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Mixtures of *d*- and *l*-carvone

IV. Transformation from a solid solution to a racemic compound

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Abstract

Undercooled mixtures of *d*- and *l*-carvone, when heated in a calorimeter, crystallize into solid solutions. Adiabatic measurements revealed that the equimolar mixture is able to recrystallize from a solid solution to a more stable crystalline form. In this study, an adiabatic calorimeter has been used to obtain the solid–liquid phase diagram of recrystallized (stable) mixtures of *d*- and *l*-carvone. During recrystallization, the system forms a racemic compound. In addition, evidence has been found for the formation of anomalous racemates in the ratios of 1 : 4 and 4 : 1.

Keywords: Carvone; Polymorphism; Solid solution; Racemic compound; Adiabatic calorimetry

1. Introduction

Chirality has become an area of interest in pharmaceutical development. Enantiomers of a chiral drug may evoke different biological responses because of their different three-dimensional structures. Many processes of drug action and disposition involve an interaction with chiral biomacromolecules, so enzymes and receptor systems usually show a stereochemical preference for one of a pair of enantiomers [1]. This has led to an increasing number of chiral drugs in modern drug design. For example, a group of drugs used for the treatment of hypertension, ACE inhibitors, are developed and marketed as single isomers [2]. Sometimes both enantiomers can be used, but with different effects. For example, *d*-propoxyphene is used as an analgesic, while *l*-propoxyphene is used as an anti-tussive. Single enantiomers are obtained by various approaches, for example by asymmetric synthesis or by separating a racemate into the two enantiomers. In the development of separation methods, it is essential to have knowledge of the mixing behaviour of enantiomers.

Another important issue in the preparation of drugs is the possible polymorphic behaviour of the biologically active substance. Polymorphs may differ with respect to their stability during storage, or one polymorph may be easier to grind than another [3]. Polymorphism involving binary mixtures of enantiomers has been investigated in several researches. For example, Kipping and Pope [4], Adriani [5], and Jacques and Gabard [6] examined the camphoroxime system. Camphoroxime forms a racemic compound at low temperatures and transforms into a solid solution at higher temperatures. Padoa and Rotondi [7] and Collet

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et al. [8] reported that α-bromocamphor exists at low temperatures as a conglomerate and is transformed into a racemic compound upon heating. Racemic 1,1′-binaphthyl has been investigated by Wilson and Pincock [9] and by Kress et al. [10]. It shows the conversion from a racemic compound to a conglomerate. Recent studies by Druot et al. [11] revealed that up to 337 K the conglomerate of *N*-acetyl-α-methylbenzylamine is stable and the racemic compound is metastable, and above 337 K, the situation is reversed.

Mixtures of the enantiomers of carvone [12] form solid solutions [13]. The phase diagram has a minimum at x=0.5. The pure components melt at 249.5 K and the melting point of a solid solution with equimolar composition is 231 K. X-ray studies revealed that a 1 : 1 solid exhibits similar molecular packing as *l*-carvone [14]. Further investigations by means of adiabatic calorimetry revealed the polymorphic behaviour of pure *l*-carvone as well as *dl*-carvone. Pure *l*-carvone shows two solid–solid phase transitions upon heating. Metastable *l*-carvone (II) transforms irreversibly into stable material (I) between 202 and 225 K, and stable *l*-carvone shows a reversible phase transition ($I_\beta \rightarrow I_\alpha$) around 200 K [15]. When partially melted, a metastable 1 : 1 solid solution is able to recrystallise to a stable crystalline form that melts at 241.2 K [16].

In this study, the mixing behaviour of *d*- and *l*-carvone in the stable solid state will be discussed. The determination of the solid–solid and solid–liquid transitions required long stabilisation times and accurate measurements of small heat effects. Hence, an adiabatic calorimeter was used to examine the thermodynamic behaviour of the recrystallised (stable) mixtures. A computer method for the thermodynamic analysis of phase-equilibrium data was used to construct a solid–liquid phase diagram describing both the metastable and the stable polymorphs of the mixtures.

2. Experimental

2.1. Materials

The enantiomers *d*- and *l*-carvone, liquid at room temperature, were obtained from E. Merck Nederland B.V. Both the products contained over 99% carvone (GC analysis), 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. The reported compositions were corrected assuming the *d*-carvone as obtained was slightly contaminated with *l*-carvone.

2.2. Apparatus

All measurements were performed using an adiabatic calorimeter that has been described previously [17–19]. The intrinsic drift of the calorimeter approaches 15 mK h^{-1}, the internal precision is ca. 0.02%, and the absolute accuracy is estimated to be 0.2%. Adiabatic measurements can be performed between 5 and 420 K. The samples, of masses between four and 6 g, were sealed with ca. 1000 Pa helium gas as heat exchanger. A special, thick-walled measuring vessel was used as the repeated passing through the glass transition resulted in deformation of the vessels normally used.

2.3. Method

The liquid mixtures were cooled to 140 K; during cooling, the samples passed the glass-transition temperature at ca. 165 K. Then, the samples were heated until they crystallised into solid solutions and, thereafter, partially melted. The partially solid mixtures were kept under adiabatic conditions for five days during which the samples had the opportunity to recrystallise. Thereafter, the samples were cooled again and, finally, their thermodynamic behaviour upon heating was determined.

3. Results

All phase transitions, determined on the recrystallised (stable) mixtures, are summarised in Table 1. Upon heating, the samples showed three types of events before the final melting. Hereinafter, x=1 refers to pure *l*-carvone, and x=0 designates pure *d*-carvone.

3.1. A transition at 200 K in samples with compositions near x=1

Four samples, with compositions $x \geq 0.8$, show a reversible transition at ca. 200 K. As an example, the

Table 1
Phase transitions in recrystallised (stable) mixtures of *d*- and *l*-carvone as determined by adiabatic calorimetry

Composition (x=1 is *l*-carvone)	Reversible transition/K	Decomposition anomalous racemate/K	Eutectic melt temperature and transition enthalpy	Liquidus temperature and transition enthalpy
0.52 Ref. [16]				241.2±0.05 K 12.70±0. 005 kJ mol^{-1}
0.60			237±1 K 3.7±0.1 kJ mol^{-1}	240±1 K 9.2±0.1 kJ mol^{-1}
0.64			238±1 K 6.4±0.1 kJ mol^{-1}	239±1 K 6.4±0.1 kJ mol^{-1}
0.68			238±1 K 7.8±0.1 kJ mol^{-1}	
0.72		229±1	238±1 K 9.7±0.1 kJ mol^{-1}	
0.80	200±2	229±1		243±1 K 7.8±0.1 kJ mol^{-1}
0.85	200±2	230±1		245±1 K 9.2±0.1 kJ mol^{-1}
0.91	200±2	228±1		247±1 K 10.1±0.1 kJ mol^{-1}
1.00 Ref. [15]	200±2			249.5±0.05 K 11.73±0. 005 kJ mol^{-1}

curves of the samples with compositions x=0.85 and x=1 are presented in Fig. 1(a and b), respectively. In a heat capacity vs. temperature plot, the heat involved in a transition is represented by the area under the transition peak after subtraction of the baseline. The heat corresponding to the effect at 200 K depends strongly on thermal history (see Fig. 1(b) and Ref. [15]). This implies that the absorbed heat could not be plotted as a function of composition. In other words, a Tammann diagram [20] could not be constructed.

3.2. An endothermic effect at 229 K in samples with compositions 0.7<x<1

The heating curves of four recrystallised samples, with compositions 0.7<x<1, show an endothermic peak around 229 K. The absorbed heat shows the following trend: the effect is largest for the sample with x=0.80, becoming smaller at higher and at lower compositions. This is illustrated with three samples in Fig. 2.

3.3. An endothermic event at 238 K in samples with compositions around x=0.5

Two samples with compositions x=0.60 and x=0.64 show two endothermic events: one at ca. 238 K, followed by a second melting peak. The samples with x=0.68 and x=0.72 were completely melted at ca. 238 K. The heating curve of the recrystallised sample with composition x=0.64 is shown in Fig. 3.

4. Discussion

In the following discussion of the results and in the phase diagram, x=1 refers to pure *l*-carvone, and x=0 designates pure *d*-carvone. Consequently, x is the mole fraction of *l*-carvone in the samples.

4.1. Reversible transition at 200 K

Pure *l*-carvone shows a reversible transition ca. 200 K. The heating curve of all seven samples was examined in order to find out whether this transition could also be seen in recrystallised mixtures. Only samples with compositions above x=0.8 show the reversible transition at ca. 200 K. The reversible transition is a pure component property, which indicates that recrystallised samples with x>0.8 contain pure *l*-carvone next to a mixture of *d*- and *l*-carvone of a certain composition.

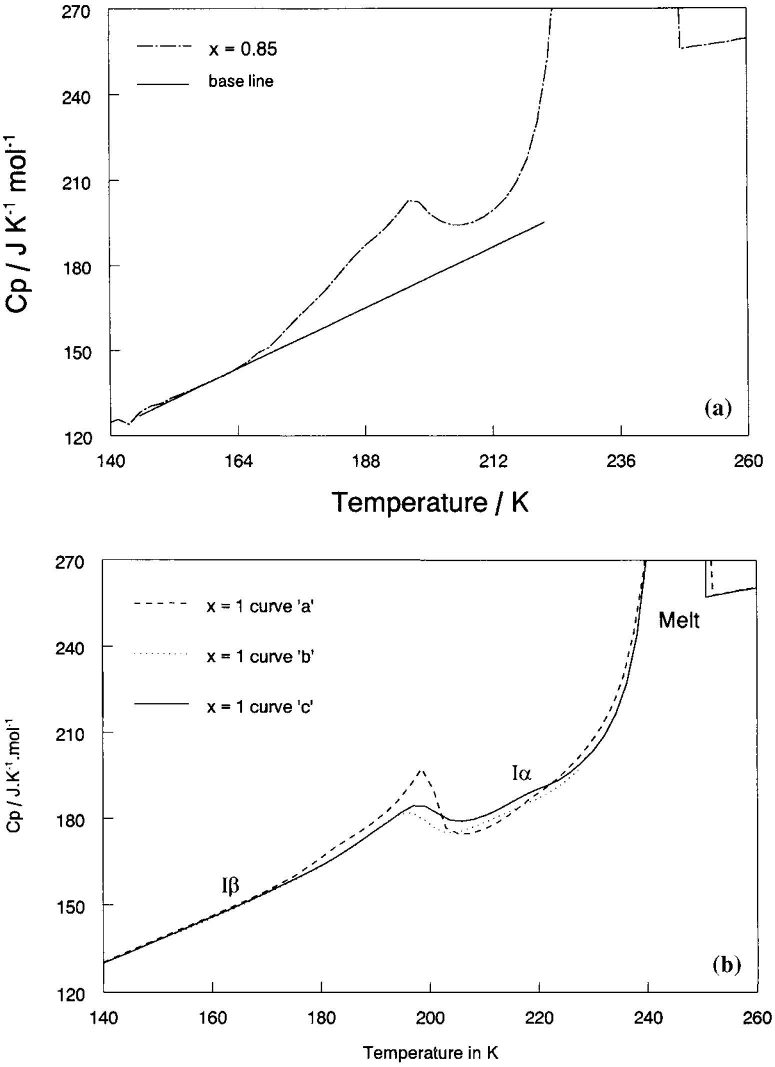

Fig. 1. The phase transition at 200 K, as measured during heating of the samples with (a) composition x=0.85 and (b) composition x=1. The thermal history of curve 'a' 'b' and 'c' in (b) is described in Ref. [15].

4.2. Three-phase equilibrium at 229 K

The endothermic effects at ca. 229 K point at a three-phase equilibrium. In our view, this indicates that the carvone system is able to form anomalous racemates. This is confirmed by the fact that only samples with a composition between x=0.8 and x=1 show a reversible transition at 200 K. In our hypothesis, the anomalous racemates to be considered contain the *d*- and *l*-molecules in a 4 : 1 and 1 : 4 ratio, respectively. These anomalous racemates would be stable below 229 K. This would imply that a recrystallised sample at a temperature below 229 K, with a composition between x =0.5 and x=0.8, consists of the racemic compound and the 1 : 4 compound. Between 229 K and the eutectic temperature at 238 K, the sample consists of the racemic compound and a solid solution containing predominantly *l*-carvone.

It is clear that X-ray or solid-state NMR are necessary to confirm the existence of anomalous racemates

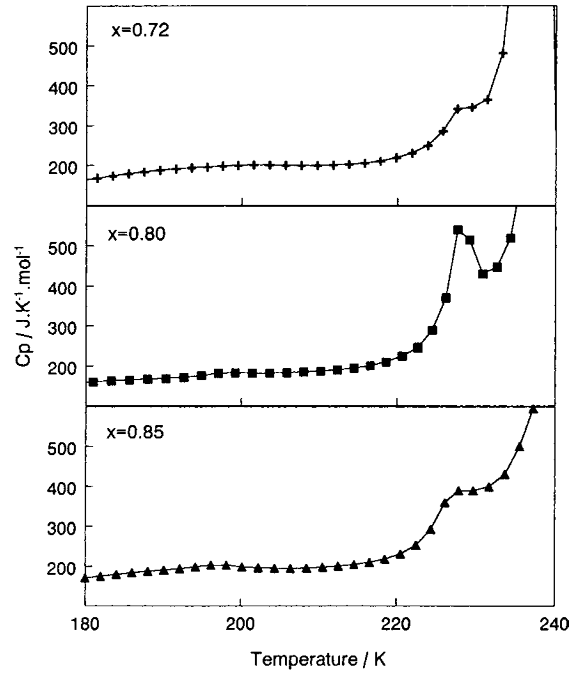

Fig. 2. Endothermic peaks at 229 K in the heating curves of the samples with compositions x=0.72, 0.80 and 0.85.

and, more importantly, to determine the exact ratio of the *d*- and *l*-molecules in the anomalous racemates. It is possible that the ratios are 3 : 1 and 1 : 3. However, up to this moment we did not succeed in obtaining X-ray data of completely stable samples below 229 K.

Though unusual, the concept of formation of anomalous racemates is not unique. Bergmann and Lissitzin [21], for example, found evidence for the formation of anomalous racemates of *d*- and *l*-4-benzoylamino-3-hydroxybutyric acids, respectively, in the ratios of 2 : 1 and 1 : 2. Fredga [22] determined that *d*- and l-2,4-dimethylglutaric acid form anomalous racemates in the ratios of 1 : 3 and 3 : 1, respectively. The formation of 1 : 3 and 3 : 1 anomalous racemates of tetramisole was discovered by Töke et al. [23].

4.3. Eutectic transition at 238 K

When partially melted, a 1 : 1 solid solution is able to recrystallise into another crystalline form that melts at 241.2 K[1]. The melting curves of recrystallised samples with compositions 0.5<x<0.8, show a eutectic melt at 238 K, followed either by the melt of racemic compound or the melt of *l*-carvone. This clearly shows that the 1 : 1 polymorph that melts at 241.2 K is a racemic compound. That is, a crystal in which the two enantiomers are not randomly, but symmetrically arranged.

4.4. Computer-aided calculation of the phase diagrams

The solid–liquid phase diagrams corresponding to the metastable and the recrystallised (stable) mixtures were calculated by means of the computer program 'Prophase' [24]. The program calculates the mole fractions of the coexisting phases for a specified set of temperatures. In both the phase-diagram calculations, the following assumptions were made:

(i) The excess enthalpy and entropy are independent of temperature.
(ii) The liquid mixtures are ideal.
(iii) The Gibbs energy of the solid state can be described by: $G^E=(h-T\cdot s)x(1-x)$.

The data given in Table 2 were used for the calculation of the phase diagram corresponding to metastable mixtures (see also Ref. [13]). For the calculation of the phase diagram corresponding to the recrystallised (stable) mixtures, the data given in Table 3 were used. These data were obtained from Refs. [13,15,16]. The results of the calculations are presented in Fig. 4. The experimentally determined phase transition temperatures and the calculated phase diagram for the

Table 2
Table of the melting properties of the pure components, and the excess function coefficients corresponding to (metastable) solid solutions of *d*- and *l*-carvone

Pure *l*- and pure *d*-carvone		Excess function coefficients	
T^*/K	$\Delta_s^l S^*$/(J K^{-1} mol^{-1})	h/(J mol^{-1})	s/(J K^{-1} mol^{-1})
249.0	47.0	10233	30.8

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[1] An undercooled liquid (x=0.5) kept at a temperature between 231 and 241.2 K did not show any crystallisation at all. This might have been due to a lack of nuclei. The crystallisation could not be initiated by adding seeds because of the experimental conditions.

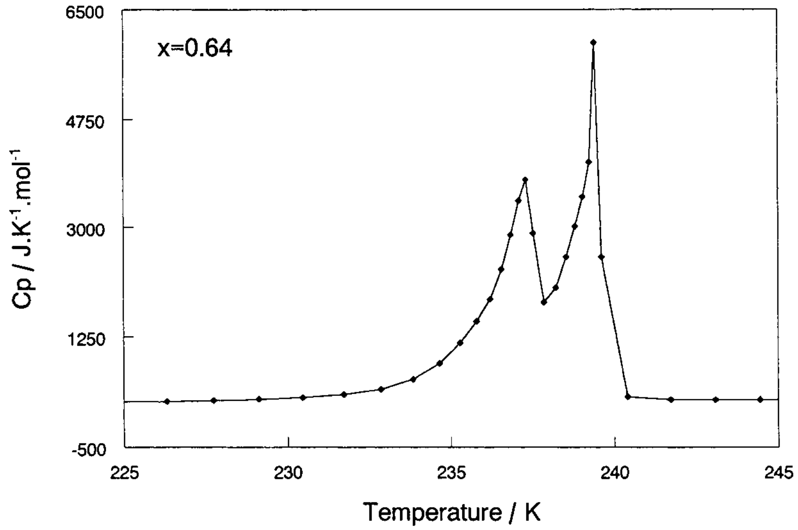

Fig. 3. The heating curve of the sample with composition x=0.64 shows the eutectic melt followed by the melting of the racemic compound.

Table 3

Table of the melting properties of the pure components, the racemic compound, the imaginary melting properties of the anomalous racemates, and the excess function coefficients corresponding to the stable crystalline form of the carvone system

Pure *l*- and pure *d*-carvone		Excess function coefficients	
T^*/K	$\Delta_s^l S^*$/(J K^{-1} mol^{-1})	h/(J mol^{-1})	s/(J K^{-1} mol^{-1})
249.5	47.0	10233	30.8
Racemic compound		Anomalous racemates 4 : 1 and 1 : 4	
$T_{(x=0.5)}$/K	$\Delta_s^l S_{(x=0.5)}$/(J K^{-1} mol^{-1})	$T_{(\mathrm{imaginary})}$/K	$\Delta_s^l S_{(\mathrm{imaginary})}$/(J K^{-1} mol^{-1})
241.2	52.7	237	67

stable mixtures coincide. It is clear that the carvone system is able to form a racemic compound, while the formation of solid solutions is still present in recrystallised samples with a composition close to x=1. The calculation shows that the formation of anomalous racemates would not oppose thermodynamic laws.

4.5. General remarks on the recrystallisation behaviour

The recrystallisation in molecular mixed crystals of *d*- and *l*-carvone only takes place when given enough ‘space’ and time. The remark that the molecules need ‘space’ to rearrange from a solid solution to a racemic compound is based upon the following. Heating experiments in an adiabatic calorimeter on solid solutions made clear that the samples did not show any exothermic event below their melting temperatures. Transformation seemed to take place only when the solid solution was partially melted. The large molecular shifts that are necessary to rearrange from a solid solution into a racemic compound take place via the liquid phase.

The transition requires a relatively long time. DSC experiments at a heating rate of 2.5 K min^{-1} did not result in a detectable amount of racemic compound. Therefore, the polymorphic behaviour of the carvone system was not noticed during DSC experiments [13]. Even at very slow heating rates in an adiabatic calorimeter, the kinetics of the polymorphic transition made it difficult to obtain completely recrystallised samples. A heating rate of 0.1 K min^{-1}, for example, applied on a 1 : 1 mixture resulted in a sample that was partially

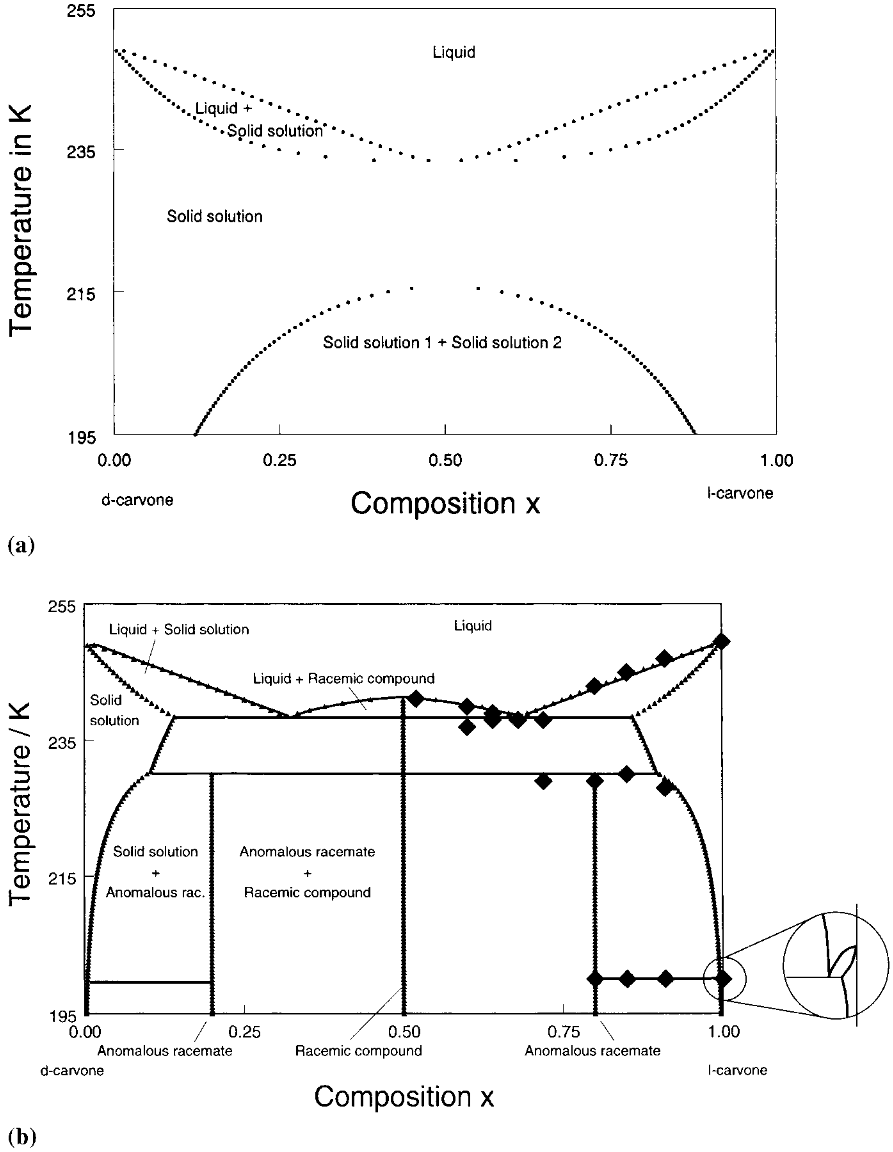

Fig. 4. The solid–liquid phase diagrams of carvone: (a) small dots, calculated diagram corresponding to metastable solid solutions; (b) solid lines, calculated diagram corresponding to stable crystalline mixtures. (◆), Measured phase transition temperatures of the stable crystalline mixtures.

transformed from a solid solution into a racemic compound [16]. Complete recrystallisation of samples of ca. 5 g with a composition around x=0.5 took, under adiabatic conditions, five days. In samples with a composition above x=0.7, recrystallisation was slower; even after five days, the samples were only partially recrystallised.

5. Conclusion

The carvone system is an example of a binary mixture of enantiomers that shows polymorphic behaviour. Undercooled liquid mixtures of *d*- and *l*-carvone crystallise into solid solutions upon heating. The solid solutions are able to recrystallise into a more stable phase. Stable mixtures show thermodynamic behaviour corresponding to a phase diagram with a racemic compound and anomalous racemates with ratios 1 : 4 and 4 : 1, respectively.

The melting temperature of the stable form of the pure components corresponds to both the metastable and the stable forms of the mixtures. The mixing behaviour in the stable solid state appears to be a combination of solid solution and the formation of a racemic compound.

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