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A DIFFERENTIAL SCANNING CALORIMETRIC STUDY OF CYSTEINE HYDROCHLORIDE MONOHYDRATE

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ABSTRACT

An irreversible phase change, ΔH (transition) $= 5.44 \pm 0.11$ kcal mol^{-1} at 337.1 ± 0.3 K has been confirmed in L-(+)-cysteine hydrochloride monohydrate. Phase transitions resulting from thermal pretreatment are also reported and discussed.

INTRODUCTION

Cysteine hydrochloride monohydrate, CySH, is one of the most efficient known radiation–protection agents, and has been extensively studied by a variety of physical methods[1–3]. The results of a detailed NMR (H^1) investigation[4,5] suggested a crystalline phase change near 333 K into *two* phases: Phase I, presumably polycrystalline, and Phase II, possibly glassy. No visual change was noted throughout the temperature range, and no analogous transitions were inferred from similar experiments on anhydrous (amorphous) cysteine hydrochloride. Since apparently no thermal investigations have been reported for CySH, a direct scanning study was undertaken to check, and define quantitatively, the reported transition near 333 K.

EXPERIMENTAL

Commercial samples of CySH of estimated purity 99% (Eastman Kodak Co. or Koch-Light Ltd.) were used directly without further purification. Since cysteine is readily oxidised to cystine, dry-box manipulation was used during transfer and storage operations. Check runs on both L-cysteine or L-cystine showed no detectable transitions.

Initial qualitative scanning runs, using a Perkin-Elmer differential scanning calorimeter (Model DSC-1B), were followed by quantitative measurements on the DSC-2 model at heating rates of 5 K min^{-1}. Sealed aluminium pans were employed for sample encapsulation, and indium metal was used as calibrant for temperature and energy. Rigorously purified samples of n-triacontane and octacosane (transition

temperatures 338.9 and 334.3$_5$ K, respectively) were used periodically to check instrument performance.

After the initial scanning runs, samples were either allowed to cool from 350 K to ambient temperature, ca. 293 K, or were shock-cooled by immersion in liquid nitrogen, ca. 77 K; they were then re-scanned after a specified time. Check thermogravimetric runs showed no detectable weight loss over the temperature range used in the DSC measurements.

RESULTS

On scanning CySH a sharp endotherm is observed, with an associated enthalpy change of 5.44±0.11* kcal mol^{-1} (13 sample runs), at an (extrapolated) onset temperature T_0 (see Fig. 1) of 337.1±0.3 K (9 samples), and peak temperature T_p, 340.4±0.4 K. Neither ΔH nor T values were affected by sample weight over the range used (0.6 to 4.5 mg), heating rate (5 to 40 K min^{-1}), or by the sample having been initially shock-cooled in liquid nitrogen.

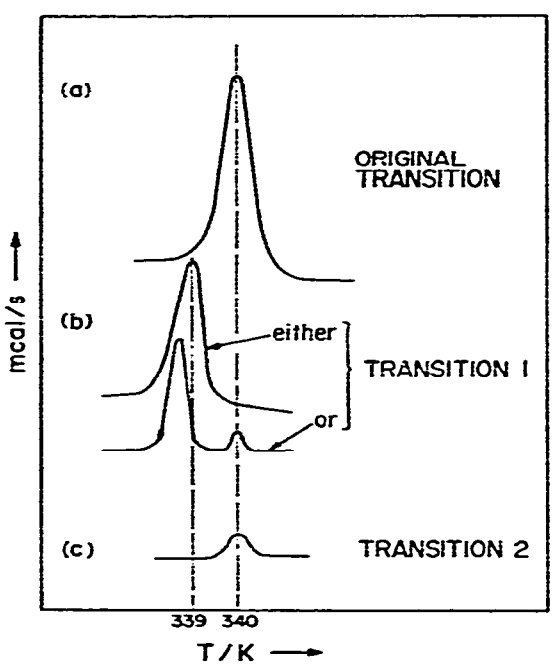

Fig. 1. Schematic representation of the possible transitions in L-(+)-cysteine hydrochloride monohydrate. (a) Thermogram from untreated CySH; (b) Thermograms from CySH heated as in (a) and cooled to ca. 298 K and rescanned; (c) Thermogram from CySH after several heating/cooling cycles.

Re-scanning, following heating and subsequent cooling to ambient temperature, ca. 298 K, were also investigated. Either a single transition (transition 1) at a signifi-

*Confidence limits are expressed throughout as twice the standard error of the mean.

cantly lower temperature ($T_0 = 334.8 \pm 0.2$ K and $T_p = 338.6 \pm 0.4$ K, five samples) was observed, or two transitions appeared. This is shown schematically in Fig. 1; the data in Tables 1 and 2 show that there is no apparent connexion between sample weight or time after cooling (24 to 144 h) and the occurrence of one, or two, transitions after initial heating.

TABLE 1

TRANSITION TEMPERATURES FOR CySH AFTER COOLING FROM 350 TO 293 K AND REHEATING AT 5 min^{-1}

CySH (mg)	*Time after cooling (h)*	*Transition 1*		*Transition 2*
		T_0 (K)	T_p (K)	T_p (K)
2.806	25.0	334.8	338.8	not seen
2.208	32.5	334.6	338.4	not seen
0.674	51.0	334.2	337.2	341.0
1.419	72.0	332.0	336.2	341.0
2.015	120.0	334.7	338.8	not seen
1.212	120.0	333.2	336.2	340.8
2.878	120.0	334.7	338.4	not seen
0.690	120.0	334.0	337.1	341.0
2.300	143.0	334.8	338.8	not seen
3.076	144.0	331.6	335.4	341.0

TABLE 2

EFFECT OF HEATING (TO 350 K) AND COOLING (TO 293 K) ON TRANSITIONS IN CySH (2.30 mg), HEATING AT 5 K min^{-1}

No. of run	*Cooling time (h)*	*Transition 1*			*Transition 2*	
		Peak area × sensitivity/wt.	T_0 (K)	T_p (K)	*Peak area × sensitivity/wt.*	T_p (K)
0		not seen			8.93	340.5
1	143	6.94	334.8	338.8	not seen	not seen
2	100	4.90	333.8	336.8	0.05	341.5
3	72	2.41	331.8	336.5	0.14	341.0
4	24	0.72	333.0	336.4	0.14	341.0
5	24		not seen		0.21	340.0
6	24		not seen		0.22	340.0

Two transitions were again found in subsequent heating/cooling cycles and several features were noted: (1) the peak area associated with transition 1 decreased progressively on further cycling; (2) the peak area of transition 2 increased correspondingly; (3) the onset and peak temperatures of transition 1 decreased progressively; and (4) the peak temperature of transition 2 remained relatively constant, near 341 K. Eventually, after several scans, only transition 2 remained (see Table 2).

Features (1) and (2) are illustrated in Fig. 2 for all 29 samples; a similar, linear, relationship holds for shock-cooled samples. Figure 3 shows the decrease in peak temperatures with decrease in peak area for transition 1, the data being normalised by plotting as area × sensitivity/weight.

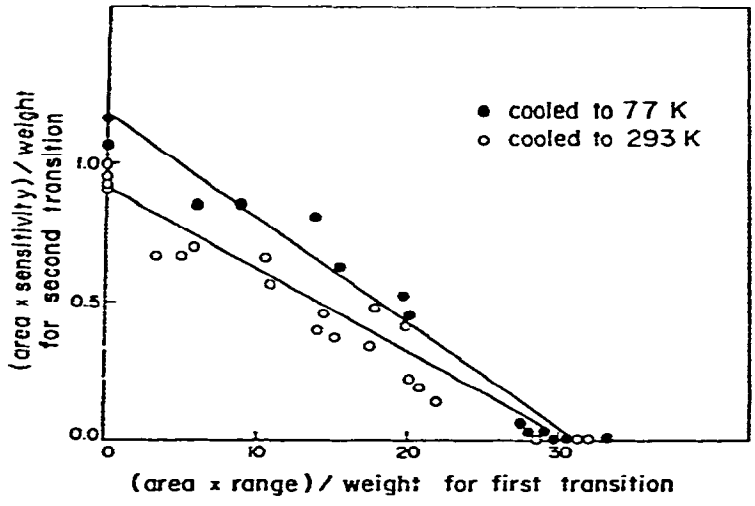

Fig. 2. The relationship between the peak areas associated with transitions 1 and 2 (see Fig. 1) in CySH.

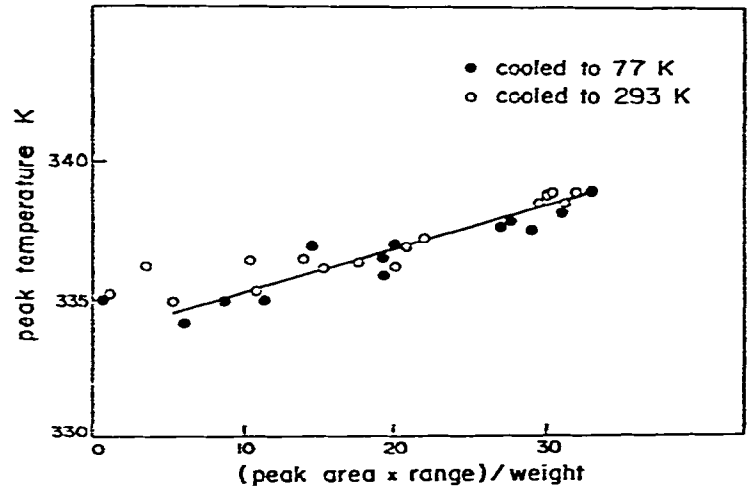

Fig. 3. The relationship between peak temperature, T_p, and peak area for transition 1 in CySH.

DISCUSSION

The phase transition inferred from the NMR results is confirmed at 337.1 ±0.3 K, with an associated enthalpy change of 5.44±0.11 kcal mol^{-1}, and is virtually

irreversible. The degree of reversibility of the species involved may be of biological, as well as thermodynamic, importance in connexion with transport mechanisms. If transition 2, found after heating/cooling cycles, is identified with the original transition, on the basis of peak temperatures, inspection of the data suggests a maximum reversibility of 3%.

A new phase is formed following the original transition, characterised by a transition with an onset temperature of 334.8 ± 0.2 K. The *maximum* value of the associated enthalpy change is 24 ± 2 cal g^{-1}, and this therefore represents a *minimum* value for a transition of the pure phase. The constancy of this maximal ΔH value, and of onset and peak temperatures, suggests that all the cooled material is in one form when transition 2 is not observed. As shown in Fig. 3, the transition temperature decreases, approximately linearly, with decreasing concentration, as judged by peak areas. Consequently this new phase may not be truly crystalline, and it is reasonable to assume it represents the glassy phase indicated by the NMR results. However, no sharp increase in heat capacity, diagnostic of a glass transition[6], was apparent, suggesting the need for further studies for this and similar compounds.

In summary, the present investigation thus indicates the existence of at least three phases: (i) original CySH, which is transformed to (ii), a form stable above ca. 340 K, and which may remain the predominant form below ca. 330 K, and (iii) a new phase formed after further heating and cooling, and which may not be crystalline.

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