valid in the temperature range from 88 to 312 K.

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

$$C_{p,m(L)} = 7.191X^3 + 4.2774X^2 + 56.365X + 498.5 \quad (2)$$

where $X = \{T - [(T_{max} + T_{min})/2]/[(T_{max} - T_{min})/2]\}$, when $T_{max} = 369$ K and $T_{min} = 326$ K, $X = (T - 347.5)/21.5$. This equation is valid in the temperagure range from 326 to 369 K and correlation coefficient $R^2 = 0.9998$.

2.2 Molar enthalpy and entropy of fusion

Fig. 1 shows there is an endothermic peak from 312 to 326 K. The melting point of this material is over the temperature range from 51 to 53 ℃ (324.15 ~ 326.15 K) according to the literature[1]. Thus, this endothermic peak is caused by the fusion of (*S*)-ibuprofen. The equilibration time within solid and liquid phase was about 8 h.

The enthalpy of fusion, $\Delta_{fus}H_m$, was calculated as (18.05 ± 0.31) kJ·mol^{-1} by the following formula[14]

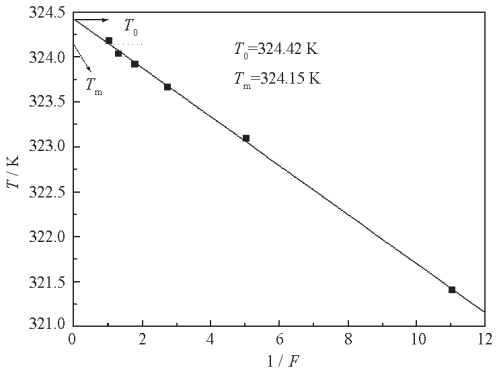

Fig. 2 Curve of *T vs* 1/*F* for (*S*)-ibuprofen

$$\Delta_{fus}H_m/J\cdot mol^{-1} = [\,Q - n\int_{T_i}^{T_m} C_{p(S)}dT - n\int_{T_m}^{T_f} C_{p(L)}dT - \int_{T_i}^{T_m} H_0 dT\,]/n \quad (3)$$

where T_i is the temperature which is slightly lower than the starting phase transition temperature; T_m, the melting point; T_f, the temperature slightly higher than the finishing phase transition temperature; $C_{p(S)}$, the average heat capacity at the temperature $(T_i + T_m)/2$; $C_{p(L)}$, the average heat capacity at the temperature $(T_m + T_f)/2$; n, the molar number of the sample; Q, overall energy absorbed by the sample and con-

Table 1 Calculated thermodynamic function data of (*S*)-ibuprofen

T/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}	T/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}
Solid							
90	83.641	−38562	−187.87	210	192.23	−24891	−97.230
95	83.147	−38146	−183.42	215	202.50	−23909	−92.619
100	82.898	−37733	−179.20	220	213.04	−22876	−87.875
105	82.940	−37321	−175.19	225	223.79	−21790	−82.998
110	83.318	−36909	−171.34	230	234.70	−20651	−77.992
115	84.071	−36495	−167.63	235	245.72	−19457	−72.858
120	85.234	−36076	−164.04	240	256.78	−18209	−67.600
125	86.837	−35650	−160.54	245	267.82	−16907	−62.224
130	88.909	−35215	−157.10	250	278.76	−15550	−56.736
135	91.472	−34768	−153.71	255	289.54	−14139	−51.142
140	94.546	−34308	−150.35	260	300.07	−12676	−45.452
145	98.145	−33830	−146.99	265	310.28	−11162	−39.674
150	102.28	−33333	−143.61	270	320.07	−9597.7	−33.818
155	106.96	−32814	−140.21	275	329.36	−7986.6	−27.897
160	112.19	−32270	−136.76	280	338.05	−6331.0	−21.922
165	117.96	−31698	−133.24	285	346.04	−4633.8	−15.906
170	124.27	−31096	−129.66	290	353.24	−2898.7	−9.8644
175	131.11	−30461	−125.99	295	359.53	−1129.7	−3.8116
180	138.47	−29791	−122.23	298.15	362.98	0	0
185	146.33	−29082	−118.36	300	364.81	668.44	2.2360
190	154.66	−28333	−114.38	305	368.96	2490.8	8.2614
195	163.46	−27542	−110.28	310	371.86	4331.5	14.247
200	172.67	−26706	−106.06	312	372.65	5071.6	16.625
205	182.28	−25823	−101.71				
			Phase fusion(solid-liquid, at 324.15 K)				
Liquid							
326	439.22	23973	86.312	350	505.12	35071	86.308
330	451.58	25714	86.282	355	518.99	37572	86.323
335	465.76	27955	86.275	360	534.13	40144	86.351
340	479.05	30263	86.283	365	551.09	42793	86.409
345	491.99	32635	86.295	368	562.37	44425	86.467

tainer in the temperature region between T_i and T_f; H_0, the heat capacity of the empty sample cell. The entropy of fusion $\Delta_{fus}S_m$ could be obtained as (55.71 ± 0.95) J·mol^{-1}·K^{-1} by

$$\Delta_{fus}S_m = \Delta_{fus}H_m / T_m.$$

2.3 Melting point and purity

The purity of the sample was evaluated from a set of equilibrium melting temperature T_F and the melted fraction F corresponding to these temperature[18, 20-21]. The relationship between T_F and F can be expressed as follows:

$$T_F = T_0 - (1/F)(T_0 - T_m) \quad (4)$$

where T_0 is the melting point of an absolutely pure substance; T_m is the melting point of the given sample; F is the rate of the partial heat required melting a part of the sample to the total heat required melting the whole sample.

Eq. (4) shows that the relationship between the equilibrium melting temperature T_F and the reciprocal of melted fraction $1/F$ is linear. Plotting T_F *vs* $1/F$ (see Fig. 2), and extrapolating the straight line to $1/F = 1$ and $1/F = 0$, then T_m and T_0 can be derived as $T_m = 324.15$ K and $T_0 = 324.42$ K. Therefore, the melting point of the (*S*)-ibuprofen is 324.15 K.

According literatures[18, 20-21], the relation between the mole fraction x of the impurities in the sample and melting point of the sample can be expressed as follows:

$$x = \Delta_{fus}H_m(T_0 - T_m)/RT_0^2 \quad (5)$$

In terms of Eq. (5), x is calculated to be 5.58×10^{-3}. The purity of the (*S*)-ibuprofen is $1 - x = 99.44\%$.

2.4 Comparing C_p of (*S*)-ibuprofen with racemic ibuprofen

The heat capacities of racemic ibuprofen have been reported[22]. Fig. 3 is the curves of heat capacities of racemate and (*S*)-ibuprofen. It clearly indicates that the heat capacities of the racemate and (*S*)-ibuprofen below 170 K are almost the same; and the heat capacities of (*S*)-ibuprofen are higher than those of racemic ibuprofen above 170 K, whether they are solid or liquid. The higher the temperature, the larger the difference of heat capacities between the racemate and (*S*)-ibuprofen is.

The above phenomena can be ascribed to the relationship of crystal structures and intermolecular environments[7] of the racemate and (*S*)-ibuprofen. According to the literature[7], the molecular arrangement of racemic ibuprofen exhibits some of the acid groups 'face-up' and others 'face-down', so that all the layers of molecules are interconnected with pairs of hydrogen bonds to carboxyl groups. However, there are a greater number of crystallographically independent molecules in the (*S*)-crystals.

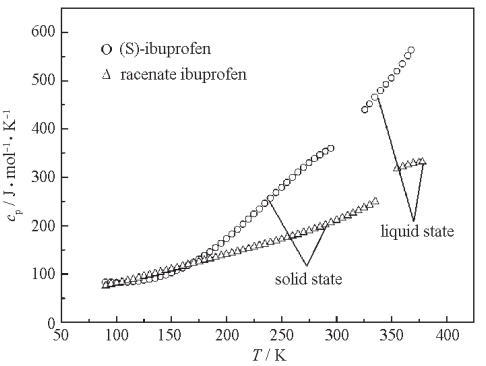

Fig. 3 Comparison of C_p of racemate and (*S*)-ibuprofen

The array of (*S*)-crystal molecules involved in homochiral interactions probably spreads the mechanical stability/strength of the crystal, and molecules of the same chirality had to be flexed in order to meet the space requirements of the lattice. This may cause that the heat capacities of (*S*)-ibuprofen is higher than that of racemate.

References

1 Morris, R.; Nagarkatti, J. Aldrich, 1996-1997. Milwaukee (Wisconsin US): Aldrich Chemical Company, Inc., 1997: 869

2 Mustranta, A. *Microbiol. Biotechnol.*, **1992, 38:** 61

3 Hutt, A. J. *Foreign Pharmacy: Subvolume of Synthetic Medicine, Biochemical Medicine, Preparation,* **1986, 7:** 11

4 Hua, W. Y. *Progress in Pharmacy,* **1991, 15**(3): 129 [华维一. 药学进展(*Yaoxue Jinzhan*), **1991, 15**(3): 129]

5 Kaiser, D. G.; Vangiessen, G. J.; Reischer, R. J. *J. Pharm. Sci.*, **1976, 65:** 269

6 Felder, E.; Pitre, D.; Zutter, H. Process for the reslution of (+)- and (−)-6-methoxy-α-methyl-2-naphthaleneacetic acid. U. S. Patent, 4246164, 1978

7 Bottom, R. *Int. J. Pharm.*, **1999, 192:** 47

8 Hill, V. L.; Passerini, N.; Craig, D. Q. M.; Vickers, M.; Anwar, J.; Feely, L. C. *J. Therm. Anal. Calorim.*, **1998, 54:** 673

9 Yoshihashi, Y.; Kitano, H.; Yonemoch. E.; Terada, K. *Int. J. Pharm.*, **2000, 204:** 1

10 Waldron, T. T.; Murphy, K. P. *Biochemistry,* **2003, 42:** 5058

11 Xu, F.; Sun, L. X.; Tan, Z. C.; Lan, X. Z.; Yu, P.; Zhang, T. J. *Therm. Anal. Calorim.*, **2003, 74:** 335

12 Xu, F.; Sun, L. X.; Tan, Z. C.; Liang, J. G.; Zhou, D. H.; Di, Y. Y.; Lan, X. Z.; Zhang, T. *Acta Phys.-Chim. Sin.*, **2004, 20**(1): 50 [徐 芬,孙立贤,谭志诚,梁建国,周丹红,邸

友莹, 兰孝征, 张 涛. 物理化学学报(*Wuli Huaxue Xuebao*), **2004, 20**(1): 50]

13 Romero, A. J.; Rhodes, C. T. *J. Pharm. Pharmacol.,* **1993, 45:** 258

14 Tan, Z. C.; Sun, G. Y.; Sun, Y.; Yin, A. X.; Wang, W. B.; Ye, J. C.; Zhou, L. X. *J. Thermal. Anal.,* **1995, 45:** 59

15 Tan, Z. C.; Sun, L. X.; Meng, S. H.; Li, L.; Xu, F.; Yu, P.; Liu, B. P.; Zhang, J. B. *J. Chem. Thermodyn.,* **2002, 34:** 1417

16 Di, Y. Y.; Yu, H. G.; Tan, Z. C.; Gao, S. L.; Liu, Y.; Sun, L. X. *J. Chem. Thermodyn.,* **2003, 35:** 885

17 Liu, B. P.; Tan, Z. C.; Lu, J. L.; Lan, X. Z.; Sun, L. X.; Xu, F.; Yu, P.; Xing, J. *Thermochim. Acta,* **2003, 397:** 67

18 Westrum Jr., E. F.; Furukawa, G. T.; McCullough, J. P. Adiabatic low-temperature calorinetry. in: McCullough, J. P.; Scoott, D. W. ed. Experimental thermodynamics, calorimetry of non-reaction system, Vol. 1. Now York: Plenum Press, 1968: 133

19 Donald, G. A. *J. Phys. Chem. Ref. Data,* **1993, 22:** 1441

20 Zhang, Z. Y.; Frenkel, M.; Marsh, K. N.; Wilhoit, R. C.; Landolt, H.; Bornstein, R. Thermodynamic properties of organic compounds and their mixtures, Group IV, Vol. 8, Subvolume A. Berlin: Springer, 1995, Chaper 7

21 Badley, J. H. *J. Phys. Chem.,* **1959, 63:** 1991

22 Xu, F.; Sun, L. X.; Tan, Z. C.; Liang, J. G.; Li, R. L. *Thermochim. Acta,* **2004, 412:** 33

右旋布洛芬的低温热容*

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摘要 在 80~370 K 温度范围内, 用精密自动绝热量热计准确测量了右旋布洛芬的摩尔热容. 其固态右旋布洛芬测量值对折和温度 $X[X=f(T)]$的拟和方程为: $C_{p,\mathrm{m(S)}} = -39.483X^4 - 66.649X^3 + 95.196X^2 + 210.84X + 172.98$; 相应的液态的拟和方程为: $C_{p,\mathrm{m(L)}} = 7.191X^3 + 4.2774X^2 + 56.365X + 498.5$. 并计算得到右旋布洛芬相对于室温(298.15 K)的摩尔焓和摩尔熵. 右旋布洛芬的熔点为(324.15±0.02) K. 基于摩尔热容的测量, 还可获得右旋布洛芬的纯度为 99.44%. 并对右旋布洛芬和消旋布洛芬的热容进行了对比研究.

关键词: 右旋布洛芬, 绝热量热, 热容

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