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Articles

Thermodynamic Properties of Crystalline *d*-Limonene Determined by Adiabatic Calorimetry

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d-Limonene has been studied by differential scanning calorimetry and adiabatic calorimetry. The heat capacities of a crystallized sample have been measured between 5 K and 250 K in an adiabatic calorimeter. The measured temperature and enthalpy of melting are (199.18 ± 0.05) K and (11.38 ± 0.02) kJ·mol^{-1}.

Introduction

Monoterpenes, abundantly available from natural sources, are used in pharmaceutical industries. Some medicines contain a mixture of monoterpenes. Consequently, the analytical evaluation of terpenic drugs by chromatography has been the subject of several studies (Sybilska *et al.*, 1994).

Limonene, the simplest cyclic olefin, enhances the penetration of 5-fluorouracil (Yamane *et al.*, 1995), and it has been shown to prevent cancer (Crowell and Gould, 1994). At room temperature, limonene is liquid. Hence, there have been studies on the thermodynamic properties of limonene as a liquid and in the gas phase. For example, Atik *et al.* (1987) measured the enthalpy of vaporization at 298.15 K. Nadais and Bernardo-Gil (1993) determined the vapor pressures of pure *l*-limonene between 320 K and 450 K. The molar liquid volume constants have been measured by Bernardo-Gil and Ribeiro (1993).

This study concentrates on the thermodynamic properties of crystalline *d*-limonene. The solid will not directly be of use in pharmaceutics as its melting point is far below room temperature. Nevertheless, it seems a worthwhile investigation in the context of the mixing behavior of enantiomers. These properties, particularly those affecting the solid state, are being studied within the REALM, a cooperation of French, Spanish, and Dutch Universities (Calvet and Oonk, 1995; Druot *et al.*, 1996; Gallis *et al.*, 1996; Gallis and van Miltenburg, 1996). A thorough knowledge of the (mixing) characteristics is important, for the antipode of an optically active drug may show a significantly different behavior in the body (Evans, 1992; Knihinicki *et al.*, 1989; Scott, 1993).

The solid−liquid transition temperature of *d*-limonene has been reported in the literature. Timmermans (1914) measured a freezing point of 176.6 K. However, Hawkins and Eriksen (1954) determined a freezing point of 198.12 K. This suggests that *d*-limonene is able to crystallize in a metastable and a stable form. Weitkamp (1959) measured a melting point of 198.80 K using a 95% pure *d*-limonene sample. Gomes *et al.* (1988) determined a freezing point of (198.65 ± 0.15) K. The measurement was performed on a 99.4% pure *d*-limonene sample, and the measured freezing point temperature was corrected to zero impurity. The enthalpy and temperature of melting, and the thermal properties of the stable crystalline form are the subject of this study.

It proved to be hard to crystallize *d*-limonene in a DSC apparatus, which will be discussed briefly. An adiabatic calorimeter has been used to determine the temperature and enthalpy of melting and the heat capacities between 5 K and 250 K. The derived properties $S^0(T) - S^0(0)$ and $H^0(\mathrm{T}) - H^0(0)$ are given.

Experimental Section

Material. (R)(+)-limonene was obtained from Fluka Chemika. It contained over 99% limonene (gas chromatography analysis). The rotation measured was $[\alpha]_{\mathrm{D}}^{20} = +114.8°$ ($c = 10$ in ethanol).

Differential Scanning Calorimetry. The DSC experiments were performed on a DSC 120 from Seico Instruments Inc. The apparatus was calibrated with the solid−solid transition of adamantane and the melting point of water. The samples were cooled with an average rate of about 6 K·min^{-1}. The measurements were made using a heating rate of 2.5 K·min^{-1}. The DSC samples had a mass between 25 mg and 45 mg. The determination of a melting temperature is estimated to be accurate to ±0.5 K. The enthalpy of melting can be determined with an accuracy of ±0.05 kJ·mol^{-1}.

Adiabatic Calorimetry. The adiabatic experiments were performed in an adiabatic calorimeter that has been described previously (van Bommel, 1986; van Miltenburg *et al.*, 1987; van der Linde, 1992). The intrinsic drift of the calorimeter approaches 15 mK·h^{-1}, the internal precision is about 0.02%, and the absolute accuracy is estimated to be 0.2%. Adiabatic measurements can be performed between 5 K and 420 K.

The Pt resistance thermometer (100 Ω at 298.15 K, Oxford Instruments) was calibrated to the IPTS-1968 scale and corrected for the new temperature scale ITS-1990. Between 5 K and 30 K the accuracy of the thermometer is ±0.003 K and above 30 K it is accurate to ±0.005 K. The heat capacities determined in the adiabatic calorimeter are estimated to deviate with ±0.02% and have an accuracy of ±0.2%.

The sample, mass 5.092 67 g, was sealed with about 1000 Pa of helium gas as heat exchanger. The mean applied cooling rate between room temperature and 80 K was 0.5

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Table 1. DSC Results on *d*-Limonene Samples

mass/mg	T^*/K	$\Delta_{\rm sol}^{\rm liq}H$/ kJ·mol^{-1}
41.52	199.6	11.14
28.56	199.7	10.08
28.56[a]	199.2	10.03
25.79	199.6	11.06
28.09	199.2	10.35

[a] Second run.

Table 2. Measured Molar Heat Capacities of Crystal *d*-Limonene Obtained by Adiabatic Calorimetry

T/K	$C_{\rm p,m}$/ J·K^{-1}·mol^{-1}	T/K	$C_{\rm p,m}$/ J·K^{-1}·mol^{-1}
	Series I		
4.639	1.6673	18.395	14.102
6.997	1.7004	20.586	17.276
9.646	4.0665	22.881	20.445
10.856	4.7123	25.067	23.484
12.591	6.0104	26.970	25.986
14.575	8.7390	28.651	28.175
16.414	11.399	30.170	29.996
	Series II		
8.027	2.9621	24.604	23.595
12.883	8.3490	26.482	26.287
14.149	8.9717	28.178	28.727
15.718	11.088	29.702	30.701
17.308	13.141	31.095	32.525
19.020	15.507	32.382	33.997
20.815	18.205	33.588	35.702
22.674	20.870	34.724	36.911
	Series III		
36.596	38.612	68.929	66.198
38.575	40.884	71.661	68.141
40.716	42.939	74.434	68.915
43.134	45.231	77.225	71.948
45.563	47.475	80.003	73.808
48.021	49.774	82.759	75.581
50.519	52.011	85.462	77.328
53.055	54.290	88.097	78.976
55.625	56.303	90.665	80.636
58.230	58.285	93.174	81.582
60.866	60.322	95.630	83.438
63.528	62.311	98.038	84.992
66.218	64.256	100.401	86.373
	Series IV		
103.513	90.600	197.226	732.09
106.847	92.741	197.971	2088.6
110.145	94.841	198.350	4558.2
113.385	96.805	198.569	7370.3
116.566	98.834	198.715	10482
119.692	100.80	198.818	14978
122.768	102.62	198.888	23425
125.799	104.56	198.935	32689
128.786	106.43	198.986	19975
131.733	108.30	199.822	537.67
134.643	110.13	201.968	213.20
137.516	112.09	204.646	214.59
140.356	114.17	207.009	215.78
143.162	116.26	209.061	216.16
145.936	118.31	211.109	216.52
148.681	120.19	213.158	216.76
151.404	121.99	215.208	217.07
154.107	123.70	217.259	217.41
156.785	125.36	219.311	217.75
159.441	127.01	221.364	218.16
162.075	128.60	223.417	218.58
164.688	130.08	225.471	219.09
167.283	131.47	227.525	219.56
169.858	133.18	229.576	220.10
172.412	135.10	231.627	220.68
174.944	137.62	233.678	221.35
177.451	140.85	235.730	221.96
179.932	143.66	237.785	222.63
182.388	146.88	239.841	223.36
184.810	153.42	241.896	224.07
187.190	159.19	243.951	224.85
189.523	168.53	246.006	225.58
191.788	183.31	248.061	226.33
193.944	212.79	250.116	227.07
195.856	307.86		

K·min^{-1}. After crystallization of the sample the molar heat capacities were determined in four series (called I−IV). In series I, between 5 K and 30 K, the input duration was 100 s and the stabilization duration 120 s. The average applied heating rate was 0.5 K·min^{-1}. During series II, between 8 K and 35 K, the input and stabilization periods were 100 s and 150 s, respectively. The average heating rate was 0.4 K·min^{-1}. In series III, 35 K to 100 K, the input and stabilization periods were 608 s and 500 s. The average heating rate was 0.14 K·min^{-1}. In series IV, 100 K to 250 K, the input and stabilization periods were 908 s and 1200 s. The average applied heating rate was 0.08 K·min^{-1}.

Results and Discussion

DSC Experiments. The DSC samples were cooled to the vitreous state. Upon heating, all samples showed a glass transition at 138 K, but only about one in five samples crystallized and subsequently melted. The samples that did crystallize were subjected to the cooling and heating procedure a second time. Only one of these samples, out of a series of four, crystallized once more. From these experiments it is not clear what parameter(s) causes a sample to crystallize. The results of the DSC experiments are presented in Table 1.

From the values listed in Table 1 it follows that the temperature of melting is (199.5 ± 0.5) K. This is a higher value than the melting point determined earlier (Weitkamp, 1959; Gomes *et al.*, 1988). The measured enthalpies of melting for the samples vary much more than expected for a DSC measurement. This is explained by the slow crystallization process. During the measurements complete crystallization might not have been reached. This implies that the enthalpy of melting of *d*-limonene is 11 kJ·mol^{-1} or higher. A more precise determination of the temperature and enthalpy of melting has been performed using adiabatic calorimetry.

Adiabatic Measurements. The sample in the adiabatic calorimeter was cooled to the vitreous state and subsequently heated. This procedure was repeated three times, and the sample crystallized (and melted) every time. The easiness of crystallization might be due to the large amount of material or the low cooling and heating rate.

A completely crystallized sample was cooled down to 5 K. The heat capacities were measured from 5 K to 240 K and are listed in Table 2. The temperature and enthalpy of melting are calculated from these data using the method described below.

It is assumed that the small concentration of impurity in the sample causes a eutectic melt. In this case the temperature and enthalpy of melting are related according to the law of van 't Hoff for freezing point depression:

$$\Delta T = \left(\frac{RT^{*2}}{\Delta_{\rm sol}^{\rm liq}H}\right)x_{\rm B} \qquad (1)$$

where ΔT is the freezing point depression, i.e. $T^* - T$, and $\Delta_{\rm sol}^{\rm liq}H$ is the enthalpy of fusion, $x_{\rm B}$ is the molar fraction of the impurity, and R is the gas constant. The temperature as a function of the fraction melted (F) in the sample is described by (see e.g. Sarge *et al.*, 1988)

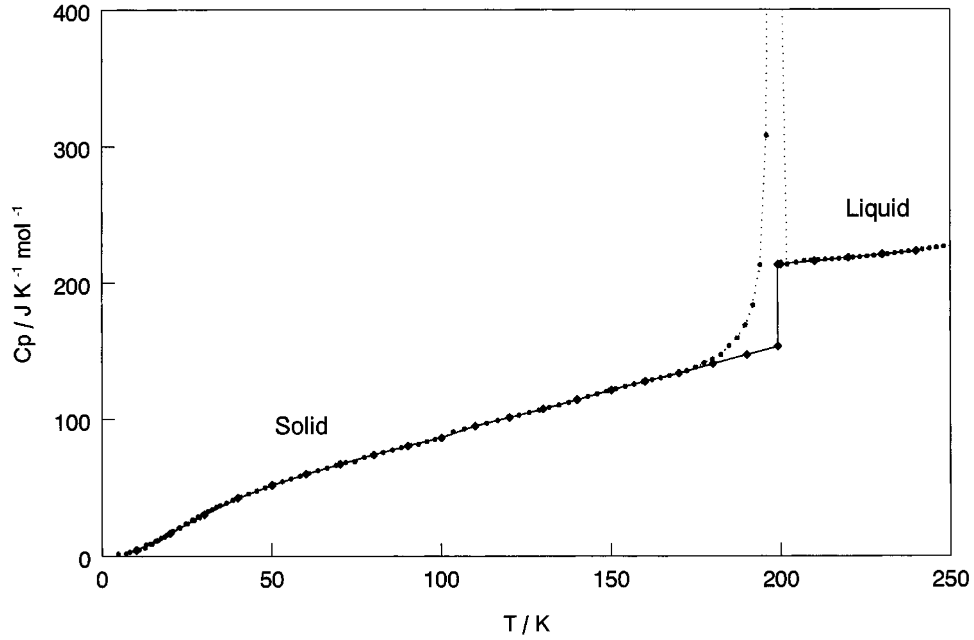

Figure 1. Adiabatic calorimetry on crystaline *d*-limonene: original (●) and smoothed (◆) data.

Table 3. Derived Thermodynamic Properties at Selected Temperatures for *d*-Limonene

(Molar Mass $M = 136.24\ \mathrm{g{\cdot}mol^{-1}}$; $\Phi^0_\mathrm{m} \overset{\mathrm{def}}{=} \Delta_0^T S^0_\mathrm{m} - \Delta_0^T H^0_\mathrm{m}/T$)

T/K	$C^0_{\mathrm{p,m}}$/ J·K^{-1}·mol^{-1}	ΔS^0_m/ J·K^{-1}·mol^{-1}	ΔH^0_m/ J·mol^{-1}	Φ^0_m/ J·K^{-1}·mol^{-1}
10	4.26	1.43	10.8	0.358
20	16.52	7.90	111.3	2.335
30	30.13	17.37	349.2	5.727
40	42.26	27.91	718.2	9.950
50	51.55	38.34	1188	14.59
60	59.65	48.48	1745	19.40
70	66.96	58.24	2379	24.25
80	73.81	67.59	3080	29.09
90	80.21	76.65	3850	33.87
100	86.13	85.39	4680	38.59
110	94.75	94.07	5591	43.24
120	100.99	102.58	6570	47.83
130	107.20	110.91	7610	52.37
140	113.91	119.09	8715	56.84
150	121.07	127.20	9891	61.26
160	127.35	135.21	11133	65.63
170	133.28	143.11	12435	69.96
180[a]	140.34	150.94	13806	74.24
190[a]	146.91	158.71	15242	78.49
199.18[a,b]	152.94	165.78	16618	82.35
199.18[a,c]	213.06	222.89	27993	82.35
200[a]	213.26	223.76	28168	82.93
210[a]	215.69	234.23	30313	89.69
220	218.12	244.32	32482	96.68
230	220.54	254.07	34675	103.31
240	222.97	263.51	36892	109.79

[a] Extrapolated. [b] Solid. [c] Liquid.

$$T = T^* - \left(\frac{RT^{*2}}{\Delta^{\mathrm{liq}}_{\mathrm{sol}}H}\right)x_\mathrm{B}\frac{1}{F} \tag{2}$$

Plotting T versus $1/F$ should produce a straight line with an intercept of T^* and a slope of $-RT^{*2}x_\mathrm{B}/\Delta^{\mathrm{liq}}_{\mathrm{sol}}H$. In practice, however, the line is observed to be convex. One reason might be that the first part of the melting process was not detected (Cooksey and Hill, 1976). The melting temperature is taken as the intercept of the straight line through the curve of T versus $1/F$ for $1.5 < 1/F < 10$. This implies that the temperature of melting can be determined with an accuracy of ±0.05 K for a pure substance containing no more than 1% impurity.

The enthalpy of melting is calculated from the added heat increments between 50 K below and 10 K above the melting point minus the heat capacity of the sample. The heat capacity of the sample was calculated from the heat capacity functions for the solid and the liquid state being $C_{\mathrm{p_{sol}}}(T) = \{22.075 + 0.65703(T/\mathrm{K})\}\ \mathrm{J{\cdot}K^{-1}{\cdot}mol^{-1}}$ and $C_{\mathrm{p_{liq}}}(T) = \{164.731 + 0.24266(T/\mathrm{K})\}\ \mathrm{J{\cdot}K^{-1}{\cdot}mol^{-1}}$. It was taken into account that during the melting of the sample its total heat capacity changes with temperature. The obtained enthalpy of melting is estimated to be accurate to 0.2%.

In an iterative procedure T^*, $\Delta^{\mathrm{liq}}_{\mathrm{sol}}H$, and x_B are determined, resulting for *d*-limonene in (199.18 ± 0.05) K, (11.38 ± 0.02) kJ·mol^{-1}, and 0.0069, respectively.

Through a cubic spline interpolation of the original data the heat capacities at selected temperatures, presented in column 2 of Table 3, were obtained. Close to the melting temperature the data have been corrected by a linear extrapolation of the heat capacity functions for the solid and the liquid state. The measured heat capacities and the smoothed data are presented in Figure 1.

The experimental values between 5 K and 10 K were fitted to the Debye function: $C_\mathrm{p} = \alpha T^3$. The parameter α was found to be (4.31 ± 0.05) mJ·K^{-4}·mol^{-1}. Starting from this result, the thermodynamic properties at selected temperatures were calculated.

The entropy and enthalpy at low temperatures follow from the heat capacity function as $S^0(T) - S^0(0) = {}^1/_3\alpha T^3$ and $H^0(T) - H^0(0) = {}^1/_4\alpha T^4$. Above 10 K the thermodynamic properties of the solid and the liquid phase were calculated using

$$S^0(T) - S^0(0) = \int_0^{T^*}\frac{C_{\mathrm{p_{sol}}}}{T}\,\mathrm{d}T + \frac{\Delta^{\mathrm{liq}}_{\mathrm{sol}}H}{T^*} + \int_{T^*}^{T}\frac{C_{\mathrm{p_{liq}}}}{T}\,\mathrm{d}T \tag{3}$$

and

$$H^0(T) - H^0(0) = \int_0^{T^*}C_{\mathrm{p_{sol}}}\,\mathrm{d}T + \Delta^{\mathrm{liq}}_{\mathrm{sol}}H + \int_{T^*}^{T}C_{\mathrm{p_{liq}}}\,\mathrm{d}T \tag{4}$$

The derived thermodynamic properties of *d*-limonene, accurate to ±0.2%, can be found in Table 3.

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