Journal of Thermal Analysis, Vol. 33 (1988) 1241–1245

THE ROLE OF BINARY PHASE DIAGRAMS IN SEPARATION OF STEREOISOMERIC MIXTURES

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Crystallization from the melt was applied to separate components of stereoisomeric mixtures. Binary phase diagrams were determined by DSC and used in the design of the crystallization process. The method is illustrated by the separation of diastereoisomeric (cis-trans) permethrinic acid and by that of the enantiomeric excess and racemic fraction of the Corey-lacton.

Both pharmacological investigations and pharmaceutical production require the possibility of preparing materals of high purity. Frequently very similar compounds have to be separated, such as geometrical isomers, or non-racemic mixtures of optical isomers. The efficiency of the separation and the number of the separation steps (may) depend on the second order interactions, in the mixture of two molecules having different (chemical, geometrical and steric) structures, different solid state structures (conglomerate , molecule compound or solid solution) can be formed [2].

Being aware of the binary phase diagram interaction types can be concluded. (No special interactions: solid solution; homostructural preference: conglomerate; heterostructural affinity; molecule compounds).

The traditional separation methods (such as fractional crystallization, distillation, different types of chromatography) involve the introduction of a new component into the system (solvents, adsorbents etc. [3]. In the case of properly stable compounds (no decomposition up to the melting point), which are forming conglomerates or molecule compounds, a well-known, easy, pure and predictable method can be recommended, in particular, crystallization from the melt. It can have outstanding importance in the case of diastereo- and optical isomer separations.

In this paper we intend to show how the method can be applied for separating the components of a diastereoisomeric (geometric) and of a partially resolved enantiomer mixtures.

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Method

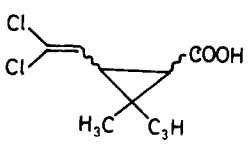
Being aware of the binary phase diagram and the melting point of the mixture to be separated, the isomer composition can be determined from the diagram. Binary phase diagrams can be either measured or calculated by using the Schröder-van Laar and the Prigogine-Defay-Mauser equations [2].

The use of the equations requires the knowledge of the melting points and enthalpies of fusion for the pure components.

Having the mixture melted, it is thermostated at that temperature where the crystallization of the desired composition can be expected. The crystallization can be accelerated by using seeding crystals. The precipitated crystalline mass is separated by filtration. One of the first and very elegant examples of the method was accomplished by Pincock & Wilsorr [4]. Combining the method with second order asymmetric transformation, they were able to transform the mixture of the recemic 1,1-binaphtyl to one of the optically pure isomers.

The selective crystallization from the melt can be applied in separating any isomeric mixtures having a composition different from the eutecic one (which composition can not be resolved in this manner).

The method is illustrated by the cis- and trans permethrinic acid (I) separation for diastereoisomeric (geometric), and for optical isomers forming conglomerate, by the separation of the enantiomer excess from the racemic fraction of the so-called Corey-lacton (II).



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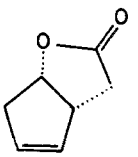

II

Separation of diastereoisometric mixture of cis- and trans permethrinic acid

During the different synthesis of permethrinic acid, the geometric isomers are forming with various compositions [5]. A number of isomer separation by crystallization have been published (for example from n-hexane [6], others have used selective ester hydrolysis for isolating the isomers [7]. As a results of these methods, either one of the pure isomers can be obtained with considerably high loss, or both isomers can be obtained with consider-

ably high loss, or both isomers can be prepared at the end of an exhausting series of the repeated crystallizations or hydrolysis, etc. Our method provides (in equilibrium) one of the pure isomers in crystalline form, while the melt is near to the eutectic composition. The material balance can be calculated (predicted) by using the "balance rule". Reaching the equilibrium is advantageous if the isomer ratio is reasonably far from that of the eutectic composition (in this case the eutectic mixture can be recycled). If the isomer composition is nearly eutectic the separation may only be achieved under kinetic control.

The binary phase diagram (Fig. 1.) is characteristic for conglomerates. The entectic composition contains 58% of the more abundant cis-isomer, its melting point is 62°, the pure cis- and trans-isomer melt at 88° and 99°, respectively. Their enthalpies of fusion are 22.4kJ mol^{-1} and 30.5kJ mol^{-1}, respectively. The data of the different separation steps are collected in Table 1.

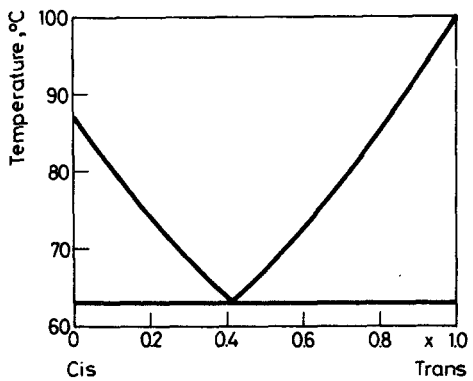

Fig. 1 Binary phase diagram of cis- and trans permethrinic acid

Table 1 Separation of cis- and trans permethrinic acid from the melt

Initial mixture cis/trans ratio, %	Crystallization temperature, °C	Solid product cis/trans ratio, %	Melt cis/trans ratio, %
35/65	50	27/73	39/61
35/65	60	20/80	50/50

Separation of the enantiomer excess from the non-racemic mixture of II

The direct optical resolution of the II-lacton has not been accomplished, yet. The optical isomers are separated as the a-methyl-benzylamine salts of the corresponding hydroxy-acid [8]. The lacton forms immediately by the influence of strong acids. As a result of the employed resolution procedure [9], optically impure lacton mixtures can be obtained. The binary phase diagram shows the caharacteristic features of a conglomerate, so the method can be applied. (Data are collected in Table 2.).

The melting point of the pure enantiomer is 46° and its enhalpy of fusion is 12.8kJ mol^{-1}.

Table 2 Separation of the enantiomer excess from partially resolved II-lacton

Initial sample op, %	Cristallization temperature, °C	Solid product op, %	Melt op, %
52.3	0–5	76.9	29.2
29.2	5	72.5	2.6
29.2	10	90.7	21.5
21.5	10	69.2	6.2
79.5	8	93.0	54.2

op: optical purity;

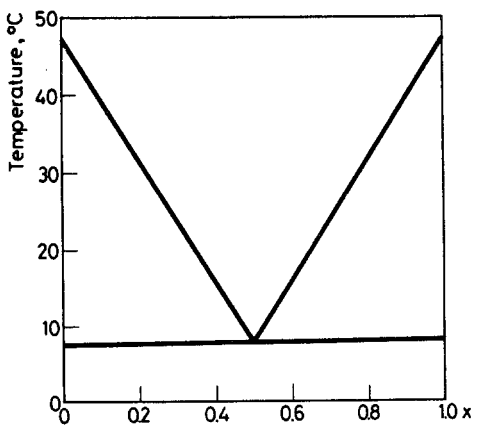

Fig. 2 Binary phase diagram of the optical isomers of Corey lacton

Conclusion

The selective separation from the melt is a powerful and effective method, which can be used for optical resolutions via diastereoisomeric salt formation, too. The method is applicable for stereoisomers forming either conglomerates or molecule compounds. In the case of conglomerates the solid product is one of the pure components (in excess), the melt is near the eutectic composition, while in the other case, there are two possibilities: the solid product is either one of the pure isomers or the molecule compound, depending on the starting compositions. The method is limited for those cases when no decomposition occurs on melting, the solid phase is ordered (crystalline) and the thermal recemization or epimerization can be neglected.

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Zusammenfassung – Zur Abtrennung von Komponenten aus stereoisomeren Mischungen wurde die Kristallisation aus der Schmelze verwendet. Die binären Schmelzdiagramme wurden mittels DSC untersucht und zur Festlegund der Parameter des Kristallisations-prozesses genutzt. Die Methode wird erläutert an den Beispielen (1) Trennung der Diastereomeren (cis/trans) Permethrinsäuren, (2) Abtrennung des Enantiomeren-Überschusses von racemischem Corey-Lacton.

РЕЗЮМЕ — Для разделения стереоизомерных смесей на отдельные компоненты была использована кристаллизация из расплава. Методом ДСК были определены двойные фазовые диаграммы, использованные затем при выборе процесса кристаллизации. Метод показан на примере разделения диастереоизомерной (цис-транс) перметриновой кислоты и разделения избыточного энантиомера и рацемической фракции лактона Корея.