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Mixtures of *d*- and *l*-carvone: II. Adiabatic calorimetry on the equimolar mixture

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Abstract

DSC measurements have revealed that *d*- and *l*-carvone form mixed crystals at all compositions corresponding to a phase diagram with a minimum. The thermodynamic data of the equimolar mixture, however, are not reproducible.

Therefore, in this study the dependency of the thermodynamic data on thermal history was investigated by means of adiabatic calorimetry. The measurements revealed the polymorphic behaviour of the formed crystalline material.

Metastable *dl*-carvone melts at (231 ± 0.5) K and the stable form at (241.15 ± 0.05) K. The heats of melting are (8.98 ± 0.05) and (12.697 ± 0.005) kJ mol^{-1} for the metastable and stable forms respectively. The heat capacities of the stable form were determined from 4 K up to room temperature; the stable form does not show any phase transition before melting.

Keywords: Adiabatic calorimetry; *dl*-Carvone; Polymorphism

1. Introduction

The active component in many drugs is a substance composed of chiral molecules, for example *d*-penicillamine. In many cases, the enantiomer of an active chiral molecule is either neutral or even harmful. The pharmaceutical industry is confronted with this behaviour. Therefore, the thermodynamic and crystallographic properties of enantiomers and their mixtures are of vital importance. This study focuses on a pair of enantiomers that show spontaneous mixing in the solid state. Mixed crystals, which are infrequently found, display unique thermodynamic properties.

Mixtures of *d*- and *l*-carvone have been investigated by differential scanning calorimetry as reported in a previous article [1]. During these experiments, the carvone

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system yielded mixed crystals at all compositions corresponding to a phase diagram with a minimum. However, due to the finite heating rate of a DSC apparatus, thermodynamic equilibrium is not always reached during the measurements: it may prevent the transition to a more stable phase. Indeed, the thermodynamic data of the equimolar mixture of *d*- and *l*-carvone (*dl*-carvone) appeared to be dependent on thermal history. For this reason it was decided to investigate the equimolar mixture with adiabatic calorimetry.

In an adiabatic calorimeter the sample can be heated very slowly, and after each input of heat kept under almost adiabatic conditions by keeping the surrounding shields at the same temperature as the sample. During a measurement the thermal behaviour of the sample can be followed and any temperature drift during stabilisation is an indication of a change in thermodynamic state.

The polymorphic behaviour of the formed crystalline material has been studied. The adiabatic measurements on the equimolar mixture are compared with the DSC data reported earlier [1]. This study clarifies the dependence of the thermodynamic data, as measured with a DSC apparatus, on thermal history.

2. Experimental

2.1. Materials

d- and *l*-carvone, liquids at room temperature, were obtained from E. Merck Nederland B.V. Both products contained over 99% carvone but had different optical purities. The rotation measured on neat samples was $[\alpha]_D^{20} = +56.0^\circ$ and $[\alpha]_D^{20} = -58.8^\circ$ for *d*- and *l*-carvone respectively. After the adiabatic experiments, the rotation of the used *dl*-carvone sample was $[\alpha]_D^{20} = -2.1^\circ$.

2.2. Apparatus and method

All measurements were performed in an adiabatic calorimeter which has been described previously [2–4]. 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%. The range of temperatures over which adiabatic measurements can be performed is 5–375 K.

The sample, weighing 5.75435 g, was sealed with helium gas as heat exchanger. The heat capacities of *dl*-carvone were measured in the temperature range between 5 and 280 K.

3. Results

A mixture containing equal amounts of *l*- and *d*-carvone was supercooled to the glass phase and subsequently heated. The sample was heated from 80 K up to room temperature which resulted in a glass transition and a solidification, followed by the

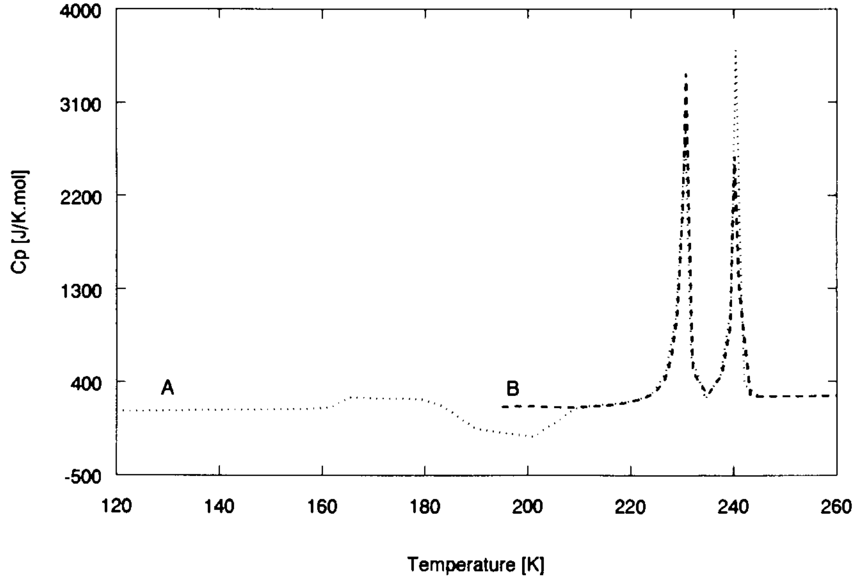

Fig. 1. Heat capacities of the *dl*-carvone sample: Curve A, heated from the glass phase; Curve B, melting curve after the first stabilisation experiment.

melting of the formed solid. The glass transition took place at 164 K and the sample solidified between 180 and 210 K. During this measurement, melting was observed to occur in two steps as can be seen in Fig. 1, curve A. The first step was at the melting temperature found by DSC measurements, 231 K. The second melting step at 241 K indicated that, in addition to the form with a melting temperature of 231 K, a more stable form had partially been formed.

In an adiabatic calorimeter, exothermic processes with very small heat transitions can be followed accurately for days, even at very low temperatures. In a first stabilisation experiment, the liquid *dl*-carvone sample was supercooled below the glass transition temperature, heated until the onset of the crystallisation at 182 K and then kept under adiabatic conditions. The total enthalpy of the vessel and its contents remained constant but the temperature increased. This implies that the enthalpy of the sample alone diminished. In Fig. 2 we see that the temperature increased immediately, which is due to the growth of the nuclei. After about 13 h, the temperature approached the intrinsic drift of about 15 mK h^{-1} at 194 K.

In a second stabilisation experiment, the liquid sample was supercooled to 185 K, which is well above the glass transition temperature. This resulted in a very slow start of the crystallisation process which can be seen in Fig. 3. The temperature increase due to nucleation and growth going from 185 K up to 200 K took about 14 h. Our interpretation is that nuclei are more rapidly formed at a temperature close to the glass transition temperature.

The solids formed during the two stabilisation experiments both melted in two steps; see, for example, the melting curve of the solid formed during the first stabilisation

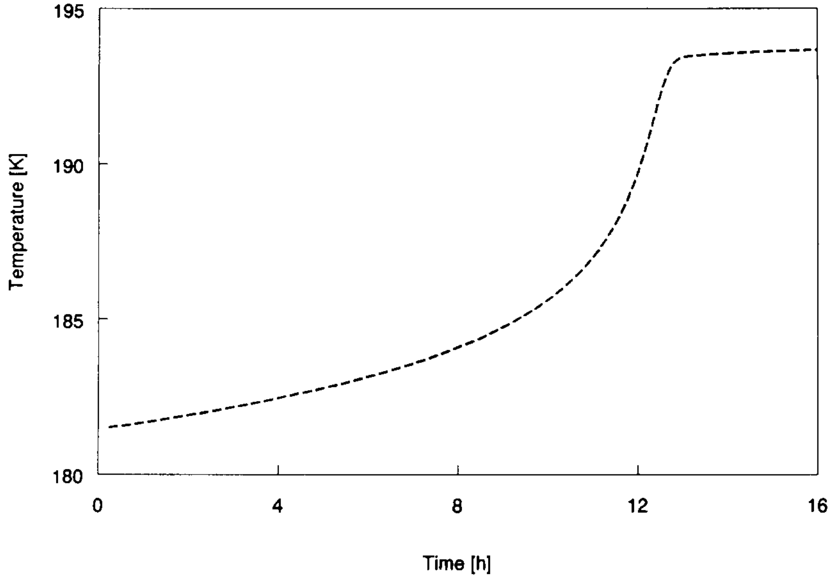

Fig. 2. Temperature increase against time during the first stabilisation experiment: the sample was supercooled below T_g.

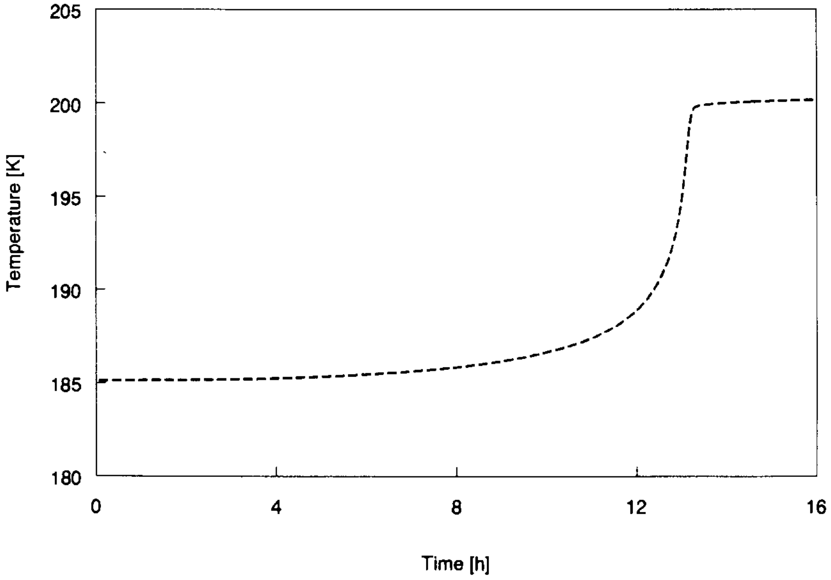

Fig. 3. Temperature increase against time during the second stabilisation experiment: the sample was supercooled to 185 K, which is above T_g.

experiment, denoted curve B in Fig. 1. This indicates that even at a slow crystallisation rate, metastable material is formed. During the melting of the metastable form some recrystallisation to the stable phase took place.

In order to get a completely recrystallised sample, the liquid *dl*-carvone mixture was again cooled to 80 K and reheated until it solidified. Then the temperature was raised until the metastable form started to melt. The sample was kept under adiabatic conditions and it started to recrystallise to the stable form in about 5 days. The sample was cooled again and thereafter a heating experiment was started. The melting of the formed crystalline material took place in one step only, proving that all carvone was recrystallised.

Fig. 4 shows the melting curve of the stable form in curve C. (Curve A shows once again the melting curve of the sample heated from the glass phase.) The thermodynamic behaviour of the stable form from 4 K up to 270 K is presented in Table 1. The stable form shows no phase transitions except for the melting at (241.15 ± 0.05) K. The heat of melting of the stable form is (12.697 ± 0.005) kJ mol^{-1}.

The results are summarised in Fig. 5, which presents the enthalpy paths of the *dl*-carvone sample during the experiments described. Curve A shows the glass transition, the solidification and the melting (in two steps) of the sample when it was heated from the glass phase, see also Fig. 1, curve A. Curve B in Fig. 5 represents the enthalpy path of the sample after the first stabilisation experiment, compare with curve B in Fig. 1. The enthalpy path of the completely recrystallised sample is presented in curve C of Fig. 5, see also Fig. 4, curve C.

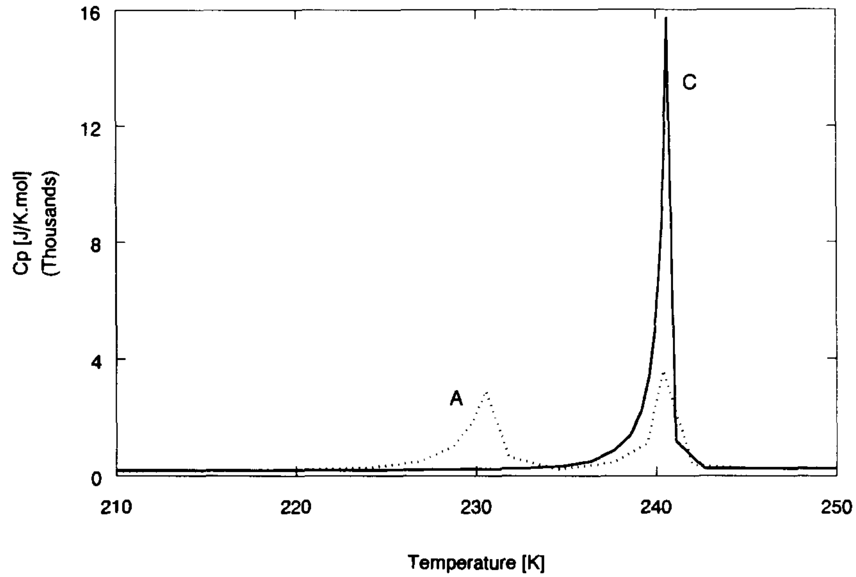

Fig. 4. Heat capacities of the *dl*-carvone sample: Curve A, heated from the glass phase; Curve C, melting curve of the stable form.

Table 1

Thermodynamic properties at selected temperature for *dl*-carvone ($M = 150.22\,\mathrm{g\,mol^{-1}}$; $\Phi^0_m \overset{\mathrm{def}}{=} \Delta_0^T S^0_m - \Delta_0^T H^0_m/T$)

T K	$C^0_{p,m}$ $\mathrm{J\,K^{-1}\,mol^{-1}}$	ΔS^0_m $\mathrm{J\,K^{-1}\,mol^{-1}}$	ΔH^0_m $\mathrm{J\,K^{-1}\,mol^{-1}}$	Φ^0_m $\mathrm{J\,K^{-1}\,mol^{-1}}$
10	4.120	1.547	11.60	0.3870
20	16.07	7.827	109.44	2.354
30	29.98	17.10	342.75	5.675
40	41.56	27.35	701.85	9.805
50	51.13	37.68	1166	14.35
60	59.58	47.76	1721	19.08
70	69.11	57.59	2360	23.88
80	83.97	67.81	3127	28.73
90	89.44	78.04	3996	33.64
100	94.42	87.70	4913	38.57
110	103.69	97.20	5910	43.47
120	110.50	106.52	6981	48.34
130	117.30	115.63	8121	53.16
140	123.99	124.57	9327	57.95
150	130.71	133.35	10600	62.68
160	137.65	142.01	11942	67.37
170	146.72	150.59	13359	72.01
180	156.99	159.27	14878	76.62
190	167.26	168.04	16500	81.20
200	174.03	176.81	18209	85.76
210	182.39	185.52	19996	90.30
220*	193.03	194.29	21880	94.83
230*	202.13	203.07	23857	99.34
240*	211.24	211.86	25923	103.85
$241.15^{\mathrm{s},*}$	212.29	212.87	26167	104.37
$241.15^{\mathrm{l},*}$	254.38	265.52	38864	104.36
250	257.19	274.74	41128	110.23
260	260.35	284.89	43715	116.75
270	263.52	294.77	46335	123.16

Key: *, extrapolated; $^{\mathrm{s}}$, solid, $^{\mathrm{l}}$, liquid.

4. Discussion

The thermodynamic data for an equimolar mixture of *d*- and *l*-carvone, when determined by DSC measurements, appeared to be dependent on thermal history. Adiabatic measurements performed in this study revealed the polymorphic behaviour of the crystalline material formed. Stabilisation experiments at the beginning of crystallisation showed that even at a slow crystallisation rate, taking about 14 h, metastable material is formed. Complete recrystallisation was obtained by keeping the partially melted sample under adiabatic conditions for 5 days.

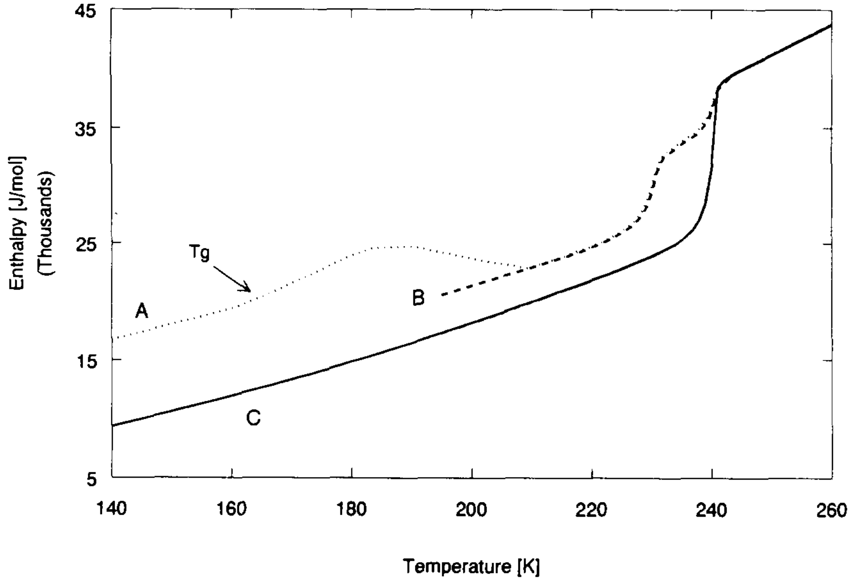

Fig. 5. Enthalpy paths of the *dl*-carvone sample during the experiments: Curve A, heated from the glass phase; Curve B, melting curve after the first stabilisation experiment; Curve C, melting curve of the stable form.

Extrapolation of the enthalpy path of the metastable crystalline material and of the liquid resulted in an enthalpy difference at 231 K of 9.71 kJ mol^{-1}. This indicates that during the solidification of the supercooled sample, only about 3% of the sample crystallised in the stable form (this follows from the numerical values given below). The stable form is mainly formed during the melting of the metastable form which resulted in a strongly fluctuating drift between 220 and 240 K.

Metastable *dl*-carvone melts at (231 ± 0.5) K and the stable form at (241.15 ± 0.05) K. The polymorphic behaviour of *dl*-carvone could not be determined in a DSC apparatus as the finite heating rate prevented the formation of a detectable amount of the stable form. The DSC results did show a dependency on thermal history. However, a second melting peak, which could have appeared at 241 K, was not seen.

During the adiabatic measurements, the stable form did not show any phase transition except for the melting. The heat of melting of the stable form is (12.697 ± 0.005) kJ mol^{-1}. The heat of melting of the metastable form, found by fitting the heats of melting of several mixtures and extrapolating to the equimolar mixture, is (8.98 ± 0.05) kJ mol^{-1} [1]. Compared with the metastable form, the entropy of the stable form is $R\ln(5.1)$ lower.

The thermal behaviour of pure *l*-carvone and the phase diagram of stable mixtures of *d*- and *l*-carvone are currently being investigated with adiabatic calorimetry. The crystallographic characteristics of the metastable and stable forms will be studied using X-ray powder diffraction.

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