Advantages of Structural Similarities of the Reactants in Optical Resolution Processes

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Abstract Advantages and limitations of the use of structurally similar compounds in racemate resolution via diastereoisomeric salt formation are discussed in this review. An effective conception on “derivative resolving agents” (use of the optically active derivatives of a racemate as resolving agents) is presented by examples and the method is
extended to the homologous series of the derivative resolving agents and/or achiral additives. A recently developed distillation version of the family approach to optical resolution and the novel, solvent-free resolution methods using a half equivalent amount of resolving agent are also discussed.

**Keywords** Optical resolution · Diastereoisomeric salt · Derivative resolving agent · Structural similarity · Homo- and heterochiral assemblies

1 Introduction

Optical resolution via diastereoisomeric salt formation is one of the most frequently used methods in the fine chemical and pharmaceutical industries for manufacture of pure enantiomers. However, selection of the optimum resolving agent and the other chiral or achiral additives have remained a game of trial and error. In order to reduce this time-consuming experimental work numerous methods are offered in the recent reviews [1, 2]. A simple and usually efficient approach is to take a survey of the known resolutions of compounds which are structurally similar to our racemate. Thus, for example, the efficiency and the absolute configuration of the crystallizing diastereoisomeric salts could be predicted by computation in a series of 2-phenylglycine derivatives [3]. In a recently developed method, the authors used a small library of structurally similar resolving agents for the diastereoisomeric salt formation with a given racemate [4]. The same authors have developed the reverse system too: mixtures of structurally similar racemic compounds have been resolved with one resolving agent. In most cases synergistic effects of such mixtures on the efficiencies of enantiomer separations have been observed.

Another approach for finding efficient resolving agents is the application of optically active derivatives of the racemic mixture to be resolved. The basis of this method is the observed strong tendency of enantiomers to form heterochiral assemblies in solution (Scheme 1) and racemate-type molecular compounds in crystalline form.

The heterochiral packing usually results in more stable supramolecular structures and it is assumed that at least 85% of the known enantiomers crystallize out in true racemate form [5, 6]. Our recently developed enantiomeric enrichment methods: the selective precipitation, selective extraction, crys-

![Scheme 1](https://example.com/scheme1.png)

*Scheme 1* Formation of homo- and heterochiral supramolecules in the solutions of D and L enantiomers \((m,n,o \geq 0)\)