

Phase diagrams of diastereomeric pairs in inclusion resolution

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Abstract—In the development and understanding of the resolution of diastereomeric salts, phase diagrams are of great importance. This study constitutes the first example of phase diagrams of diastereomeric complexes formed from simple chiral compounds, as used in inclusion resolutions. Simple melting diagrams and DSC thermograms could not be used, because of the decomposition of the complex caused by the escape of the guest from the inclusion complex upon heating. A ternary solution phase diagram was constructed from the diastereomeric inclusion complexes of phenethylamine with a taddol. Solid solution behavior was found and confirmed by powder diffraction and X-ray studies. The limited scope of inclusion resolutions, as already indicated by our earlier studies, was confirmed by these results.

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1. Introduction

In our longstanding research series¹ on resolutions through selective crystallization of diastereomers, we have recently explored the scope and limitations of resolution through inclusion compounds.² The many successful inclusion resolutions described by Toda³ have been used as the basis for our studies. Whereas Toda found numerous resolutions with taddol **1a** as resolving agent, we have found that the *p*-tolyl substituted taddol **1b** is also suitable for resolving a diversity of racemic guest compounds. The type of inclusion complexes formed by taddols and other simple compounds differs significantly from complexes formed by cavity containing compounds, such as cyclodextrins. For those hosts, strong interactions exist between the guest and the host, often already in solution. Taddol-type inclusion complexes, however, are formed and stabilized mainly by multiple interactions in the crystal lattice, while individual interactions between host and guest are much less pronounced.

In a classical resolution using diastereomeric salts, binary and ternary phase diagrams have proven to be of great value in optimizing the efficiency of resolutions

and in identifying problems.⁴ In particular, the existence and composition of the eutectic point, an important condition for easy and efficient resolution, can be determined from a phase diagram. In many cases, a single DSC thermogram can provide an approximation of the binary phase diagram, giving valuable information about the existence and composition of the eutectic⁵ in the melt, which also often is a useful approximation of the eutectic composition in solution. For inclusion complexes the knowledge concerning phase diagrams and thermodynamics is much scarcer. A number of interesting studies concerning crystalline diastereomeric cyclodextrin-type host–guest complexes have been published,⁶ but the taddol-type of complexes has been mostly neglected (Fig. 1).

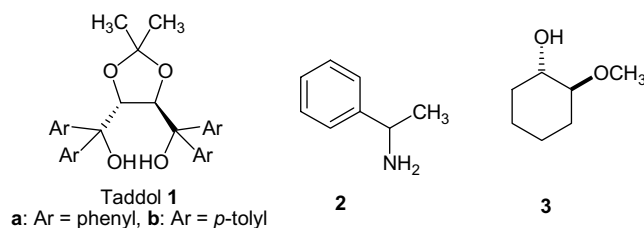


Figure 1. Taddols and guest compounds.

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2. Results and discussion

To determine a phase diagram for an inclusion resolution, the preparation of mixtures of compounds in exactly known ratios in a wide range of compositions is required. This can only be achieved if the two diastereomers of an inclusion compound are both available in pure form. The available literature only provides information on the least soluble host–guest diastereomer. No examples could be found concerning hosts capable of giving stable, taddol-type, inclusion compounds with both enantiomers of a guest compound, that is, the existence of two pure inclusion diastereomers. In the many inclusion experiments we performed with taddols as host molecules, we found only two pairs of diastereomeric inclusion compounds, where both diastereomers were stable crystalline compounds, suitable for further thermodynamic investigations. Taddol **1b** was found to have the ability to include the two enantiomers of phenylethylamine **2**, as well as the two enantiomers of *trans*-2-methoxycyclohexanol **3**, separately. Thus for the first time, a description and comparison of both diastereomers of an inclusion compound and the construction of phase diagrams appeared to be possible.

2.1. Binary (melt) phase diagrams

In general, binary (melting) phase diagrams can be determined quickly and with less effort than the corresponding ternary (solution) diagrams, and therefore an attempt was first made to determine the binary phase diagram. A simple DSC analysis of the pure diastereomeric inclusion compounds **1b**(*R*)-**2** and **1b**(*S*)-**2** showed no unusual behavior. As expected for diastereomers, different melting points for **1b**(*R*)-**2** and **1b**(*S*)-**2** were found: 103.2 and 143.2 °C, respectively, and it was assumed that a binary diagram could be easily prepared. The diastereomers were re-crystallized three times from heptane in order to ensure the purity of the samples, and mixtures were prepared by accurately weighing the two solid compounds and grinding them in a mortar to obtain a homogeneous sample. The DSC curves of these mixtures of the diastereomers were determined. Besides the mechanical mixtures, mixtures of the two enantiomers of phenylethylamine in different compositions were also co-crystallized with taddol **1b** from a heptane solution. The enantiomeric excesses of the thus prepared crystals were determined, followed by analysis with DSC. However, using this co-crystallization method only a limited range of *R/S* ratios could be obtained.

Two separate melting points were observed by DSC for each of the mechanical mixtures (illustrated with the open circles and triangles in Fig. 2), but surprisingly in each mixture, the observed melting points were constant and almost equal to the apparent melting points of the two pure enantiomers (approx 105 °C and approx 145 °C, respectively). In contrast to this, the diastereomeric mixtures obtained by crystallization from solution, showed only a single varying melting point (diamond dots), indicating a solid solution type behavior. Neither of the two measured sets corresponded to the curve calculated using the Schröder–Van Laar equation (solid

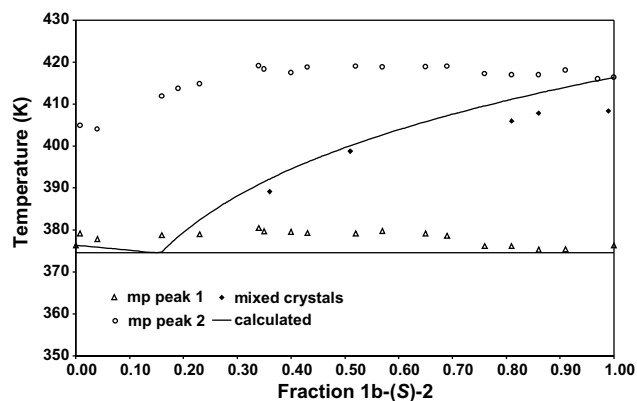


Figure 2. Binary phase diagram of complexes **1b**(*R*)-**2** and **1b**(*S*)-**2**.

line). Also the Schröder–Van Laar equation predicts an eutectic with an ee of approx 83% (*R*)-phenylethylamine, whereas the actual ee measured after a single crystallization is 77%, with the (*S*)-amine preferably included.

It was soon discovered that the inclusion complexes **1b**(*R*)-**2** and **1b**(*S*)-**2** and the mixtures thereof do not display true melting behavior. Apparently the complex dissociates, possibly with simultaneous evaporation of the amine, leaving liquid taddol **1b** (pure **1b** melts at approx 80 °C) behind. Visually and by DSC, this behavior cannot be discerned from true melting behavior. It is clear that the Schröder–Van Laar equation does not apply in this case and also that a binary phase diagram cannot be obtained.

The situation with the mixed crystals obtained by co-crystallization from heptane solution is somewhat different. Also in this case no real melting points were measured, but dissociation temperatures and heats of dissociation of the complex instead. The varying temperature for this dissociation clearly indicates a solid solution behavior.

The behavior discussed above was also observed in two additional systems of inclusion resolution. The second system involved a reverse resolution of racemic taddol **1b** with enantiopure (*R*)-**2**. As expected this resulted in very similar results.⁷ Again two dissociation temperatures were observed with mechanical mixtures: the first at approx 105 °C, and the second at 143 °C.

The third example is the complex of taddol **1b** with *trans*-2-methoxycyclohexanol **3**. Compound **3** can be resolved using **1b** with an ee of 94%. Again both diastereomers of the inclusion complex could be obtained. The pure enantiomers of alcohol **3** are not commercially available, thus the resolution with **1b** and with its enantiomer was used to prepare both pure enantiomers of **3**.

The dissociation temperature of pure **1b**(*R,R*)-**3** was 143.2 °C and that of pure **1b**(*S,S*)-**3** 153.3 °C (Fig. 3). As seen before, two dissociation temperatures were observed for the mechanical mixtures, and the filled diamond shaped dots represent the dissociation temperatures obtained for each diastereomeric mixture pre-

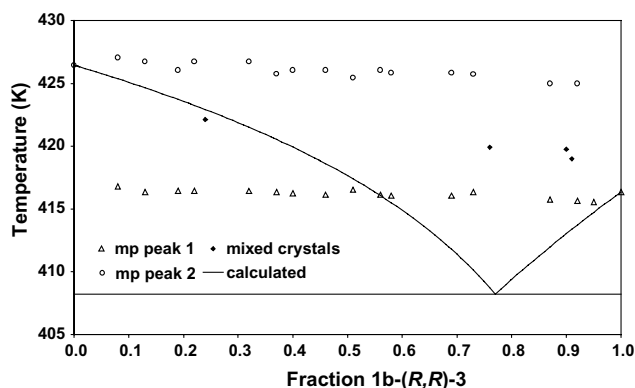


Figure 3. Binary phase diagram of complexes **1b**-(*S,S*)-**3** and **1b**-(*R,R*)-**3**.

pared by co-crystallization from heptane solution. The solid lines show the calculated curves predicting an ee of 77% (*R,R*)-*trans*-2-methoxycyclohexanol. The actual ee determined after a single crystallization from the racemic diol was 68% with preference for inclusion of the (*S,S*)-enantiomer.

It is clear that for taddol-type inclusion compounds binary melting phase diagrams cannot be used in the same way as for diastereomeric salts, and also that conclusions cannot be drawn on single DSC measurements. What at first sight appears to be a normal (reversible) melting process will in the case of these complexes often be an (irreversible) dissociation.

2.2. Ternary (solution) phase diagrams

Although binary melting phase diagrams can be of practical help in understanding and developing resolutions, they are at best only approximations of the ternary diagrams. Ternary solution diagrams take into account all compounds present in a resolution process: resolving agent, racemic compound and solvent. The readily accessible host–guest system of enantiopure taddol **1b** with racemic phenethylamine **2** and hexane as solvent, was selected for a first attempt in constructing a ternary phase diagram with taddol-type inclusion compounds. Mixtures of crystals of the two diastereomeric forms in varying ratios, were dissolved in hexane in sufficient quantities to ensure that some solid undissolved material remained, and a solution saturated with respect to both diastereomeric forms was obtained. The suspension was stirred in a water bath at 22 °C for three days to ensure complete equilibrium. Samples of the supernatant liquid were analyzed; the concentration of taddol **1b** was determined by HPLC-analysis while the ee of the amine was determined by chiral GC after derivatization with camphanoyl chloride. Knowing the compositions in the liquid phase as well as the initial composition, the composition in the remaining solid material could be easily calculated. However, for verification, the ees of the amines in some solid phases were additionally determined and found to be in agreement with the respective calculated ones. Three independent series of mixtures have been used to construct the following diagram in order to ensure the accuracy of the results (Fig. 4).

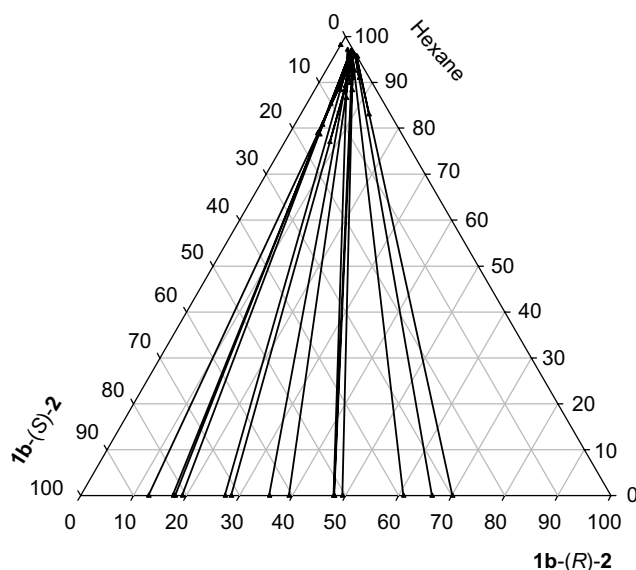


Figure 4. Ternary phase diagram of taddol **1b**/phenylethylamine **2**/hexane.

The ternary solubility diagram of this system clearly shows a solid solution behavior, which is in accordance with the observations from the corresponding binary phase diagram using co-crystallized mixtures. In the enlarged segment (Fig. 5), no eutectic point can be observed. Practical difficulties were encountered in the region with a high content of (*S*)-**2**. Consequently no data could be obtained for this part of the diagram.

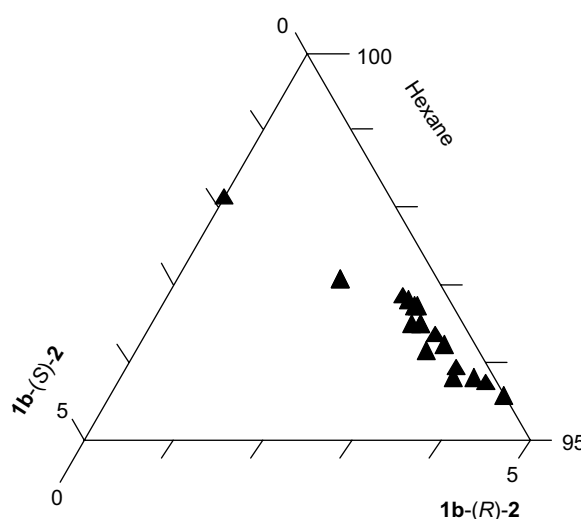


Figure 5. Enlarged segment of the ternary phase diagram (Fig. 4).

2.3. Powder diffraction and X-ray analyses

The initially obtained powder diffraction patterns of the diastereomeric pair from **1b** with (*R*)-**2** and (*S*)-**2** were found to be substantially identical, indicating a nearly indistinguishable crystal packing and structure. Subsequently, suitable single crystals for more detailed X-ray studies could be obtained for the inclusion complexes **1b**-(*S*)-**2**, **1b** (*rac*)-**2**, and **1b**-(*R*)-**2**. Crystals suitable for single crystal X-ray determination of the last

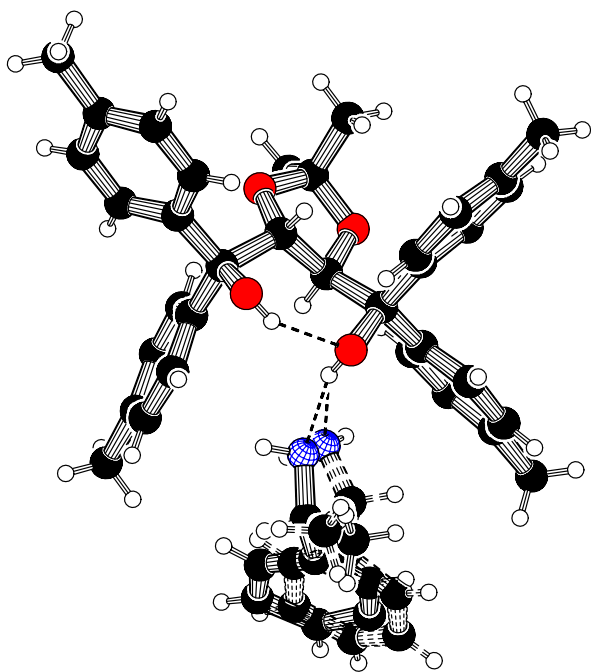


Figure 6. PLUTON drawing of the inclusion complex **1b**–(*rac*)–**2**.

complex could only be obtained with (*R*)-**2** in 65% ee, higher ees resulted in powder. The crystal structures of the complexes with pure (*S*)-**2** and with mainly (*R*)-**2** are practically identical, confirming the powder diffraction results. The crystals with (*rac*)-**2** clearly show a superposition, that is, a random irregular distribution of the two enantiomers of **2**, providing a final proof for solid solution of the amine guest. The corresponding crystal structure is shown in Figure 6. Additional details can be found in Ref. 2a.

3. Conclusions

Since this, to the best of our knowledge, constitutes the first solubility phase diagram of a diastereomeric inclusion complex of the taddol-type, no general conclusions concerning the behavior of diastereomeric complexes in the inclusion resolution can be drawn. A comparison can be made with solubility diagrams of diastereomeric salts, but only a few ternary phase diagrams showing solid solution behavior are described in the literature.

Although full solid solution is not frequently observed for diastereomeric salts, it has been reported that solid solution between diastereomeric salts is more common than solid solution between enantiomers.⁸ Probably the presence of an identical counter-ion in both diastereomers increases their similarity as compared to enantiomers. Analogous conclusions can be drawn in the case of diastereomeric inclusion complexes. The presence of the same (neutral) host in both complexes may lead to an increase in molecular similarity. Also, in diastereomeric salts the strong electrostatic interactions lead to a tighter and more inflexible crystal packing compared to inclusion complexes. The much weaker

interactions in inclusion compounds can be expected to allow a higher degree of flexibility, where small distortions will not entail a high free energy penalty. This leads one to speculate that the chance of observing solid solution behavior in inclusion complexes could be much higher than in salts. This would present a substantial disadvantage for this method of enantiomer resolution, confirming the results of our related studies.²

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