Perspectives in Supramolecular Chemistry

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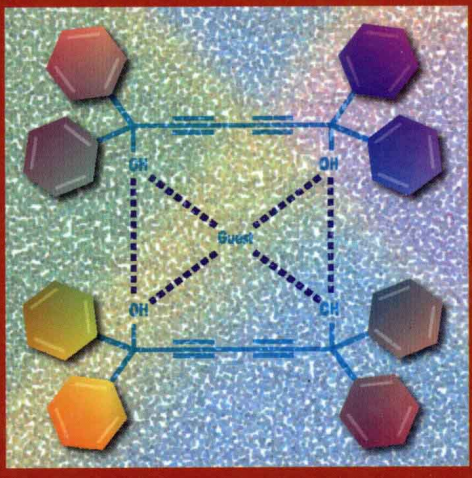

Separations and Reactions in Organic Supramolecular Chemistry

Edited by

Fumio Toda
and Roger Bishop

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Perspectives in Supramolecular Chemistry
Volume 8

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Preface

Classical organic chemistry largely involves making new molecules by means of structural changes involving strong attractive forces (covalent and ionic bonds), and concomitant studies (structure, reactivity, spectroscopy, applications) of the pure substances thereby produced. Supramolecular chemistry, on the other hand, involves the relationships between molecules that result from weak noncovalent bonding forces. This modern science currently is expanding rapidly in many different exciting directions. A number of excellent books have been written in recent years, covering the general scope of supramolecular chemistry, but less attention has been given to specific areas of application that are developing within this new field. In this volume we therefore present a selection of topics, written by experts in these fields, dealing with aspects of separation and reaction that are specific to supramolecular chemistry.

Fumio Toda
Okayama

Roger Bishop
Sydney

May 2003

Contents

Chapter 1

Inclusion Complexation as a Tool in Resolution of Racemates and Separation of Isomers

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1 INTRODUCTION

Molecular chirality is one of the most intriguing phenomena on Earth. It originated with the evolution of simple achiral molecules into more complex ones, and, as a result, the structure and functions of biological systems are controlled by direct recognition between chiral molecules. The physical and biological properties of various man-made materials depend on their chirality, and careful control of chirality at the molecular and supramolecular level is important for their performance. Recently, an increased demand for enantiopure materials has led to the intensive development of strategies to the selective introduction of new chiral centres into molecules. In contemporary synthesis, apart from using chiral starting materials (amino acid derivatives, carbohydrates, etc.), the creation of chiral centres via biocatalysis or asymmetrical synthesis is commonly used. Nevertheless, the resolution of racemates is still necessary in order to prepare optically

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pure chiral auxiliaries and to purify products of low enantiomeric excess. Another significant problem is the resolution of low-molecular-weight isomeric products obtained in the laboratory or on a commercial scale. Both approaches require a careful design strategy based on understanding intermolecular interactions at the supramolecular level.

This chapter reviews recent methodologies for the effective resolution of racemates and mixtures of isomers, applying the inclusion complexation technique.

2 DEFINITIONS

Chirality is a property of nonidentity of an object with its mirror image. Therefore, a chiral object may exist in two enantiomorphic forms that are mirror images of one another. This means that both a chiral single object and collections of chiral objects should not contain symmetry elements such as mirror planes, centres of symmetry, as well as complex elements of symmetry containing one of the latter. All objects that contain such symmetry elements are *achiral.* At the molecular level, the lack of the above symmetry elements in a molecule means that it is *chiral* and can exist in two forms, called *enantiomers*, that are mirror images of one another. It is well appreciated that the relationship between *enantiomorphic forms* resembles that between the left and right hands. On a macroscopic level, a collection of *homochiral* molecules, or even a collection of *heterochiral* molecules containing an excess of one enantiomeric form and whose composition is defined by its enantiomeric purity p or its enantiomeric excess, ee, is called an *enantiomer.* One physical property that is inherently connected with chirality is *optical activity*, i.e. the ability to rotate plane-polarized light–α_D. Two enantiomers exhibit the same absolute value, but opposite signs, of rotation. Another property that may differentiate two enantiomers is the presence of hemihedral faces in their monocrystals. Except for their interactions with polarized light and their different crystal habits, enantiomers have identical physical properties (melting or boiling points, solubility, chromatographic behaviour, etc.).

An equimolar mixture of two enantiomers is called a *racemate.* The separation of two enantiomers that constitute a racemate is called *optical resolution* or *resolution.* Their crystalline forms best characterize types of racemates. A *racemic mixture* is a crystal where two enantiomers are present in equal amounts. A *conglomerate* is a case where each enantiomer has its own crystalline form. Sometimes their crystals have so-called hemihedral faces, which differentiate left and right crystals. For over a hundred years, crystallization processes have been used for the separation and purification of isomers and optical resolution, both in the laboratory and on an industrial scale.

Various methodologies can be applied for resolving racemates, depending on their type. The most useful method for separating racemates that crystallize as a collection of enantiomorphous left and right crystals (a conglomerate) is preferential crystallization (or crystallization by entrainment). It involves alternate

stereoselective crystallization of a single enantiomer out of a conglomerate and, after each filtration, recycling the mother liquor in order to crystallize the other enantiomer. Since the reason why, and under which conditions only *c.* 10 % of racemates crystallize spontaneously as conglomerates is unknown, this method is of limited use. However, the method could be enhanced by a phenomenon called stirred crystallization, in which the resolution rate is enhanced due to secondary nucleation caused by stirring or by introduction of an amount of chiral impurities sufficient to catalyse the reaction [1,2]. In the latter method, selective chiral recognition between chiral impurities and one of the enantiomeric forms of the conglomerate may result in the transient crystallization of the opposite enantiomer [3,4].

The conventional way to obtain homochiral products in the laboratory is by diastereo-isomeric crystallization. Louis Pasteur developed this method back in 1853 [5]. He demonstrated that one could resolve racemic tartaric acid into 'non-superposable right and left bodies' by co-crystallization with an optically active amine. Basically, the general strategy involves the conversion of mixtures of enantiomers into a pair of diastereoisomeric derivatives that can be further separated by fractional crystallization. This is possible because although enantiomers have identical physical properties (melting or boiling points, solubility, chromatographic behaviour, etc.), apart from their interactions with polarized light, the properties of the diastereoisomers may differ significantly. This method involves the formation of a crystalline acid–base pair with an optically active resolving agent, mostly of natural origin. In their book *Enantiomers, racemates and resolutions*, Jacques and Collet listed over 200 of the most representative compounds used for optical resolution [6]. However, one disadvantage of this method is the fact that every natural compound used as chiral auxiliary has only one enantiomeric form, and another is that the technique becomes more expensive when it is scaled up for commercial applications. This is because, in order to make the technique industrially feasible, it requires versatile, cheap, chiral host compounds that are able to form diastereoisomeric inclusion complexes with vast groups of compounds.

Another way to obtain pure enantiomers is the separation of racemates through preparative chromatography on chiral stationary phases. In fact, the most significant developments over the last 20 years have been the application of GLC and HPLC techniques to the effective resolution of enantiomeric mixtures and to determining the enantiomeric ratio [7,8].

Several new techniques or significant improvements of the known techniques with the application of a recent technology are worth mentioning. These are the use of capillary electrophoresis [9], and the design of tailor-made polymers [10].

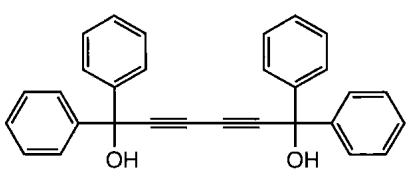
3 INCLUSION PHENOMENA

The classic, chiral auxiliaries used in the optical resolution process were natural acidic or basic compounds, able to form crystalline organic salts preferentially

with one enantiomer of the resolved species. Typically, they formed molecular complexes by proton transfer from acid to amine. Electrostatic interactions, intermolecular hydrogen bonds and other much weaker interactions like dispersive or van der Waals' forces assembled such diastereoisomeric pairs in crystals. With advances in supramolecular chemistry, knowledge of the formation of molecular complexes turned attention to inclusion phenomena [11]. Inclusion compounds are formed by the noncovalent insertion of *guest* molecules into the *host* lattice during the crystallization process. Several factors, such as topographic complementarity, hydrophobic effects, van der Waals' and dispersive forces, as well as much stronger ionic- and hydrogen-bond interactions, play a key role in the molecular recognition between two molecules forming an inclusion complex. This technique allows resolution of both racemic compounds and conglomerates. However, if the industrial application of optical resolution methods is being considered, it is very important to design new, versatile chiral compounds that can be prepared in both enantiomorphic forms, and can recognize enantio- or diastereoselective organic guests. Of particular interest are those that can be obtained from cheap natural sources.

4 THE MOLECULAR BASIS OF INCLUSION COMPLEXATION

Although, at that time, the term 'supramolecular chemistry' had not yet been coined, the practical potential for inclusion complexation for acetylene alcohol guests **1** and **2** was recognized back in 1968 [12]. Spectroscopic studies showed that **1** and **2** formed molecular complexes with numerous hydrogen-bond donors and acceptors, i.e. ketones, aldehydes, esters, ethers, amides, amines nitriles, sulfoxides and sulfides. Additionally, **1** formed 1:1 complexes with several π-donors, such as derivatives of cyclohexene, phenylacetylene, benzene, toluene, etc. The complexation process investigated by IR spectrometry revealed the presence of OH absorption bands at lower frequencies than those for uncomplexed **1** and **2** [12]. These data, followed by X-ray studies, confirmed that the formation of intermolecular hydrogen bonds is the driving force for the creation of complexes [13].



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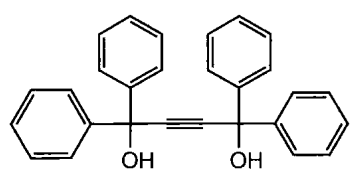

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However, differences in the host to guest ratio and the inability to form aggregates with all guests suggested that–apart from strong H-bond formation – the

shape and size of cavities, the electrostatic interactions and the π–π compatibility were also important factors affecting recognition events. Further X-ray studies confirmed the complex nature of molecular recognition [14]. It was assumed that the primary reason for the complexing ability of these molecules was the steric hindrance of the diphenylhydroxymethyl moiety, which prevented dimerization of the bulky host molecules via formation of intermolecular OH···OH hydrogen bonds. Therefore, small organic guest molecules could be included in the crystal, with the formation of hydrogen-bonded host–guest aggregates. This principle has been used to design new classes of chiral host compounds, where the diphenylhydroxymethyl moiety was a necessary building block. In the early 1980s, numerous new diols and polyols with steric hindrance around hydroxyl groups were synthesized from tartaric acid by Seebach *et al.* (so-called taddols) and were used as chiral auxiliaries in stereoselective synthesis, as catalysts in the preparation of new materials, and as chiral selectors [15]. Independently, in Japan, Toda *et al.* designed various types of new chiral host compounds for the extensive study of nonsolvent processes such as enantioselective organic solid-state reactions and the optical resolution of low-molecular-weight racemic compounds. For each new group of chiral hosts, NMR, UV, FTIR and X-ray crystallographic methods were used to study the structures of the above compounds, in solution and in the solid state, and their numerous molecular complexes [16].

Some of the first, and most versatile hosts are compounds **3a–c**, which can be prepared from optically active tartaric acid. It has been found that they work as chiral selectors in solution [17], and in a powdered state [18]. In the crystal structure of the free host compound (*R,R*)-(−)-*trans*-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.5]decane (**3c**), only one hydroxyl group is intramolecularly hydrogen bonded (Figure 1). As long as no suitable guest molecules are present, the other OH-group remains unbonded in both media.

Since the observed O···H distances and OH···O angles are in the range 1.60–1.62 Å and 165–175°, respectively, formation of this intramolecular H-bond is energetically favourable. The other OH group is free. The same situation is observed in solution, where two OH bands: one for hydrogen-bonded and the other for free hydroxyl groups, were found in the FTIR spectra [19]. It appears that a hydroxy group that is not involved in intramolecular hydrogen bonding shows a strong tendency for interactions with guest molecules that act as hydrogen-bond donors or acceptors. It is interesting that–in contrast to enantiomerically pure compounds–racemates and *meso* forms of such diols often form dimers in the crystals. These compounds have been used as versatile resolving agents with high complexation potential when applied to mixtures of isomers and racemates [17].

In a typical resolution procedure, two equivalents of a racemic compound and one equivalent of a chiral host dissolved in an 'inert' solvent (toluene, benzene or hexane) are left to crystallize. The resulting crystalline product is an inclusion compound with a typical host:guest ratio of 1:1 or 2:1. The guest compound

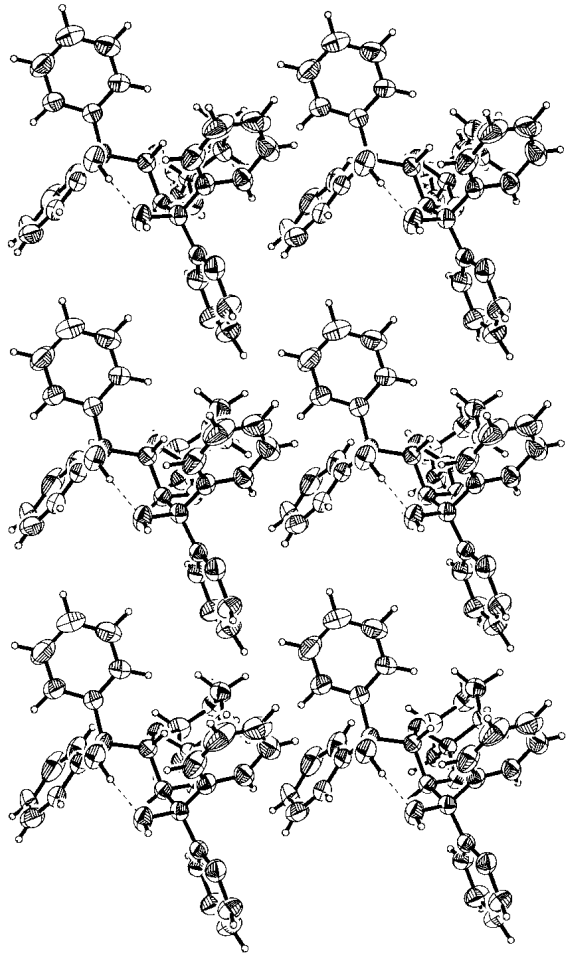


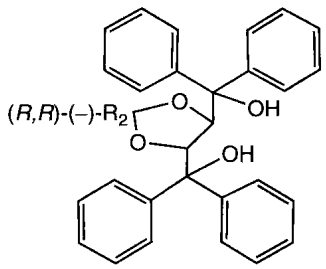
Figure 1 Crystal structure of (*R,R*)-(−)-*trans*-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.5]decane **3c** (courtesy of B. Szczesna).

can be removed from the complex by heating the solid compound *in vacuo*. The opposite enantiomer is left in solution. Inclusion compounds can also be formed by the insertion of guest molecules into channels created by the crystal structure of the host. In such a case, a stirred suspension of the host in hexane or water is added to a racemic mixture of a guest. After filtration of the solid compound, the pure enantiomeric guest is distilled off *in vacuo*.

4.1 Optical Resolution of Alcohols and Epoxides

Another variation of the enantioselective inclusion complexation procedure leading to optical resolution is the application of powdered host compounds in the

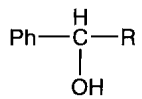
form of a suspension [20]. Chiral hosts **3a–c** are not soluble in hexane and water, and therefore they have been used in suspension in order to resolve oily racemic alcohols **4a–c** and **5a–b**.

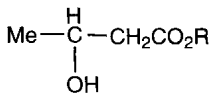


3a: R_2 = Me_2

3b: R_2 =

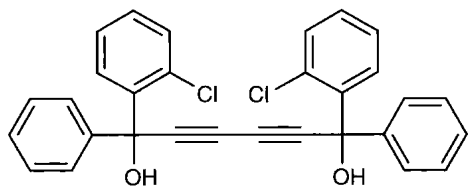
3c: R_2 =





4a: R = Me
4b: R = Et
4c: R = C≡CH

5a: R = Me
5b: R = Et



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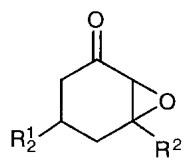

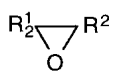

7a: R^1 = H, R^2 = Me
7b: R^1 = R^2 = H
7c: R^1 = R^2 = Me

8a: R^1 = Et, R^2 = CO_2Et
8b: R^1 = Me, R^2 = CO_2Et
8c: R^1 = Me, R^2 = CO_2Me
8d: R^1 = H, R^2 = Ph

For example, when a suspension of powdered optically active host **3a** was mixed with racemic 1-phenylethanol (**4a**) in a 1:1 molar ratio and stirred at room temperature for 6 h, a 2:1 inclusion complex was formed. When the filtered solid complex was heated *in vacuo*, it gave (–)-**4a** (95 % ee, 85 % yield). For the host compounds **3a–c**, approximately the same ee (78–99.9 %) and high yield (75–93 %) could be achieved in the resolution of alcohols of the **4** and **5** series in water and hexane. It has been found that introducing