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Low-temperature thermodynamic properties of DL-cysteine

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Abstract Heat capacity $C_p(T)$ of the crystalline DL-cysteine was measured on heating the system from 6 to 309 K by adiabatic calorimetry; thermodynamic functions were calculated based on these data smoothed in the temperature range 6–273.15 K. The values of heat capacity, entropy, and enthalpy at 273.15 K were equal to 142.4, 153.3, and 213.80 J K^{-1} mol^{-1}, respectively. At about 300 K, a heat capacity peak was observed, which was interpreted as an evidence of a first-order phase transition. The enthalpy and the entropy of the transition are equal, respectively, to 2300 ± 50 and 7.6 ± 0.1 J K^{-1} mol^{-1}.

Keywords Low temperatures · Heat capacity · Phase transitions · Amino acid crystal

Introduction

Our previous studies have shown that the crystals of chiral amino acids and of their racemic counterparts can differ significantly in the dynamical properties, in the stability with respect to phase transitions, and in the thermodynamic parameters, L- and DL-serine ($^{+}NH_3$–CH–(CH_2OH)–COO^{-}) providing up to now the most striking example [1–5]. Cysteine ($^{+}NH_3$–CH–(CH_2SH)–COO^{-}) is a structural analog of serine, in which the oxygen atom is substituted for the sulfur atom, and the dynamics of the side residue is different from that of the side group in serine, both because of the weakening of the intermolecular hydrogen bonds, and because of a larger mass of the side group in cysteine, as compared to that in serine.

The thiol or sulfhydryl group in cysteine residues has attracted a great deal of attention because of its ability to take part in a variety of biochemical reactions [6–8]. Crystals of cysteine and *N*-acetyl-cysteine can be considered as models to get a better insight into the dynamics of the thiol group and the hydrogen bonds, in which it can be involved [9, 10]. Crystal structures of several polymorphs of L-cysteine [11–15], of DL-cysteine [16], and of L-acetylcysteine [9] have been solved and refined at different temperatures. The thiol group was shown to act as a possible hydrogen donor and hydrogen acceptor, and to bind either to oxygen, or to sulfur in the structure (giving hydrogen bonds N–H···S, S–H···O, and S–H···S). The type of bonding can be affected by variations in temperature and pressure, thus resulting in phase transitions. In particular, ordering of the thiol-groups on cooling of the crystals of the orthorhombic polymorph of L-cysteine, which has been observed by X-ray diffraction [15], manifests itself in an adiabatic calorimetry measurement as an extended phase transition (at about 70 K on heating, the shape of C_p-curve in the region of phase transition depending on the temperature, down to which the sample was preliminary cooled [10]). A significant discrepancy in the heat capacity of L-cysteine reported in our recent papers [10, 17] with data published in 1935 by Huffman and Ellis [18] was

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observed, especially at temperatures close to room temperature, when the difference reaches 12%. We have supposed [17] that the reason of such a discrepancy should be sought in different composition of the samples in the two studies, in particular—in the presence of either monoclinic L-cysteine, or DL-cysteine, or both as impurities in considerable amounts in the sample studied in [18]. To test this hypothesis, measurements of the heat capacity of DL-cysteine and of the monoclinic form of L-cysteine were required.

To the best of our knowledge, the thermodynamic properties of DL-cysteine have not been properly studied before. The only paper on thermal properties of DL-cysteine, which we have found, describes a phase transition at about 283 K, as evidenced by DTA (with the endothermic effect corresponding to the transition equal to 1.36 kJ mol^{-1}), IR-spectroscopy and X-ray powder diffraction [19]. Unfortunately, the experimental procedure of the thermal treatment of the sample was not described in details in [19], but as far as we could judge from Fig. 2 and from [19], the phase transition was detected on heating the sample from a lower temperature. The transition was reported to be reversible, but it was not mentioned, if any hysteresis existed. In a later publication devoted to the structure solution of DL-cysteine by single-crystal X-ray diffraction technique [16], the crystals were repeatedly reported to be destroyed at about 217 K on cooling down from ambient temperature, and it was supposed that a phase transition could occur at this temperature, although no other evidence was available.

The aim of this study was to investigate the temperature dependence of the heat capacity of DL-cysteine on heating the sample from 6 to 310 K, to check the occurrence of phase transitions in this temperature range, to calculate the thermodynamic functions for DL-cysteine, and to compare the results with the thermodynamic data previously reported for L-cysteine [10, 17].

Experimental

Sample

A sample of DL-cysteine, $C_3H_7NO_2S$, purchased from Aldrich (mol. mass 121.16, melting temperature 225 °C, purity declared as 97.0%) was studied. X-ray powder diffraction analysis (Bruker D8-GADDS diffractometer) has shown that the crystal structure of DL-cysteine was the same as reported in [16], and has revealed the orthorhombic and the monoclinic L-cysteine as the only minor crystalline impurities. A chromatographic study (Milichrom AO-2) and the measurements of the optical activity (Polamat A polarimeter) have proven that there were no other impurities in the sample, at least in noticeable (>1%) amounts. Any attempts to purify the sample by re-crystallization resulted in an opposite effect: the sample enriched with the chiral form. Therefore, the sample was eventually used in the studies as purchased.

Results

The heat capacity $C_p(T)$ was measured in the temperature range 5.93–309.01 K. The same automatic adiabatic calorimeter and the same technique of filling in the calorimeter and carrying out the measurements were used, as for the studies of L-cysteine [17, 20]. A total of 113 calorimetric experiments have been performed (Table 1). The procedure of the thermal treatment was different for several series of measurements, as one can see from Table 1

Table 1 Experimental values of the heat capacity C_p^o of DL-cysteine in J K^{-1} mol^{-1}

T/K	C_p^o	T/K	C_p^o	T/K	C_p^o	T/K	C_p^o
Series 1		292.13	241.0	8.10	0.5597	269.68	140.1
296.45	146.3	296.75	417.4	9.67	1.078	272.68	142.2
299.44	147.5	301.51	207.0	11.25	1.697	275.66	143.7
Series 2		Series 3		12.87	2.466	278.63	145.2
84.10	57.53	83.63	57.24	14.45	3.343	281.10	145.9
89.17	60.37	88.70	60.11	16.04	4.360	283.08	147.3
94.22	63.12	Series 4		17.63	5.491	285.04	149.6
99.25	65.77	174.73	99.90	19.23	6.725	287.00	151.6
105.98	69.10	179.74	102.1	21.57	8.670	288.94	155.8
112.98	72.47	Series 5		23.64	10.48	290.91	159.1
119.94	75.77	225.73	121.6	25.72	12.35	292.88	181.0
126.90	78.97	230.71	123.7	27.78	14.20	294.29	169.7
133.90	82.14	235.64	125.8	29.85	16.11	295.19	237.8
140.85	85.19	240.70	128.0	32.46	18.57	296.04	224.8
150.09	89.22	245.78	130.1	35.57	21.51	296.90	218.5
160.06	93.53	Series 6		38.68	24.36	297.78	210.1
170.02	97.79	296.39	274.7	41.83	27.07	298.65	228.4
180.01	102.2	Series 7		44.98	29.78	299.51	222.0
189.92	106.8	6.43	0.2279	49.07	33.17	300.83	377.3
199.86	111.2	7.64	0.4389	54.13	37.14	301.44	389.3
209.85	115.3	9.42	0.9747	59.19	40.94	302.23	420.6
219.97	119.1	10.80	1.520	64.25	44.58	303.40	248.3
230.16	123.5	12.22	2.135	69.27	48.10	304.73	213.0
240.23	127.8	13.63	2.876	74.27	51.57	306.14	188.5
250.22	132.1	15.02	3.702	79.29	54.68	307.55	178.2
257.70	135.3	16.41	4.622	84.30	57.63	309.01	172.4
262.72	137.8	17.99	5.704	89.34	60.43	Series 11	
267.71	140.2	19.48	6.922	Series 9		124.56	77.91
272.65	142.5	21.07	8.218	93.77	62.82	131.58	81.07
277.55	145.1	22.74	9.651	98.85	65.51	272.44	142.07
282.49	148.5	Series 8		Series 10		277.38	144.7
287.39	162.8	5.93	0.1737	266.67	139.4		

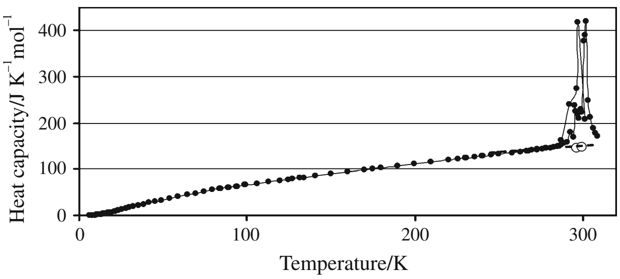

Fig. 1 The $C_p(T)$ measured for DL-cysteine in a wide temperature range. *Open circles*—series 1; *black circles*—series from 2 to 11; *dotted line*—regular part of C_p

(heating without preliminary cooling in Series 1, heating after preliminary cooling down to various temperatures in other series). The general view of the $C_p(T)$ in all the temperature range is shown at Fig. 1. The $C_p(T)$ curve in the temperature range from 6 to 287 K is smooth and does not have any anomalies. At the temperatures above 287 K, the time of temperature equilibration after the heat input into the calorimeter increased noticeably, and the experimental points also became much more scattered. At about 300 K, a large (about 300%) maximum at the $C_p(T)$ curve was observed, which can indicate at a phase transition. Several series of the C_p were measured in this temperature range. The results of the four series of measurements carried out using pulse heating in the vicinity of the anomaly are shown in Fig. 2. Besides, a continuous heat capacity curve was obtained, i.e., the calorimeter was heated continuously at a rate of 0.2 K/min (Fig. 2, *dotted line*). The $C_p(T)$ curves obtained in different series of measurements differed much from each other, the temperatures of the C_p maxima being 297, 300, and 302 K. We would like to attract a special attention to the two experimental points at Fig. 2 (series 1), which look like outlets as compared to the results of measurements of the $C_p(T)$ in other series of the experiments. These points were obtained immediately after the calorimeter was filled with the sample, without any preliminary cooling. These points could fit well to the low-temperature part of the $C_p(T)$ curve, if there were no anomalous increase in the heat capacity at about 300 K, i.e., the heat capacity of the initial sample at $T = 300$ K was much lower than that measured after a deep cooling of the sample. This observation can be interpreted as a consequence of a first-order phase transition accompanied with a considerable hysteresis. After a prolonged storage of the sample at ambient temperature, the anomaly in the heat capacity decreased and almost disappeared. The C_p values measured at ambient temperature in a 5 months time after low temperature measurements exceeded the values obtained before low temperature measurements at 3% only. The data for $C_p(T)$ measured during a continuous heating were used to calculate the enthalpy and the entropy of the transition. To get the "regular contribution of the heat capacity" (corresponding to the absence of any anomalies), we have taken the curve corresponding to the experimental data at $T < 200$ K and the "regular values" of C_p, measured at about 300 K in the first series of experiments, prior to cooling the sample (*dotted line* in Fig. 1). The enthalpy and the entropy of the phase transition could be estimated as 2300 J mol^{-1} and 7.6 J K^{-1} mol^{-1}, respectively. As can be seen from Fig. 1, the phase transition is not complete in the studied temperature range; the phase transition is not finished at 310 K, and, hence, the values of the enthalpy and the entropy calculated for the 220–310 K temperature range are under-estimated. Unfortunately, the adiabatic calorimeter used in the experiments does not allow one to carry out the measurements at higher temperatures. Raman spectroscopy [21] has revealed the occurrence of a phase transition in DL-cysteine between 250 and 240 K (on cooling down), the reverse transformation on heating being observed with a large hysteresis at about 300 K.

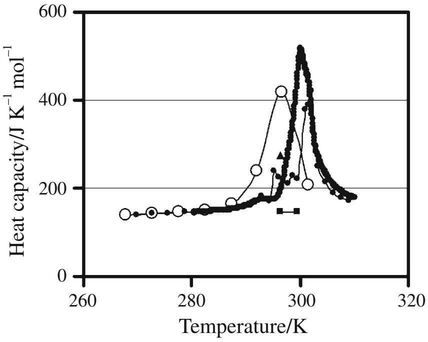

Fig. 2 Heat capacity of DL-cysteine in the vicinity of the phase transition. *Squares*—series 1; *open circles*—series 2; *triangle*—series 6; *filled circles*—series 10; *dotted line*—a continuous heat capacity curve. Series 2 was obtained after a preliminary cooling down to 77 K, series 10 and the continuous $C_p(T)$; curve after cooling down to 4 K

In order to calculate the values of the enthalpy and entropy of the DL-cysteine in a wide temperature range, the experimentally measured $C_p(T)$ data were smoothed; since the temperature equilibration time and the scattering of the data increased near the anomaly at about 300 K, the data were smoothed only at temperatures below 273.15 K. The corresponding data are summarized in Table 2.

Discussion

The $C_p(T)$ data obtained for DL-cysteine in this work were compared with those reported previously for L-cysteine in the work by Huffman and Ellis [18] and in our papers [10, 17] (Fig. 3). The data on DL-cysteine in this work are in a good agreement in the temperature range 85–200 K with those reported in [18] for a sample defined as L-cysteine.

Table 2 Heat capacity and the thermodynamic parameters of DL-cysteine $C_p^o(T)$, $S^o(T) - S^o(0)$/J K^{-1} mol^{-1}; $H^o(T) - H^o(0)$/J mol^{-1}

T/K	C_p^o/T	$S^o(T) - S^o(0)$	$H^o(T) - H^o(0)$
5.93	0.1740	0.05801	0.2580
10	1.189	0.3366	2.605
15	3.685	1.249	14.27
20	7.326	2.785	41.40
25	11.65	4.877	88.67
30	16.25	7.405	158.4
35	20.89	10.26	251.2
40	25.42	13.35	367.1
45	29.76	16.59	505.1
50	33.88	19.94	664.3
60	41.57	26.81	1042
70	48.63	33.76	1494
80	55.04	40.68	2013
90	60.83	47.50	2593
100	66.13	54.19	3228
120	75.82	67.12	4649
140	84.82	79.49	6256
160	93.54	91.38	8040
180	102.3	102.9	9998
200	110.9	114.1	12130
220	119.3	125.1	14430
240	127.7	135.8	16900
260	136.5	146.4	19540
273.15	142.4	153.3	21380

One could suppose that the sample studied in [18] actually was not L-cysteine, but contained a large amount of DL-cysteine. At the same time, above 200 K the data reported in [18] start to deviate noticeably from the curves obtained for both L-cysteine and DL-cysteine in our experiments, the discrepancy grows on heating, and reaches at ambient temperature 12% and 5% for L- and DL-cysteine, respectively. No anomaly in the $C_p(T)$ curve was reported in [18]. Since the data on the chemical and the phase purity of the sample were not given in [18], it is difficult to interpret unambiguously the discrepancy between the data in [18] and the results of our recent measurements [10, 17].

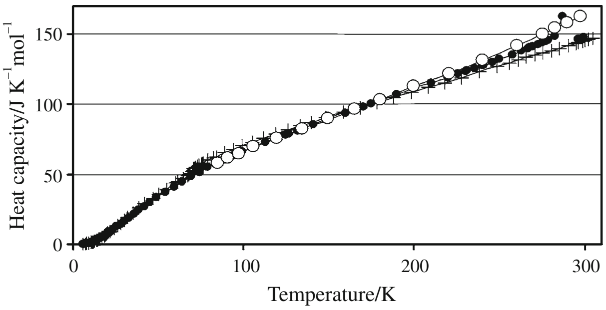

Fig. 3 A comparison of the $C_p(T)$ measured for DL-cysteine in this study (*filled circles*), with L-cysteine [17] (*crosses*), and with a sample claimed to be L-cysteine [18] (*open circles*)

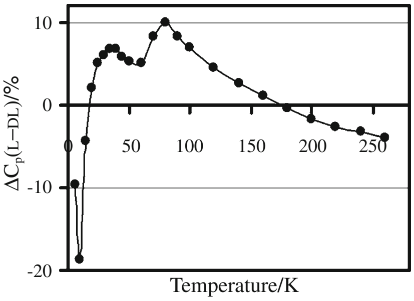

Fig. 4 The difference between heat capacities of L- and DL-cysteines

Our previous study has revealed a large difference in the values of the heat capacity of chiral and racemic crystals of serine (about 6–7% at 200 K) [3], in accordance with the differences in their dynamics manifesting itself in the Raman [4, 5] and inelastic neutron scattering spectra [4]. For cysteine, the heat capacity for the chiral form is also larger than that for the racemic one in a large temperature range, although the difference in the values of the heat capacity of the chiral and racemic forms is smaller (4% at 273.15 K) than that for serine (Fig. 3). Anomalies in the $C_p(T)$ curves that could be interpreted as consequences of the phase transitions were observed for both L- and DL-cysteine, but the one for L-cysteine—at a much lower temperature [10, 17]. Interestingly enough, the $C_p(T)$ curves for L- and DL-cysteine cross each other, which was not the case for chiral and racemic serine crystals (Fig. 3). Figure 4 presents the calculated ΔC_p values for L- and DL-cysteine to show the difference more clearly. This way of presenting the data has proved to be efficient, when comparing the $C_p(T)$ for the polymorphs of glycine [22, 23], and for the chiral and racemic serine [3]. The maximum observed for the difference in the values of ΔC_p for L- and DL-cysteine in Fig. 4 at 70–80 K corresponds to the phase transition in L-cysteine. The transition of the ΔC_p-curve into the region of negative values is related to the increase in the C_p of the racemic form in the vicinity of the phase transition of DL-cysteine. When Fig. 4 is compared with Fig. 2 from [3], one can see much similarity in the ΔC_p curves measured for chiral and racemic serine and for chiral and racemic cysteine, with the exception of the regions of these two phase transitions.

In a previous publication [17], the $C_p(T)$ dependence for the orthorhombic L-cysteine was compared with those previously reported for L-serine and D-serine. The heat capacity of the orthorhombic L-cysteine is higher than those of L- and D-serine, in accordance with a higher molecular mass of L-cysteine. The curves were brought to the same scale taking into account the difference in the

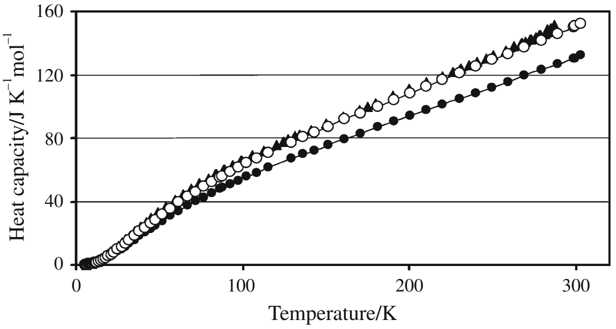

Fig. 5 Comparison of DL-cysteine with DL-serine. *Triangles*—DL-cysteine; *black circles*—DL-serine; and *open circles*—scaled C_p curve for DL-serine taking into account the molecular mass difference

molecular mass—the C_p values for serines were divided by the molar mass of serine and multiplied by the molar mass of cysteine. After that, the curves $C_p(T)$ for L-serine and orthorhombic L-cysteine look similar in the low-temperature range, the Debye temperature being lower for L-cysteine (i.e., the lattice modes in L-cysteine correspond to lower frequencies, as should be expected from a larger molecular mass). With increasing temperature, the scaled C_p values for L- and D-serine deviated significantly from $C_p(T)$ of orthorhombic L-cysteine, becoming higher as compared to the latter [17].

A similar comparison has been done for DL-serine [3] and DL-cysteine (Fig. 5). As should be expected, the $C_p(T)$ for DL-cysteine is higher than that for DL-serine, in accordance with the higher molecular mass of cysteine (Fig. 4). The two $C_p(T)$ curves become very close to each other (with the exception of the anomaly region) after being brought to the same scale taking into account the difference in the molecular mass, similarly to how it has been done for L-serine and L-cysteine in [17].

In order to test the applicability of the Debye isotropic continuum approximation to the description of the heat capacity of crystalline DL-cysteine, the function C_p/T was plotted versus T^2 (Fig. 6). At low temperatures, obvious deviations from a straight line can be seen, which indicate that the $C_p(T)$ dependence differs from that predicted by Debye's model ($C_p \sim T^3$). The extrapolation of the straight line connecting the two experimental points at 5–6 K does not go through the origin, as should be expected for the $C_p \sim T^3$ dependence. If this dependence holds for the system at all, then only at temperatures below 5–6 K. Similar results were obtained previously for L-cysteine (Fig. 6). The deviation of the experimental points from the "Debye straight line" toward higher values (Fig. 6) shows that the heat capacity at low temperatures grows faster according to the cubic law. One can suppose that in this temperature region the values of heat capacity are determined to a large extent by vibrations of individual molecules acting as weakly bound Einstein oscillators. For a comparison, Debye approximation does not work also for D-serine [3], although it is valid for DL-serine [3], glycilglycine [24], and diglycilglycine [25]. For the polymorphs of glycine, Debye approximation is valid for α- and β-glycines but is not valid for γ-glycine [22, 23]. In the case of β-glycine, besides Debye cubic term, there is also a linear term ($C_p \sim \mathrm{AT} + \mathrm{BT}^3$) probably due to the interaction of zwitter-ions in β-glycine [23].

The phase transition observed in this paper deserves a special discussion and a further study. The temperature of the C_p maximum (296 K–302 K) on heating after a preliminary cooling differs noticeably from the two, also quite different values, which were reported in [19] and in [16] (283 and 217 K, respectively). The value estimated for the enthalpy of transition (2.3 kJ mol^{-1}) also differs noticeably from that reported in [19] (1.4 kJ mol^{-1}). It is difficult to make an unambiguous conclusion, whether the three phase transitions (the two described in the literature and the one observed in this study) are the same, or different. In our experiments, the curve $C_p(T)$ near phase transition is not well reproduced in the different seria of measurements. The transition temperature was shown to depend strongly on the preliminary thermal treatment of the sample (Fig. 2). The sample that was not preliminary cooled below the ambient temperature, showed no anomalies in the $C_p(T)$ curves at about 300 K (series 1 in Table 1); after cooling the sample down to 77 K, the maximum of the $C_p(T)$ anomaly on reverse heating was observed at 296 ± 2 K, and after the preliminary cooling down to 4 K this maximum shifted to higher temperatures (300 ± 0.05 K for a continuous heat capacity curve, and 302 ± 0.5 K for series 10 at a pulse heating technique). In the paper [16], the fragmentation of the crystal (considered as an indication at a phase transition) was observed on cooling the sample down to 217 K, and in all our experiments the $C_p(T)$ were always measured on heating only. Therefore, the

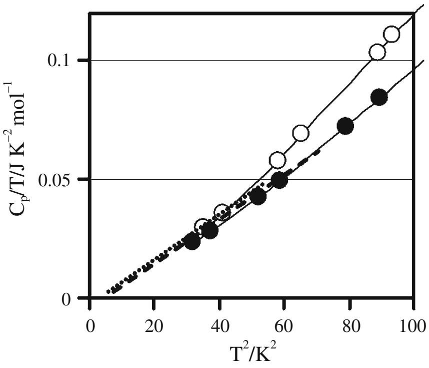

Fig. 6 A test of the applicability of the Debye model to describe the temperature dependence of the heat capacity in the crystalline DL-cysteine and orthorhombic L-cysteine. *Open circles*—DL-cysteine; *black circles*—L-cysteine

discrepancy in the observed transition temperatures can be related to a pronounced hysteresis of the transformation due to the kinetic effects (i.e., due to the existence of a large barrier for the transformation, that hinders the transformation to occur exactly at the *T*, *P* point, at which it should be expected according to the thermodynamics). A strong dependence of the anomaly in the heat capacity on the thermal pre-history of the sample was already observed in our recent study of the extended low-temperature phase transition in L-cysteine at about 70 K, but in that case only the shape of the anomaly, and not the transition temperature was affected [10]. It is also important to keep in mind that the phase transition at 217 K was supposed for a single crystal, whereas in our experiments powder samples were studied. For kinetically controlled transformations, the particle size effect on the transition temperature can be quite large.

The anomaly observed at about 300 K in our experiments can be supposed to be related to a structural transition involving the re-orientation/disordering of the cysteine zwitter-ions or of their fragments (–CH_2SH and/or –NH_3 groups). The estimated value of the entropy of the transition $\Delta S = 7.6$ J K mol^{-1} does not contradict this assumption, but still it does not allow one to make a definite conclusion on the nature of the molecular fragments involved in this re-orientation/disorder, and on the degree of disorder. Spectroscopic and structural studies in the wide temperature range, including the detailed studies in the vicinity of the transition, may be expected to be more informative.[1]

Conclusions

This study has revealed one more example of a pronounced difference in the dynamics and in the thermodynamic properties of the crystalline amino acids in racemic and chiral forms. The $C_p(T)$ curves for L- and DL-cysteine differ (although the difference is somewhat smaller than that measured previously for chiral and racemic serine [3]). In contrast to the case of serine, the $C_p(T)$ curves for L- and DL-cysteine cross each other at some point. A phase transition was observed for DL-cysteine at a much higher temperature and with a much larger heat effect than for L-cysteine [10]. As in the case of the L-cysteine, the transition in the sample of DL-cysteine is strongly dependent on the preliminary thermal treatment of the sample (whether it was cooled, and, if yes, down to which temperature); the transition can be supposed to have a large hysteresis due to the kinetic control.

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[1] Due to a technical reason, the manuscript has been stuck in the production process, so that by the time, when this paper is being published, the structural and spectroscopic experiments have been successfully carried out in our group by other researchers (see [21]) and the results have confirmed the correctness of the assumptions made in this study based on calorimetry.

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