Molecular Mechanisms of Dielectrically Controlled Resolution (DCR)

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Abstract  It is widely believed that the chiral discrimination process is solely dependent on the stereochemistry of the relevant molecules. However, through systematic studies on several resolution systems with popular chiral selectors, we have discovered a new fact that triggers modification of this prevailing concept of chiral resolution. The studies have demonstrated that one enantiomer of a chiral selector can recognize both enantiomers of a target molecule in different solvent systems with different dielectric constants. The phenomenon was termed dielectrically controlled resolution (DCR). Since DCR was observed in different resolution systems and was not too specific to a particular system, DCR was expected to widely occur in various resolution systems. We have investigated the molecular mechanism underlying this interesting phenomenon based on X-ray analysis of the relevant diastereomeric salts. The disclosed mechanism clearly indicates that a chiral selector can inherently recognize both enantiomers of a target molecule and only the dielectric property of the solvent employed in the resolution process governs the selection of the enantiomer.

Keywords  Chiral resolution · Dielectrically controlled resolution · Molecular recognition · Solvent effect · X-ray crystallography

Abbreviations
ACL  $\alpha$-amino-$\varepsilon$-caprolactam
TPA  N-tosyl-phenylalanine
MPRD  2-methylpyrrolidine
TA  tartaric acid
PTE  phenyl-2-$p$-tolyl ethylamine
MA  mandelic acid
CHEA  cyclohexylethylamine

1 Introduction

Diastereomeric salt formation using a resolving agent as a chiral selector is one of the most useful methods for obtaining a target stereoisomer from its racemic mixture [1]. It is widely believed that the chiral discrimination process is solely dependent on the stereochemistry of the relevant molecules. The conventional idea of chiral separation takes it for granted that where a chiral selector of molecule ($R$)-A is necessary to obtain a less soluble diastereomeric salt with a target molecule of ($R$)-B, ($S$)-A is absolutely necessary to separate the enantiomer of the molecule B.

No special attention has been given to the effect of the solvent on the process of discrimination. The role of the solvent is obviously to dissolve both the chiral selector and target molecule, but it is highly probable that the properties of the media influence molecular recognition more than a little. Therefore, we have undertaken a series of experiments to study the effects of solvent on chiral resolution, which is a typical phenomenon of molecular recognition.