394e Chiral Resolution Via Diastereomeric Salt Crystallization

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Chiral crystallization with the use of resolving agent to form diastereomeric salts is a widely used technique for resolving chiral compounds. However, the approach to resolve chiral compounds by this method is still conducted mainly on a trial-and-error basis.

We propose that the solid liquid phase equilibrium of the diastereomeric salts system should be understood first. By constructing the corresponding phase diagram, namely the Janecke projection of the conjugate salts system, of the two diastereomeric salts and the enantiomers, we can identify the diastereomeric salt that can be potentially recovered under equilibrium conditions. The phase diagram also elucidates how the stoichiometric ratio of the resolving agent employed affects the phase equilibrium of the system. If the desired diastereomeric salt can be separated under equilibrium conditions, process pathway can be readily drawn on the phase diagram and process alternatives can also be identified.

It is not uncommon that the desired enantiomers cannot be recovered under equilibrium conditions. They have to be recovered under kinetic processes. Supersaturated diastereomeric salts solution will be seeded with pure form of the desired diastereomeric salt and the crystallization will be stopped well before reaching equilibrium. We propose that by investigating the induction time of the two diastereomeric salts and the crystal growth rate at different temperatures and supersaturations, optimal conditions can be found for chiral resolution.

The approach is illustrated by using a chiral non-steroidal anti-inflammatory drug, Ibuprofen (IBU), as a model system. (S)-IBU is more potent than (R)-IBU and there is a great deal of interest to separate them. N-methyl-D-glucamine (NMDG) is chosen as the resolving agent. After constructing the phase diagram, it is found that under equilibrium conditions, only the undesired diastereomeric salt NMDG-(R)-IBU can be collected. However, seeding can be employed to collect NMDG-(S)-IBU. Low temperature and high supersaturation favors such resolution. In this presentation, an integrated approach for this resolution will be discussed.