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Optical Purification of Chiral Glycidyl Arenesulfonates

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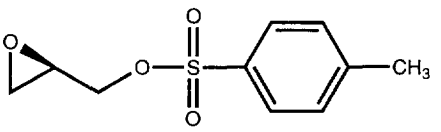
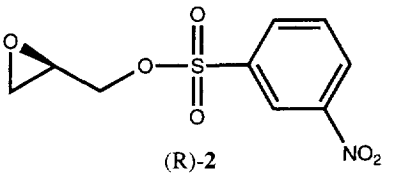
Abstract: The melting point phase diagrams of glycidyl tosylate (**1**), glycidyl 3-nitrobenzenesulfonate (**2**), and *trans*-3-methylglycidyl tosylate (**3**) have been investigated. Compounds **1** and **2** are found to exhibit a more significant solid solution behavior in the terminal zones of the phase diagram than **3**, and are therefore more difficult to enrich enantiomerically by recrystallizations. The crystallization of **2** in ethanol is further complicated by polymorphism which can be followed by differential scanning calorimetry. The effects of these properties on the optical purification of **1-3** are discussed.

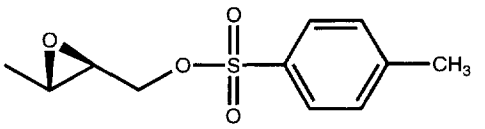
Chiral glycidyl arenesulfonates have found wide applications in the syntheses of many biologically-active compounds in recent years. These compounds can be conveniently prepared from chiral glycidols that are made by the Sharpless Asymmetric Epoxidation route.[1] A useful feature of some of these compounds is their ability to undergo enantiomeric enrichment via recrystallizations. Despite the numerous claims in the literature on the successful crystallizations of chiral glycidyl arenesulfonates of high enantiomeric purity,[2,3] there have been no reports on the melting point phase diagrams of these compounds. These diagrams are of importance to the basic understanding of their enantiomeric enrichment behavior.[4] We report here our detailed phase diagram studies on glycidyl tosylate (**1**), and glycidyl 3-nitrobenzenesulfonate (**2**), two of the most widely-used arenesulfonate derivatives of chiral glycidol, and trans-3-methylglycidyl tosylate (**3**) which is prepared from the asymmetric epoxidation of crotyl alcohol.



(R)-**1**



(R)-**2**



(R,R)-**3**

The development of a direct HPLC method[5] for the determination of enantiomeric excess (ee) of **1**, **2**, and **3** has greatly facilitated the construction of the melting point phase diagrams of these compounds. Solid samples of various enantiomeric purity were isolated from mixtures of (R)- and (S)-enantiomers that had been individually purified by recrystallizations in absolute ethanol to remove traces of the arenesulfonyl chlorides used in the syntheses, and in the case of **3**, to remove the diastereomeric *cis*-3-methylglycidyl tosylate impurity. The chemical purity of all samples used for the determination of melting point by the differential scanning calorimetry (DSC) method was analyzed to be better than 99.8%. This stringent control on sample purity is required for obtaining accurate and reproducible melting point data.

The binary melting point phase diagrams of **1-3** are presented in Figure 1. The features of the diagrams for **1** and **3** are typical of those of racemic compounds. The eutectic compositions for **1** and **3** are 42% ee and 30% ee respectively. These results imply that **1** must have at least an ee of about 42%, and **3** at least an ee of about 30% before crystallization will result in further optical purification. Indeed we have been able to effect optical purification on **1** and **3** at these predicted enantiomeric purity levels by recrystallizations in absolute ethanol. However, the effectiveness in obtaining enantiomeric enrichment by multiple recrystallizations in

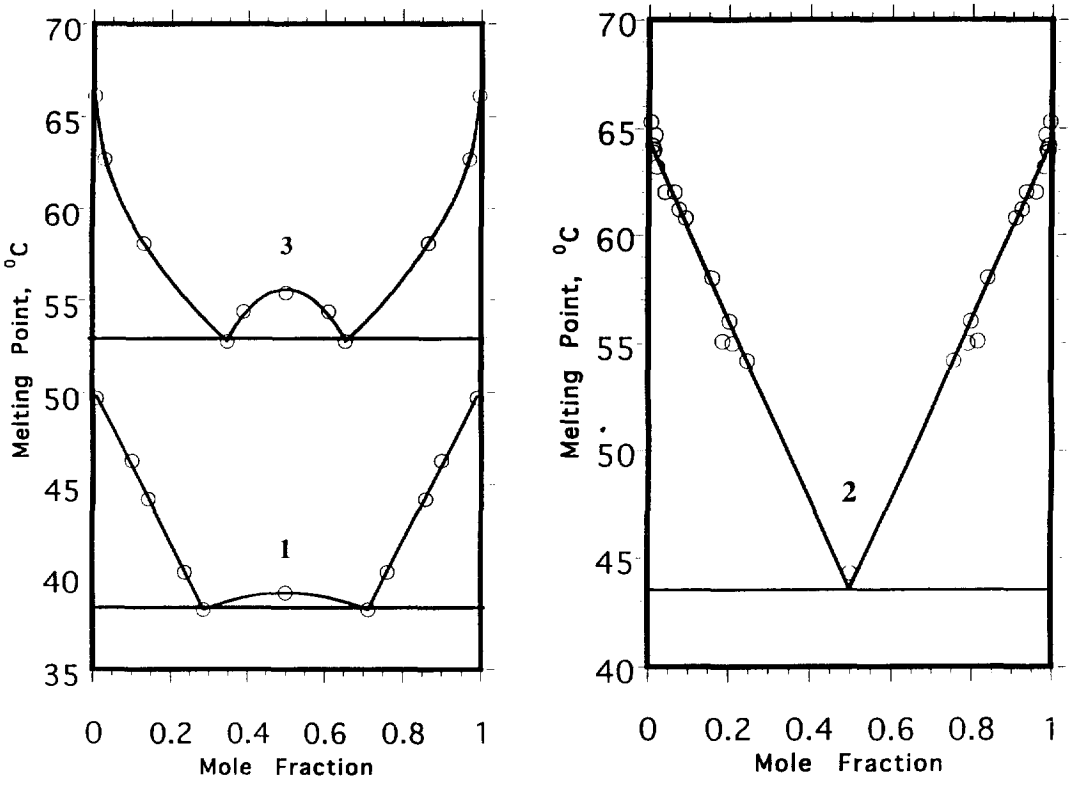


Figure 1. Melting point phase diagram of **1-3**

absolute ethanol is very different for these compounds. Although **3** can be readily enriched to 99.3% ee by carrying out two recrystallizations, **1** is found to be significantly more difficult to purify by this method. Starting from a crude product of 89% ee, we were able to enrich its enantiomeric purity up to only 97.4% ee after four recrystallizations. Therefore, the solid solution behavior of **1** in the terminal zones of its phase diagram has made it very difficult to achieve enantiomeric purity above 95% ee. The existence of terminal solid solutions must not be overlooked in the crystallization of enantiomerically ultrapure compounds.[6]

The distinctive V-shape found in the phase diagram of **2** is typical for a conglomerate. There is a very significant melting point difference of about 21 °C between its racemic and chiral forms. Their solid-state infrared spectra are also found to be identical. This compound is therefore predicted to be very favorable for optical purification by crystallization. We have been able to obtain 28% overall yield on the 96.1% ee recrystallized product from a partially enriched mixture of 27% ee by carrying out six consecutive recrystallizations in absolute ethanol without recycling of the mother liquor. The relatively low efficiency in enantiomeric enrichment is indicative of solid solution interference.[7] Furthermore we have found that enrichment above 97% ee is exceedingly difficult. The attainment of enantiopure **2** is therefore also impeded by the existence of terminal solid solutions. It is noteworthy that preferential crystallization experiments carried out on seeded solutions of this compound did not afford enantiopure product.[8]

In our recrystallization studies of **2** in absolute ethanol, we have observed the formation of two different types of crystalline products. The co-crystallization of these two polymorphs (blocks and needles) is especially noticeable during recrystallizations of the lower ee mixtures. Above 92% ee, only the highly crystalline needles

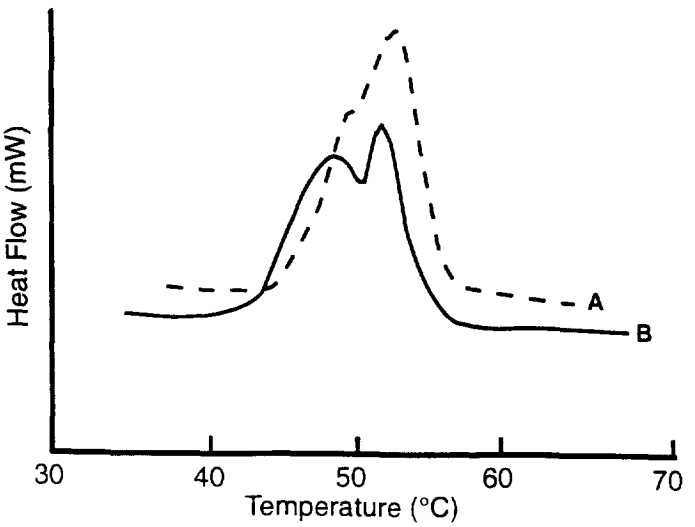


Figure 2. DSC traces of polymorphous mixtures of **2**.
A. 59.6% ee. B. 50.9% ee.

are obtained. The needles, manually separated from the recrystallized solids, are always found to have higher enantiomeric purity than the blocks. This polymorphism of **2** can be followed by DSC analyses on the recrystallized product as shown in Figure 2. The peak with a lower melting point is assigned to the block-liked polymorph which is the predominate product in the recrystallizations of low ee mixtures. As the overall enantiomeric purity of the compound increases from 50.9% ee to 59.6% ee, both polymorphs exhibit an increase in their melting points. It is therefore only through a series of DSC analyses on samples of appropriate enantiomeric purity that these two peaks become discernable. The very broad line-widths of the observed peaks are consistent with the solid solution nature of these polymorphs.

In conclusion, we have demonstrated that the existence of terminal solid solutions can be a deciding factor in the pursuit of enantiomerically ultrapure glycidyl arenesulfonates by the crystallization methodology. The heterogeneous nature of the recrystallized solids that contain polymorphs of disparate enantiomeric purity as shown by **2** can complicate the interpretation of analytical results in the optical purification process.

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References and Notes.

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6. For a discussion on the subject, see Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*, John Wiley & Sons, New York, 1981, pp.423-424.
7. It has not been possible to construct accurately the solidus and liquidus curves based on the line-widths of its DSC peaks due to complications from polymorphism to be discussed in the following paragraph.
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