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HEAT CAPACITY OF α-GLYCYLGLYCINE IN A TEMPERATURE RANGE OF 6 TO 440 K
Comparison with glycines

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Heat capacity of α-glycylglycine was measured using adiabatic calorimetry (6 to 304 K) and DSC (264 to 443 K), and then thermodynamic functions were calculated. Heat capacity has no anomalies. The molecular crystal melts at 493 K (enthalpy of melting is about 62 kJ mol^{-1}). The melting is accompanied by decomposition.

$C_P(T)$ function for glycylglycine is very similar to those of three glycine polymorphs. The ‘universal’ curve consists of two parts: low-temperature Debye-like function (from 0 to about 120 K) and a straight line (up to the melting point). At very low temperatures rigid molecules oscillate as a whole, and the Debye temperature is proportional to the molecular mass to the power of 3/2.

Keywords: *adiabatic calorimetry, DSC, glycine, glycylglycine, heat capacity, molecular crystals*

Introduction

Glycylglycine, $C_4H_8N_2O_3$, crystallizes in three polymorphs, α, β and γ [1]. Structure of two first polymorphs was solved [2, 3]. For the first time, heat capacity of glycylglycine was measured using adiabatic calorimetry in a temperature range of 90 to 298 K [4], and then repeated from 11 to 305 K [5]. It was necessary to repeat the measurements because thermodynamic functions, first of all entropy, have had significant uncertainty in their values due to the extrapolation of $C_P(T)$ from 90 K down to zero temperature. Measured $C_P(T)$ values were very similar in both reports, with $C_P(298.15)=164.0$ J mol^{-1} K^{-1} [5]. Later, heat capacity of glycylglycine was measured using DSC from 298 to 348 K, together with other dipeptides [6]. The new values were about 10% less than those measured with adiabatic calorimetry: $C_P(298.15)=149$ J mol^{-1} K^{-1}. The discrepancy was not discussed. Neither of three reports has indicated the crystal structure of the sample investigated.

The situation is very similar to that with glycine. Heat capacity of unidentified polymorphs of glycine was measured by the same authors [6, 7] and their results at 298.15 K were found to differ from one another by about 5%. We measured the heat capacity of both polymorphs and found that $C_P(298.15)$ of α-glycine is equal to the value measured in [7] and that of γ-glycine is equal to the value measured in [6].

The objective of this work was to conduct the calorimetric measurements of α-glycylglycine over the whole temperature range where the polymorph exists and to compare the results with heat capacity of glycines.

Experimental

Glycylglycine of ICN Biomedicals Inc. (catalog number 101856, 132.1 g mol^{-1}) was used as purchased. Its X-ray powder diffraction pattern is identical to that of α-glycylglycine calculated after single-crystal X-ray diffraction structure refinement. The unit cell is monoclinic (s.g. P21/c) with a=0.81273, b=0.95837, c=0.78489 nm, β=107.68°. The parameters were refined using software TOPAS after X-ray powder diffraction measurements on diffractometer D8-GADDS (Bruker).

Low-temperature calorimetric measurements were carried out using vacuum adiabatic calorimetric system working over the temperature range of 4.2–320 K, described elsewhere [8]. Sample mass in the calorimeter of 2 cm^3 was 1.3996 g. The calorimeter was evacuated at ambient temperature and filled with helium at a pressure of 30 mm Hg.

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Calorimetric measurements at moderate temperatures were carried out using DSC-204 (Netzsch) in a standard aluminum crucible (40 mL) with a lid (not sealed) in a flow of high-purity argon (25 mL min^{-1}). Heat capacity was measured using enthalpy method with a temperature program consisting of alternative dynamic (temperature increment of 5 K at a heating rate of 3 K min^{-1}) and isothermal (8–12 min, depends on temperature and sample mass) segments. Sensitivity of the DSC was calibrated against heat capacity of corundum (reference sample COTC-1a, purchased from Sverdlovsk Branch of Physico-Technical and Radio-Technical Measurements Institute). Two parts of the measurements were carried out one by one for every sample, one from 253 to 338 K and the other from 313 to 443 K. The first part was measured under the cooling by a vapor of boiling nitrogen. This increases the noise of the signal measured. The second part was performed without cooling. Glycylglycine was measured three times (sample masses 24.893, 23.242 and 23.099 mg), corundum two times (69.358 and 52.854 mg), and empty crucible two times. Sample mass was measured with an accuracy of ±0.003 mg.

Above 440 K, DSC measurements were carried out only at scanning heating (a heating rate of 6 K min^{-1}, sample mass 2.51 mg), since glycylglycine melts with decomposition, like glycine [9].

Results and discussion

Low-temperature heat capacity of glycylglycine was measured at 61 points over the temperature range of 6 to 304 K. Measured values are listed in Table 1 in time order. The standard deviation of the experimental points from the smoothed curve is 0.87% for $T<10$ K, 0.38% for $10<T<50$ K, and 0.06% for $T>50$ K. At very low temperatures (below 10 K) the heat capacity obeys the Debye model $C_P=aT^3$ with $a=0.702$ mJ mol^{-1} K^{-4}. The fitting of the experimental values to the cubic function is shown in Fig. 1. Heat capacity of glycylglycine is a smooth function of T over the whole temperature range where α-polymorph exists. No traces of ice melting were found near 273.13 K, indicating that no water inclusions are there in glycylglycine crystals. The same was mentioned in [5].

Table 1 Experimental heat capacity of α-glycylglycine (adiabatic calorimetry), 132.1 g mol^{-1}

T/K	C_P/J mol^{-1} K^{-1}	T/K	C_P/J mol^{-1} K^{-1}
	Series 1		Series 3
293.92	162.48	6.08	0.1563
296.44	163.56	7.41	0.2770
	Series 2	8.43	0.4068
84.41	64.50	9.51	0.6012
89.50	67.87	10.58	0.8520
94.59	71.07	11.65	1.1758
99.60	74.12	12.71	1.5467
104.55	77.03	13.76	2.0381
110.54	80.31	15.00	2.6784
117.61	84.08	16.33	3.5269
124.67	87.72	17.69	4.4428
131.69	91.32	19.05	5.504
138.69	94.76	20.41	6.586
147.17	98.75	22.10	8.103
157.14	103.39	24.19	10.105
167.09	107.81	26.27	12.190
177.03	112.34	28.34	14.350
186.99	116.70	30.42	16.562
196.98	120.85	32.49	18.777
207.00	125.15	35.06	21.538
217.06	129.23	38.18	24.859
227.17	133.76	41.32	28.125
237.21	138.16	44.43	31.334
247.08	142.36		Series 4
257.03	146.46	64.86	49.842
267.04	150.75	70.90	54.66
277.02	155.15	76.91	59.14
286.97	159.63	82.93	63.37
296.25	163.57		Series 5
298.90	164.72	48.43	35.29
301.33	165.62	53.01	39.63
		57.57	43.73
		62.13	47.64

Heat capacity measured by DSC is listed in Table 2. Two first points of each part were dropped out and not used in the evaluation of smoothed $C_P(T)$ function. The first part of DSC measurements overlaps with the adiabatic measurements over the temperature range 264–301 K and with the second part of DSC over 325–335 K. The error of an individual DSC measurement in a series is a sum of a random error (δC_R) and systematic error of the whole series (δC_S). Values of δC_R for all series except the first series in the low-temperature part of glycylglycine are within the limits of ±0.5%, only two points in the first series of glycylglycine scatter from the smoothed curve by +0.9 and –1.1%. Values of δC_S range within the limits of ±3 %. This is the main source of inaccuracy in DSC measurements of heat capacity. The values of Table 2 were fitted to a polynomial, each part separately. The standard deviation is 0.40% for the low-temperature part and 0.25% for the high-temperature part.

Smoothed value of $C_P(300)$ for the first part of DSC is 0.4% less than that derived from the adiabatic measurements, and its $C_P(330)$ is 1.0% greater than that for the second part of DSC. As adiabatic calorimetry is much more accurate in heat capacity measurements than DSC, we used the smoothed values of adiabatic calorimetry as a reference point and multiplied the first part of the DSC results by 1.004 and divided the second part by 1.006.

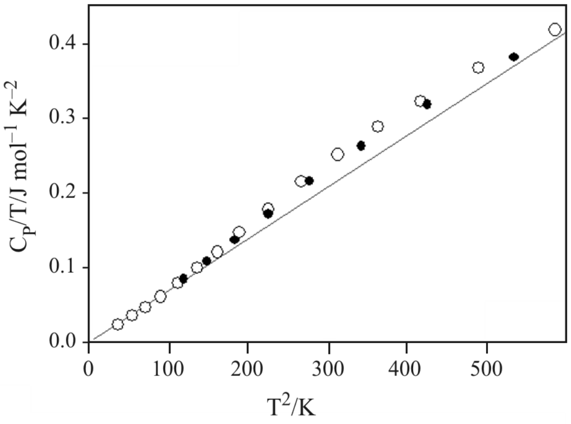

Fig. 1 Low-temperature heat capacity of glycylglycine: α-polymorph, this work (open circles), unidentified polymorph (filled circles) [5], fitting cubic function $C_P=aT^3$ (solid line)

Table 2 Experimental heat capacity of α-glycylglycine (DSC), 132.1 g mol^{-1}

T/K	C_P/J mol^{-1} K^{-1}	T/K	C_P/J mol^{-1} K^{-1}
	Series 1		Series 2
264.9	148.3	324.8	175.4
269.9	150.8	329.8	177.9
274.9	152.5	334.7	179.3
279.8	155.0	339.7	181.4
284.8	158.0	344.7	182.7
289.8	159.5	349.6	185.8
294.8	160.4	354.6	188.6
299.7	164.7	359.6	189.5
304.7	167.2	364.6	191.0
309.7	169.7	369.5	194.6
314.7	169.6	374.5	196.1
319.7	172.3	379.5	198.2
324.7	174.2	384.5	200.1
329.6	175.8	389.4	202.1
334.6	176.7	394.4	204.3
		399.4	205.8
		404.4	207.1
		409.3	210.1
		414.3	211.1
		419.3	213.6
		424.2	216.1
		429.2	217.3
		434.2	219.9
		439.2	221.3

The corrected values were used for the evaluation of thermodynamic functions of glycylglycine above 300 K, together with the results of adiabatic calorimetry. Below 9 K the functions were calculated using the cubic function. The results are shown in Table 3.

Table 3 Thermodynamic functions for α-glycylglycine

T/ K	C_P/ J mol^{-1} K^{-1}	H_T–H_0/ J mol^{-1}	S/ J mol^{-1} K^{-1}
(5)	(0.0878)	(0.1097)	(0.0293)
10	0.7057	1.755	0.234
15	2.688	9.516	0.837
20	6.259	31.33	2.067
25	10.90	73.89	3.947
30	16.09	141.2	6.388
35	21.48	235.1	9.27
40	26.80	355.9	12.49
45	31.91	502.8	15.94
50	36.79	674.7	19.56
60	45.82	1089	27.08
70	53.98	1588	34.77
80	61.38	2166	42.47
90	68.14	2814	50.09
100	74.37	3527	57.60
110	80.02	4299	64.96
120	85.35	5126	72.15
130	90.45	6005	79.18
140	95.35	6934	86.07
150	100.09	7912	92.81
160	104.69	8936	99.42
180	113.60	11119	112.26
200	122.19	13478	124.68
220	130.65	16006	136.72
240	139.23	18704	148.46
260	147.84	21575	159.94
280	156.47	24618	171.21
298.15	164.33	27529	181.28
300	165.13	27834	182.30
320	173.2	31221	193.2
340	180.6	34754	203.9
360	188.8	38448	214.5
380	197.0	42306	224.9
400	205.0	46325	235.2
420	212.8	50503	245.4
440	220.2	54833	255.5

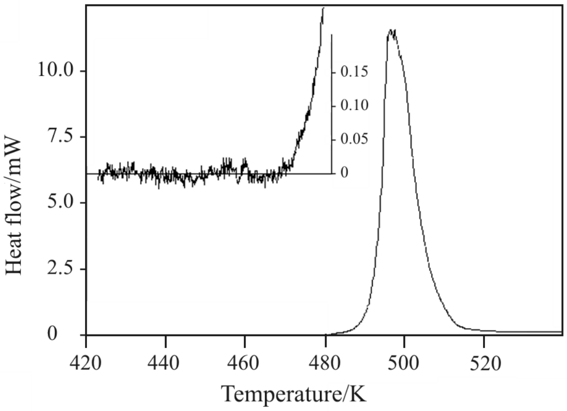

Fig. 2 DSC measurements near the melting point. In the insert: fitting DSC signal to a linear function. Melting (with decomposition) starts near 470 K

The results of DSC measurements above 440 K are shown in Fig. 2. Glycylglycine melts near 493 K with decomposition, enthalpy of melting is about 62 kJ mol^{-1}.

Comparison between literature data and this work

Heat capacity of glycylglycine at 298.15 K measured in this work is about 0.2% greater than the value published in [5]. Such a difference is an acceptable value for the interlaboratory error in calorimetric measurements. Figure 3 shows the difference between our data and those published in [5] over the whole temperature range. Average difference is about 0.5%. It is quite large value, but the difference can be attributed partly to the difference in the samples measured. The difference increases with decreasing temperature, and the greatest discrepancy (of ~3%) is in the interval of 15 to 20 K. It is very interesting to compare these results with those shown in Fig. 1. A plot of C_P/T *vs.* T^2 indicates evidently that in a temperature range of 10 to 18 K the heat capacity of glycylglycine increases with temperature faster than a cubic function of Debye model. This is valid both for our data and those of [5]. The difference between the experimental data and cubic fitting function is 17% near 17 K. The nature of the anomaly is unknown.

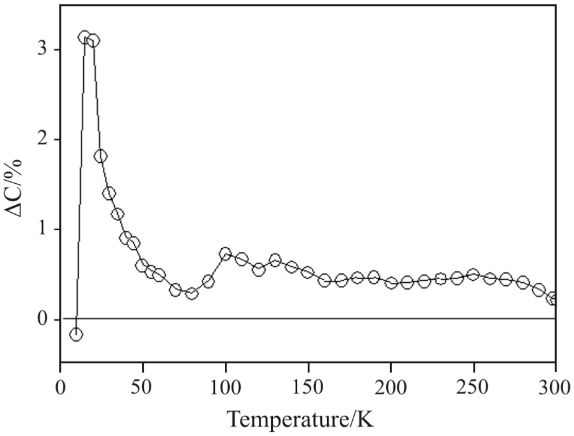

Fig. 3 Difference between heat capacity of α-glycylglycine (this work) and unidentified polymorph [5]

Similar anomaly in heat capacity was found in γ-glycine [8]. As the anomaly is smooth and broad, it can be detected evidently only at the plot of the difference between experimental data for γ-glycine and the cubic temperature function that fits the Debye model. Fortunately, heat capacity of α-glycine obeyes the Debye model well, and the difference between heat capacity of γ- and α-polymorphs of glycine showed a maximum of 26% near 17 K.

Comparison between glycylglycine and glycine

Like glycine, glycylglycine is formed by zwitter-ions. Its molecule can be considered as a product of the reaction between two glycine molecules forming a peptide bond:

$$^{+}NH_3CH_2COO^{-} + {}^{+}NH_3CH_2COO^{-} =$$

$$= {}^{+}NH_3CH_2CO\text{–}NHCH_2COO^{-} + H_2O$$

Zwitter-ions of glycines and glycylglycine are packed in various crystal structures with very similar interatomic interactions. For glycine, the molecules are arranged in three different types (polymorphs) with very close heat capacities. One can anticipate that the thermodynamic functions of a molecular crystal with a slightly different molecule of glycylglycine will be close to those of glycine. The heat capacities for three polymorphs of glycine and α-glycylglycine are shown in Fig. 4. The values of heat capacity are normalized to the average gram-atom (J $g\text{-}at^{-1}$ K^{-1}), which is equal to the mole divided by a number of atoms in the molecule (n=10 for glycine, but 17 for glycylglycine). Heat capacity of glycylglycine is really very close to that of glycine. It is difficult to distinguish the curves of glycine from that of glycylglycine on the plot, and here we will discuss the generalities in this ‘universal’ $C_P(T)$ function.

First, heat capacities of four molecular crystals on Fig. 4 are very small as compared to the value predicted by the classical theory ($3nR\approx25n$ J mol^{-1} K^{-1} or 25 J $g\text{-}at^{-1}$ K^{-1}). It means that the heat capacity of the molecular crystals investigated here is fundamentally quantum at room temperature. Formally, we can calculate the Debye temperature of glycines at 298.15 K. It is close to 1500 K, a very high value. Suffice it to say that the greatest value of the Debye temperature is about 1800 K for diamond, but ranges from 150 to 300 K for most metals and pure elements. Second, the shape of function $C_P(T)$ for glycines differs significantly from the curve predicted by the Debye model.

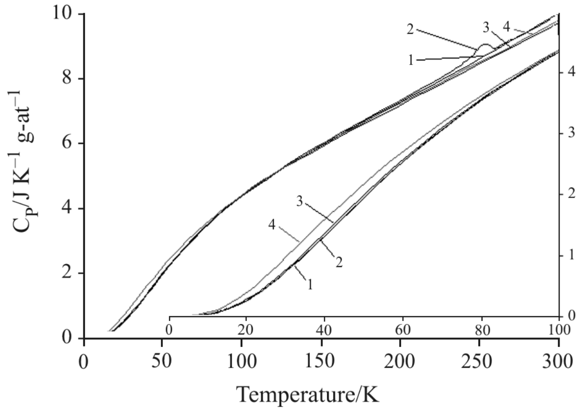

Fig. 4 Normalized heat capacities of α- (1), β- (2), γ-glycine (3), and α-glycylglycine (4)

Starting from 125 K, heat capacity increases along a straight line ($dC_P/dT \sim$const.), and for glycylglycine this continues up to the melting point. Heat capacity of α- and γ-glycines increases with temperature in a similar way ([6] and our own data, not published yet). Despite the steady increase, near the melting point the heat capacities of glycines are much less than the classical value of $3R$.

Quasilinear function $C_P(T)$ in the temperature range of $120<T<300$ K was found for the coordination compounds of 4-amine-1,2,4-triazole with nickel nitrate [10] and copper nitrate [11], and in the range of $300<T<430$ K for two polymorphs of indomethacin [12]. For crystalline nicotinic acid and aspirin, heat capacity increases linearly from 80 to 325 K, and then the slope becomes yet greater [13, 14]. Probably, linear growth of heat capacity with temperature can be considered typical of solids formed by molecules with high-energy interaction among constituent atoms but low-energy interaction among molecules themselves.

At very low temperatures, the difference between α-glycylglycine and three polymorphs of glycine is much greater (about 50%). In the insert to Fig. 4, the line of glycylglycine is separated well from the line of α, β, and γ-glycine, merging together. This can be explained in terms of molecular vibration. Below 10 K heat capacities of three substances obey the Debye model:

$$C_P = aT^3 \tag{1}$$

with a=0.238 mJ mol^{-1} K^{-4} for α-glycine and a=0.702 mJ mol^{-1} K^{-4} for α-glycylglycine and

$$C_P = aT^3 + bT \tag{2}$$

with a=0.239 mJ mol^{-1} K^{-4} for β-glycine. The linear term in the heat capacity of β-glycine is a contribution from dipole electric interaction among zwitterions [15]. Vibrations with the lowest energy in a molecular crystal are those when a molecule interacts with neighboring molecules as a rigid unit. In mechanical balls-and-springs model, the frequency of a vibration is:

$$\omega = 2\pi\sqrt{\frac{k}{m}} \tag{3}$$

where k is the spring constant, and m is the mass of a ball. In applying this model to the vibration of glycine and glycylglycine zwitterions in their crystals, one can expect that the frequency of vibration of glycylglycine will be greater than that of glycine, for the molecular weight of the former (132.12) is nearly two times greater than that of the latter (75.07). In the Debye model, vibrational spectra of a solid governs its heat capacity and is characterized by a single value of frequency, which can be expressed in units of kelvins:

$$\Theta_D = \frac{h\omega_{\max}}{k_B} \tag{4}$$

At very low temperatures the Debye model predicts

$$C_V = aT^3 = \frac{12\pi^4 R}{5}\frac{T^3}{\Theta^3} \tag{5}$$

Using a values for glycines and glycylglycine, one can calculate the Debye temperatures for the molecular crystals: Θ_1=201 K for glycines and Θ_2=140 K for glycylglycine. These values look quite reasonable. We can test our consideration in another way. As the heat capacity of molecular crystals is really the result of the vibrations of molecules as rigid units, one can apply the balls and springs model to the relation between the mass of a molecule and its frequency of vibration:

$$\frac{a_1}{a_2} = \frac{\Theta_2^3}{\Theta_1^3} = \left(\frac{m_1}{m_2}\right)^{3/2} \tag{6}$$

Here, we used Eq. (3), taking the spring constants equal, k_1=k_2. The ratio of coefficients a is 0.34 but the ratio of masses to the power of 3/2 is 0.43. The values are quite close, for this rough test does not consider the differences in structure and energy of interaction among molecules.

Conclusions

Heat capacity of α-glycylglycine measured in the temperature range from 6 K to the melting point has revealed several regularities, probably typical of organic molecular crystals. First, at ambient temperature the heat capacity is 2.5 times less than the value $3R$ predicted by classical theory, i.e., quantum effects play the important role in thermodynamic description of the substances of this kind. Second, function $C_P(T)$ in general view differs from that predicted by quantum models of heat capacity (Einstein, Debye, Tarasov [16]). Instead of fast growth at low temperatures and nearly constant value at moderate temperatures, heat capacity of molecular crystals grows from 0 to ~120 K by 20% of $3R$ according to Debye model and then increases linearly with temperature. The Debye characteristic parameter at very low temperatures is defined by the mass of the molecule.

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