Chapter 1

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

ZOFIA URBANCZYK-LIPKOWSKA

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

FUMIO TODA

Department of Chemistry, Okayama University of Science, Okayama 700-0005, Japan

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

Separations and Reactions in Organic Supramolecular Chemistry. Edited by F. Toda and R. Bishop
 ISBN: 0-470-85448-0

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].

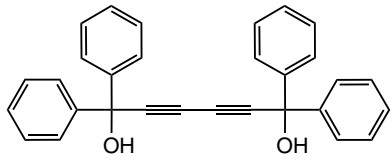
3 INCLUSION PHENOMENA

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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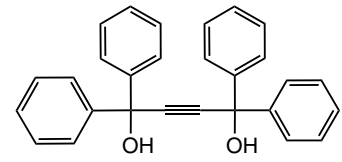

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However, differences in the host to guest ratio and the inability to form aggregates with all guests suggested that – apart from strong H-bond formation – the

shape and size of cavities, the electrostatic interactions and the $\pi-\pi$ 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

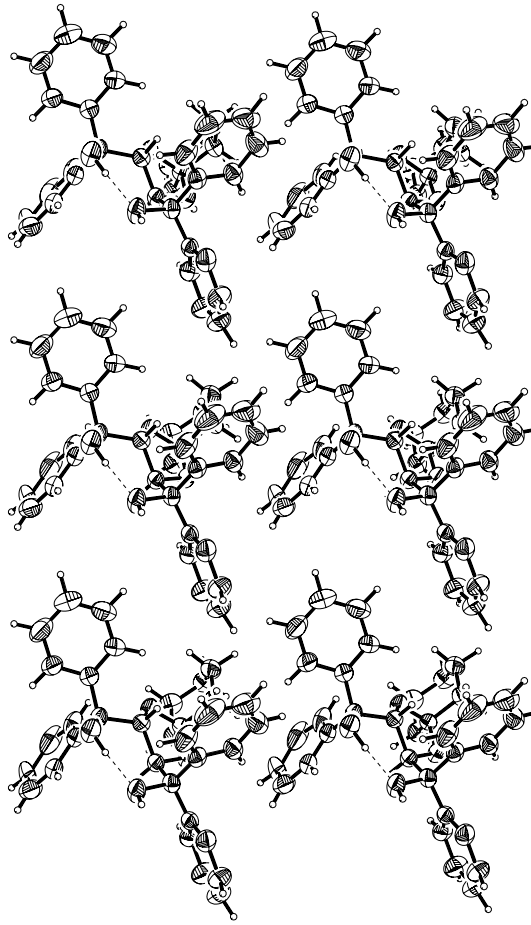


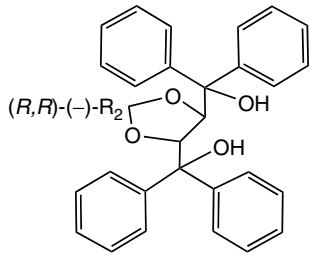
Figure 1 Crystal structure of (*R,R*)-(−)-*trans*-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.5]decane **3c** (courtesy of B. Szczesna).

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

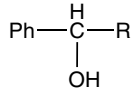
form of a suspension [20]. Chiral hosts **3a–c** are not soluble in hexane and water, and therefore they have been used in suspension in order to resolve oily racemic alcohols **4a–c** and **5a–b**.



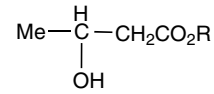
3a: R_2 = Me_2

3b: R_2 =

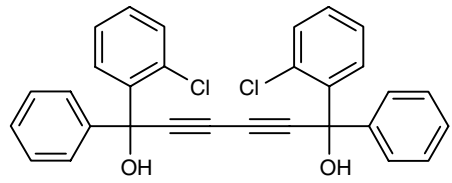
3c: R_2 =



4a: R = Me
4b: R = Et
4c: R = C≡CH



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



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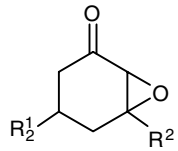
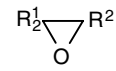


7a: R^1 = H, R^2 = Me
7b: R^1 = R^2 = H
7c: R^1 = R^2 = Me

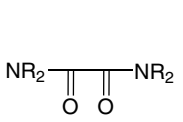


8a: R^1 = Et, R^2 = CO_2Et
8b: R^1 = Me, R^2 = CO_2Et
8c: R^1 = Me, R^2 = CO_2Me
8d: R^1 = H, R^2 = Ph

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

N-hexadecyltrimethylammonium bromide as a surfactant helped to prevent coagulation of the two substrates in aqueous suspension. It is interesting that, although bulky but small molecules of epoxides (**8**) easily penetrated the void space in crystals of **3b–c** and underwent optical resolution, compounds **5a–b** (with long aliphatic chains) and **7b** did not form inclusion compounds. The application of suspension conditions resulted in a very efficient optical resolution, sometimes better than that achieved by the classic formation of complexes by recrystallization of host and guest from a common solvent. For comparison, optical resolution of **4c** by co-crystallization with the host **6** after two recrystallizations gave the crude product at 100 % ee but only 35 % yield [21], in comparison with 57 % and 85 %, respectively, in hexane and water suspension [20].

Among the different types of compounds whose complexation properties have been studied are various amides: linear oxoamide **9** [22], fumaramide **10** [23,24] and methanetricarboxamide **11** [25], biphenyl derivatives **12** [26], and derivatives of tartaric acid **13–16**, that can also be prepared in an optically active form [27]. The above-mentioned chiral hosts have been found to form inclusion complexes with chiral guests **17** and **18**. Molecular recognition between chiral hosts and



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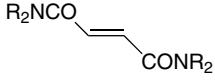

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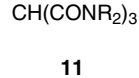

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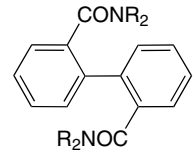

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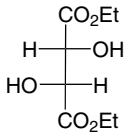
R = iPr, C_6H_6



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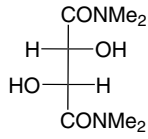

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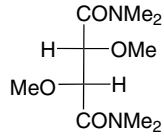

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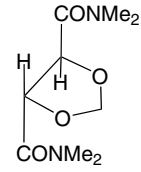

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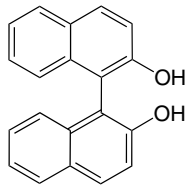

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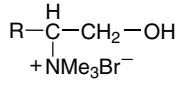


18a: R = Me
b: R = Pr^i
c: R = Bu^i
d: R = Bu^s

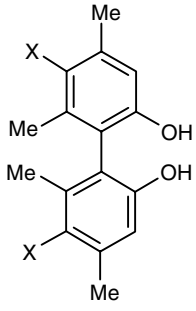
17–18 is enantioselective, and this technique has been used for optical resolution of their racemates. For example, when a solution of (*R,R*)-(+)-**15** in benzene was kept at room temperature with a hexane solution of *rac*-**17**, after 12 h it produced colourless prismatic crystals of a 1:1 inclusion complex of (+)-**15** and (−)-**17**. The crude product recrystallized from benzene was chromatographed on silica gel, using benzene as a solvent, to give (*S*)-(−)-**17** with 100 % ee and 72 % yield. The (*R*)-(+)-**17** was obtained in 100 % ee and 59 % yield by co-crystallization of the filtrate with (*S,S*)-(−)-**15** and subsequent chromatography of the deposited crystals using the above-mentioned conditions. The number of possible chiral auxiliaries is effectively unlimited. Recently, the new chiral host compounds **18a–d** have been obtained from amino acids, which resolved *rac*-**17** very efficiently [28].

4.2 Resolution of Bi-aryl Compounds

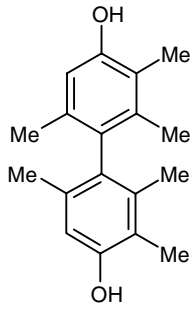
Optical resolution of biphenyl and binaphthyl derivatives is of particular interest in contemporary chemistry. Both families of compounds serve as a source of chiral catalysts used in asymmetrical synthesis [29–31], chiral shift reagents [32] or chiral host compounds for the optical resolution of various racemic guests. The classic preparative method for obtaining optically active **17** describes the formation of diastereoisomeric salts of cyclic binaphthylphosphoric acid with cinchonine, and subsequent reaction with $POCl_3$ followed by hydrolysis [33,34]. Recently, optically active 1,1′-binaphthyl-2,2′-diols have been synthesized by the oxidative coupling of 2-naphthols using *Camelia sinensis* cell culture as a catalytic system [35]. The inclusion complexation method used with such a system does not require application of preparative chemistry or expensive natural resolution agents. Moreover, both enantiomers of **17** can be obtained easily using this method.

Optically active **19a** was previously obtained by inclusion complexation with *N*-benzylcinchonidium chloride **21** [36]. Compound **21** was also a very efficient resolving agent for *rac*-**17** [37]. Crystal structure analysis of a (1:1) complex of **21** and selectively included (+)-**17** showed that the molecular aggregate was associated by formation of a $Cl^- \cdots HO$ hydrogen bond. Racemic compound **20** could be efficiently resolved only by complexation with (*R,R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane **3b**. A crude inclusion complex of 1:1 stoichiometry of **3b** was formed selectively with (+)-**20** in a 2:1 mixture of dibutyl ether/hexane. One recrystallization from the above combination of solvents gave a 34 % yield of the pure complex. Optically active (+)-**20** was obtained by dissolving the complex in 10 % NaOH, followed by acidification with HCl and then recrystallization. The optical purity determined by HPLC (Chiralpack As) was >99.9 %. As far as we know, this is the only report of the resolution of 4,4′-dihydroxybiphenyl derivatives. Conversely, an inclusion

complexation technique using a chiral form of **17** has been reported recently as a very efficient method for the resolution of the important pharmaceutical compound omeprazole (**22**), with an ee of over 99 % for both (*S*)-(−)- and (*R*)-(+)-enantiomers [38].



19a: X = H
b: X = Cl



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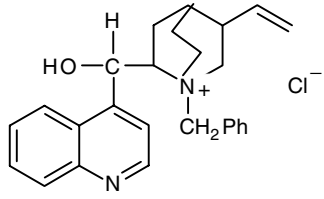

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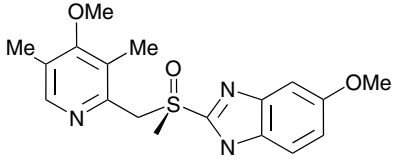


22 (*S*)-(–)-omeprazole

Data from the literature show that even if new convenient preparative methods are being developed for the resolution of 1,1′-binaphthyl-2,2′-diol (**17**) via a phosphite using (−)-menthol as a resolving agent [39], the inclusion complexation method can still compete with these, owing to its simplicity, efficiency, and low cost.

4.3 Resolution of P-Chiral Phosphorus Compounds

Among the preparative methods used for obtaining P-chiral phosphorus compounds, there are procedures involving the use of optically pure auxiliaries like (−)-menthol [40], (−)-ephedrin [41,42], or more recently, the kinetic resolution of 1-hydroxymethylalkylphenylphosphine oxides using *Pseudomonas* or *Candida antarctica* lipases [43]. It has been found that some [(alkyl-substituted)arene] phosphinates and phosphine oxides can also be resolved efficiently by inclusion complexation with optically active 2,2′-dihydroxy-1,1′-binaphthyl (**17**) [44].

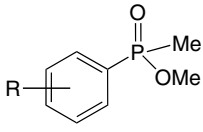
The resolution process however, depends on place of substitution at the benzene ring and on bulkiness of the alkyl residue. Compounds **23** and **26** could not be

Table 1 Optical resolution of compounds **22–25** with (−)-**17** (from ref. 44).

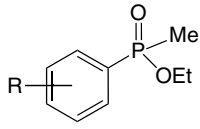
1:1 complex	Enantiomer	ee (%)	Yield (%)
(−)-**17** and **22a**	(+)-**22a**	100	12
22b	(+)-**22b**	100	47
22c	(+)-**22c**	100	31
22d	(+)-**22d**	100	32
24a	(+)-**24a**[a]	>10 %	20
24b	Complex decomposition		–
25a	(−)-**25b**	100	60
25b	No resolution	–	–
25c	(−)-**25c**	100	33
25d	No resolution	–	–

[a] (+)-**20a** was obtained after four recrystallizations followed by decomposition.

resolved using this method. Among the *o*-, *m*-, and *p*-isomers of **22** and **25**, resolution of the *m*-derivatives was best, reaching the yields and ee shown in Table 1. The optical resolution procedure involved formation of 1:1 co-crystals between (−)-**17** and **22a–d**, **24a–b**, and **25a–d** from benzene solution. Twofold recrystallization gave pure crystalline complexes. These were resolved by column chromatography on silica gel using benzene as an eluent, with the yields shown in Table 1. Similarly, the filtrate was treated with a benzene solution of (+)-**17** and the crystalline 1:1 complexes thus obtained were chromatographed on silica gel (benzene).



22a: R = H
b: R = *o*-Me
c: R = *m*-Me
d: R = *p*-Me



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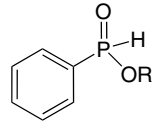
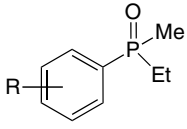
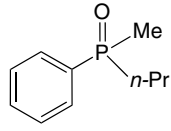


24a: R = Me
b: R = Et



25a: R = H
b: R = *o*-Me
c: R = *m*-Me
d: R = *p*-Me



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The resolution studies have been followed by thorough analysis of X-ray structures of the two isomeric complexes formed by both enantiomers of **17** with

(+)-**22a**. In both structures, oxygen atoms from phosphine oxides in (+)-**22a** were hydrogen bonded with two OH-groups of the neighbouring molecules of binaphthyl. However, in the case of the 1:1 complex of (+)-**17** with (+)-**22a**, the packing pattern was less efficient, resulting in less-dense packing. Similar efficiencies of the optical resolution of alkylaryl-substituted sulfoxides [45,46] and selenoxides [47] have been reported previously.

4.4 Resolution By New Dimeric Hosts Containing 1,4-Diol Units

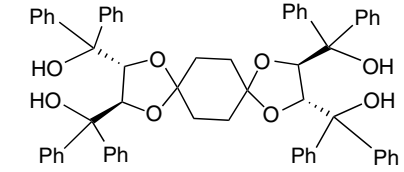
Recently, dimeric hosts containing two 1,4-diol units–**27** and **28**, possessing large hydrophobic areas on both sides of cyclohexane ring, have been designed [48]. A dual action of these hosts might be expected during the molecular recognition process, hydrogen-bond formation with guests bearing groups being hydrogen bond donors or acceptors and enclathration of hydrophobic guests. Table 2 shows that a variety of organic molecules can be accommodated in crystals of hosts **27** and **28**. Host compound **27** has been found to be extremely efficient in the resolution of small chiral alcohols that could not be resolved by the monomeric compound **3c**. The role of multiple recognition sites on the complexing properties of these new host compounds, and their role in chiral discrimination processes, were studied in the solid state using X-ray diffraction methods.

For example, when powdered host **27** was mixed with volatile *rac*-but-3-yn-2-ol (**29**) and left for 24 h, a 1:1 inclusion complex with (+)-**29** was formed. The alcohol can be removed from the complex by heating *in vacuo* yielding 29 of 59 % ee and 77 % yield. A second complexation, followed by distillation *in vacuo*, gave (+)-**29** of 99 % ee and 28 % yield. The best resolution of *rac*-**29** reported to date was by enzymatic esterification, and gave chiral alcohol at 70 % ee and 31 % yield [49]. Host **27** could be used for optical resolution of *rac*-2-hexanol

Table 2 Complexing properties and host:guest ratio for **27** and **28** in comparison with **3c** (from ref. 48).

Guest	**3c**	**27**	**28**
MeOH	1:1	1:2	1:1
Acetone	2:1	1:2	1:1
Cyclopentanone	2:1	1:1	1:1
Ethyl acetate	–[a]	1:1	1:1
γ-Butyrolactone	1:1	1:2	1:1
THF	1:1	1:2	2:1
DMF	1:1	1:2	1:1
DMSO	2:1	1:1	1:1
Toluene	–[a]	1:1	1:1
Cyclohexane	–[a]	1:1	–[a]

[a]No complex was formed.



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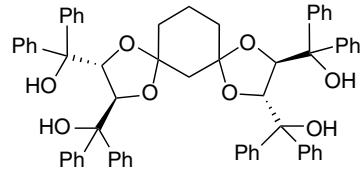

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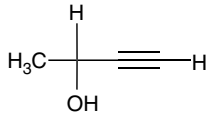

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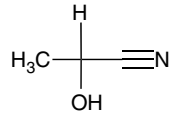

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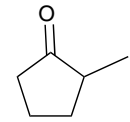

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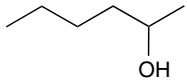

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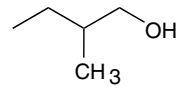


32

(**31**) and *rac*-2-methyl-1-butanol (**32**), after two complexation–distillation steps giving optically pure (+)-**31** and (−)-**32** in 34 % and 5 % yields, respectively. An attempt at optical resolution of 2-methylcyclopentanone (**33**) was less efficient, and although a 1:1 inclusion complex was formed easily, the distilled alcohol gave only 15 % ee.

The X-ray structure of the 1:1 complex of (*R,R,R,R*)-(−)-**27** and (−)-**33** (see Figure 2) shows that the host compound can interact with guests, or via hydrogen-bond formation, or by inclusion of less-polar molecules into the hydrophobic cavity. In the case of (*R*)-(−)-**33**, the carbonyl group of the guest is hydrogen bonded by the OH group of the host and its hydrophobic part fits the hydrophobic cavity of the second host molecule. The same pattern was found in the case of the 1:2 complex of (−)-**27** with amphiphilic (−)-**32**, where two recognition sites worked cooperatively, binding selectively two molecules of (−)-**32**. Hydrophobic cavities contain the lipophilic portion of an alcohol molecule (Figure 3). As a result of (1:2) stoichiometry, no host-to-host hydrogen bonds were found in the latter crystal structure.

4.4.1 Chiral discrimination in the competitive environment of a solvent

Interesting, solvent-dependent chiral discrimination properties have been observed for chiral host **28** [48]. In the absence of toluene, compound **28** forms a 1:2 crystalline complex with *rac*-cyanohydrin (**30**). When both **28** and *rac*-**30** were dissolved in toluene, the crystalline product contained **28** and (+)-**30** and toluene in 1:1:1 ratio. One recrystallization of the complex from toluene gave crystals which upon heating *in vacuo* gave (+)-**30** at 100 % ee and 24 % yield.

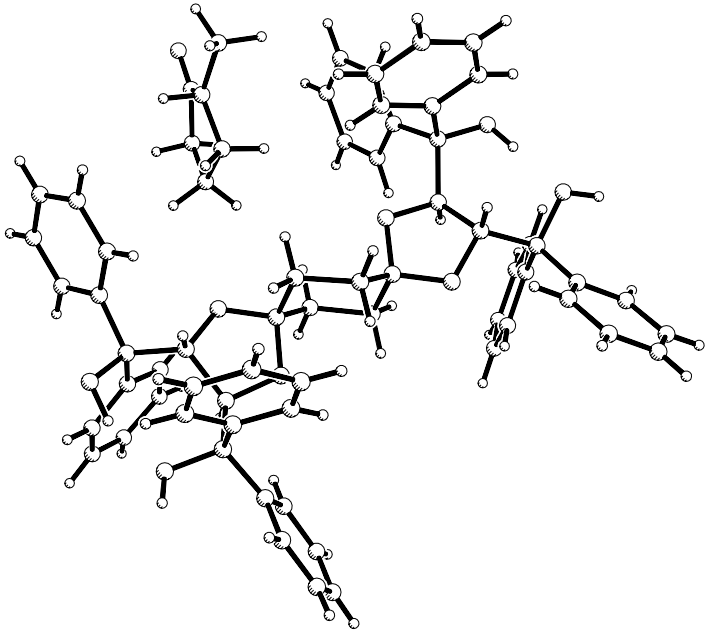


Figure 2 Molecular recognition pattern found in the crystal of the 1:1 complex of (*R,R,R,R*)-(−)-**27** and (−)-**33**. Reprinted with permission from ref. 48. © 2000, Wiley-VCH Verlag GmbH.

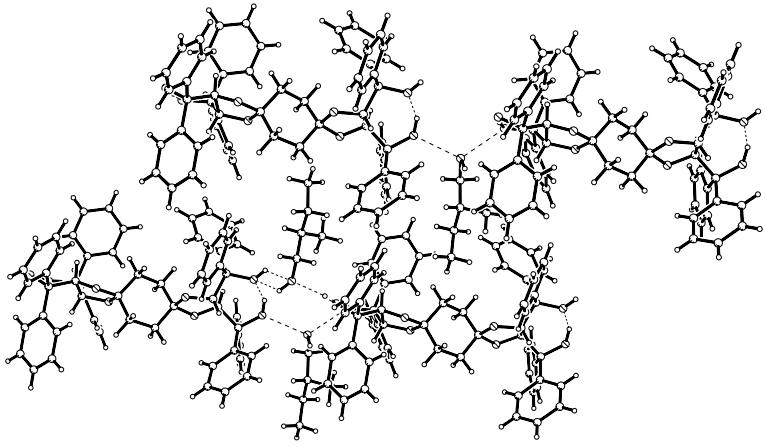


Figure 3 Crystal structure of the 1:2 complex of (−)-**27** and (−)-**32**. Reprinted with permission from ref. 48. © 2000, Wiley-VCH Verlag GmbH.

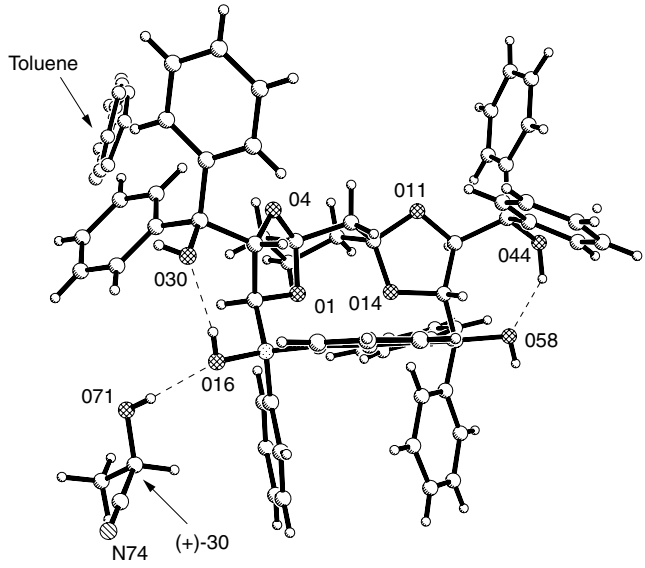
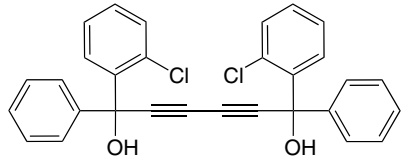
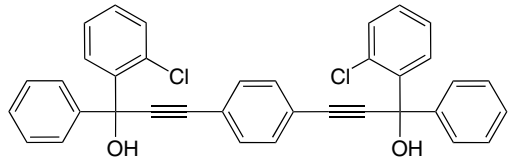


Figure 4 Molecular recognition pattern found in a 1:1:1 complex of (*R,R,R,R*)-(−)-**28** with (−)-**30** and toluene. One enantiomer of cyanohydrine is bound to the enantioselective binding site of the host. The disordered toluene molecule fits well into the hydrophobic cavity. Reprinted with permission from ref. 48. © 2000, Wiley-VCH Verlag GmbH.

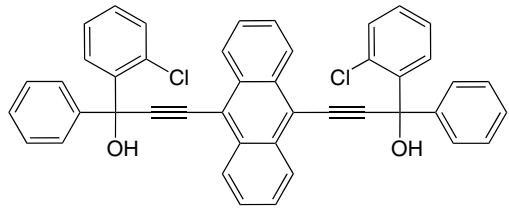
According to X-ray studies, the host **28** has two recognition mechanisms: enantioselective binding via hydrogen-bond formation with hindered hydroxyl groups, and nonselective enclathration into hydrophobic cavities formed in the crystals by numerous phenyl rings. As can be seen in Figures 3 and 4, the same enantiomer of the cyanohydrin is hydrogen-bonded to the alcohol OH group, regardless of whether the complex is formed from the enantiomerically pure or racemic **30**. Phenyl groups can fit into the crystal forming cavities, of the host which can unselectively bind disordered toluene molecules as in the (1:1:1) complex of **28** and toluene (Figure 4) or a molecule of the second enantiomer of **30** ((+)−30 giving a 1:2 complex of **28** with racemic **30**; Figure 5). Solvent-dependent chiral discrimination properties have been found previously, during optical resolution of *rac*-2-methylpiperidine (**36**) by the host **35**. Hosts of the same chirality included (*R*)-(−)-**36** in the presence of toluene, and (*S*)-(+)-**36** in the presence of methanol [50]. X-ray structural analysis of these two crystals revealed that MeOH and (*S*)-(+)-**36** molecules compete for the free proton of the host. Finally, both of them are included in the host lattice via hydrogen bonding in a 1:1:1 ratio. Toluene molecules under the same conditions are repelled and only (−)-**36** forms a 1:1 inclusion complex with the host. Similarly, in toluene, the host (*S,S*)-(−)-**34** formed a crystalline 1:2 complex with (+)-4-hydroxycyclopent-2-enone, (+)-**37**. This high host:guest ratio allowed separation of (+)-**37** at 38 % ee but in 72 % yield.



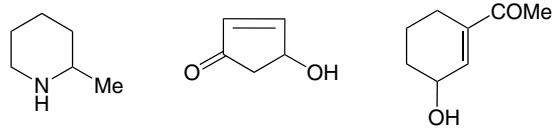
(*S,S*)-(–)-**6**



(*S,S*)-(–)-**34**



(*S,S*)-(–)-**35**



36 **37** **38**

When complexation was carried out in MeOH, a 1:1:1 complex of the host, (−)-**37** and MeOH was formed. Distillation *in vacuo* gave (−)-**37** in 42 % ee and 44 % yield. In the case of complexes formed by the host **28**, the large hydrophobic void space can competitively include a disordered toluene molecule or (−)-cyanohydrin [48]. (*S,S*)-(−)-**6**, which in the solid state forms much smaller hydrophobic cavities, could not resolve *rac*-**36** in either solvent. Under the same conditions, however, it successfully resolved *rac* 3-acetylcyclohex-2-enol, **38**, forming 1:2 complexes in both solvents. From these (+)-**38** was obtained in 40 % ee and 86 % yield, and 66 % ee and 79 % yield, respectively, from toluene and MeOH solutions. The above cases suggest that each of the hosts (**28, 34** and **35**) contains two recognition sites–one enantioselective, located around sterically hindered OH groups, and the other nonspecific, and located in the hydrophobic cavity. If molecules of one enantiomer and a solvent compete for the enantioselective recognition site (with H-bond formation), the enantioselectivity of the host

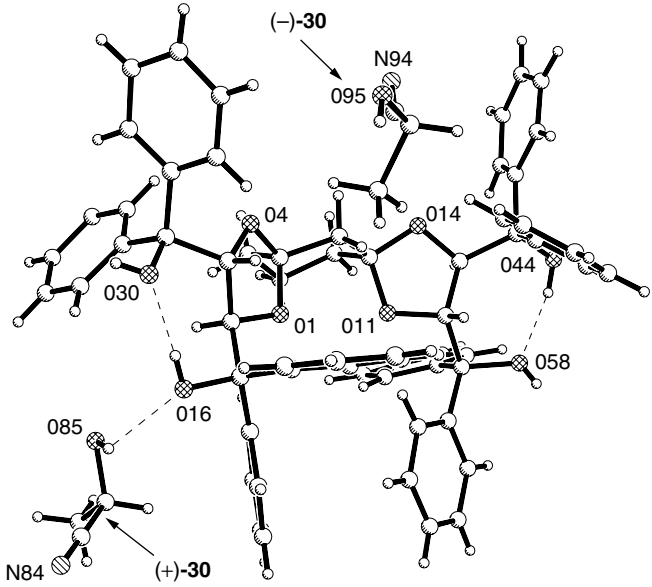
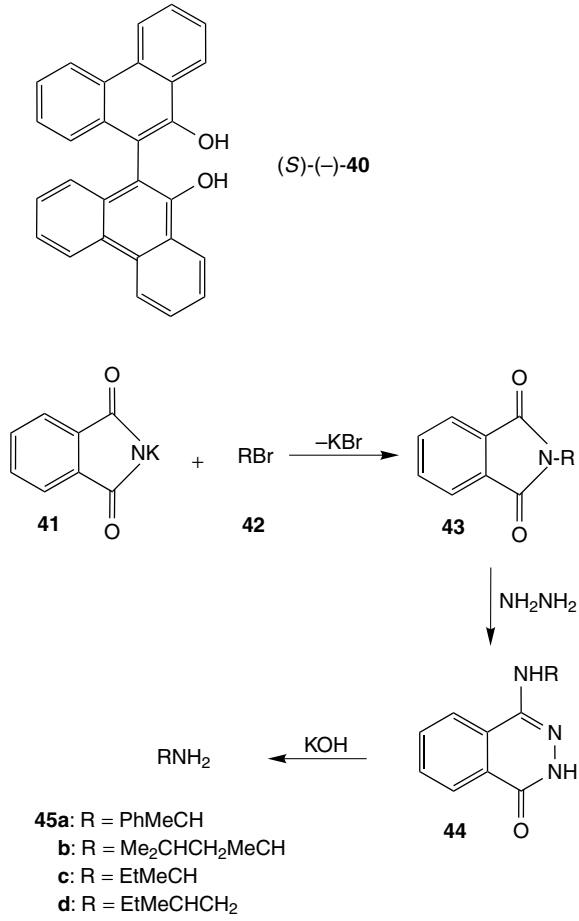


Figure 5 Molecular recognition pattern found in a 1:2 complex between (*R,R,R,R*)-(−)-**28** and *rac* **30**, formed in the absence of toluene. One enantiomer of the cyanohydrine is bound to the enantioselective binding site of the host. The second enantiomer fills the hydrophobic cavity. Reprinted with permission from ref. 48. © 2000, Wiley-VCH Verlag GmbH.

may be changed with a change of solvent. When molecules of one enantiomer and a solvent compete for a space in the nonspecific cavity, they are interchangeable with one another in the crystal cavity, and the enantioselectivity of the host is retained.

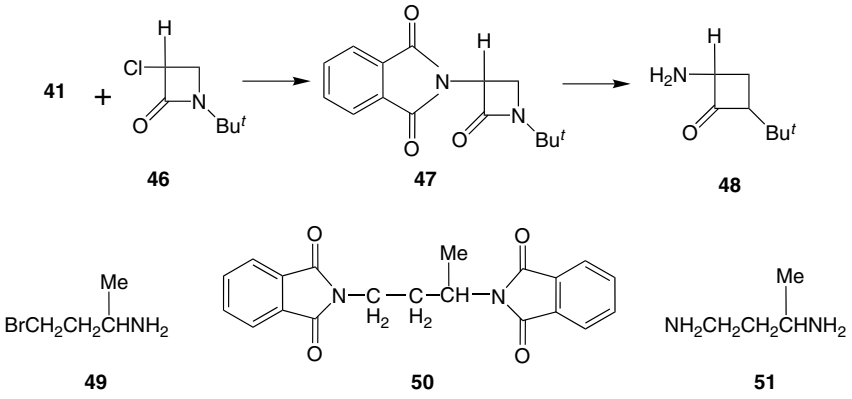
4.5 The Optical Resolution of Reaction Intermediates by Inclusion Complexation

The enantioselective complexation technique can also be applied as one step in the reaction sequence, providing chiral substrates for the next step. We will now discuss the example of Gabriel synthesis between potassium phthalimide **41** and alkyl bromide **42**, which leads to optically active amines (Scheme 1) [51]. Instead of the complicated preparation of chiral alkyl bromides (halides), imides (**43**), which are reaction intermediates, have been resolved. Upon treatment with hydrazine and KOH, these gave optically active amines. The chiral host (*S,S*)-(−)-**6** or the chiral biaryl host (*S*)-(−)-**40** was used for the effective resolution of the intermediates **43**. Racemic mixtures **43a–d** were resolved by complex formation with the host (*S,S*)-(−)-**6** in a mixture of diethyl ether and light petroleum.



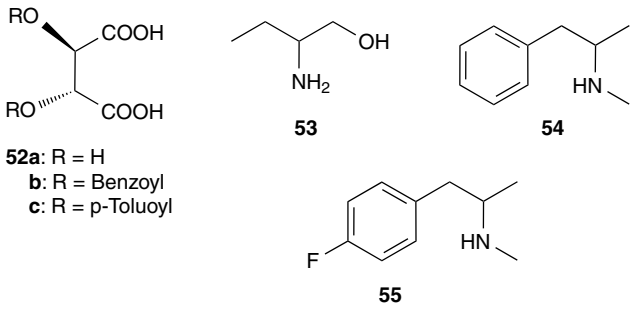
For example (+)-**43a** was obtained after two purifications at 55 % ee and 10 % yield. Treatment of (+)-**43a** with hydrazine and KOH gave (+)-**45a** at 55 % ee and 40 % yield. The chiral host (*S*)-(−)-**40** has been found to be extremely effective as a chiral selector towards comparatively bulky molecules of the phthalimide formed from of 1-*tert*-butyl-3-chloro-azetidin-2-one, **47**. A crystalline inclusion complex of 1:1 stoichiometry was formed between one mole of (*S*)-(−)-**40** and two moles of *rac*-**47** dissolved in benzene/hexane 1:1 solution. After one recrystallization, the complex was chromatographed on silica gel, and the crystalline product was treated with hydrazine. Optically pure (−)-3-amino-1-*tert*-butyl-azetidin-2-one (−)-**47**, was obtained at 100 % ee and 44 % yield [51]. Primary diamines, like 1,3-dibromobutane (**49**), can undergo a similar reaction with potassium phthalimide, yielding diphthalimide, **50**. The complexation process between *rac*-diphthalimide **50** and host (*S,S*)-(−)-**6** gave a 1:1 complex containing (−)-**50**

and (*S,S*)-(−)-**6** at 100 % ee and 42 % yield. Subsequent decomposition of the complex with hydrazine and KOH gave optically pure (−)-**51** at 100 % ee and 50 % yield.



4.6 Optical Resolution with Application of Mixtures of Resolving Agents

Recently, several new findings have been reported in the area of optical resolution methodology. It has been found that the enantiomeric excess of some separation processes does not correlate linearly with the optical purity of the resolving agents. The so-called 'Dutch method', shows, that if the resolving agent belongs to the homologous series, then it is worthwhile trying to accomplish resolution using all the compounds in the series [52]. Applying a mixture of resolving agents, even if they do not show individually good resolving properties, may significantly enhance the effectiveness of enantiomer separation by fractional crystallization. This method has also been found to work in the case of liquid racemates [53]. Elevated yields and enantiomeric enhancement, ee, have been observed in some cases of racemic amines **53–55** resolved with the appropriate mixtures of tartaric acid derivatives **52a–c**. Moreover, this technique could be

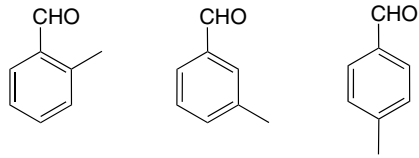


of industrial importance. Although the two above methods are quite new empirical observations with no theoretical explanations, they are assumed to have a common supramolecular background.

5 ISOMER SEPARATION

Inclusion phenomena employing organic hosts with high potency complexation can also be successfully used for the resolution of technical mixtures of isomers. The basic property that qualifies a group of compounds as good selectors is the presence of proton-donors and/or proton-acceptors within the molecule, and the ability, during crystallization, to form host frameworks containing layers, channels and various other types of cavities. On the other hand, the host structure has to be flexible enough to accommodate a variety of guests. Several techniques are commonly used in evaluating the complexing abilities of the host and for selecting the best complexor. The competitive experiments can be performed in parallel [54], or in a so-called cocktail [55] fashion. They are based on assumption that the complex will be preferentially formed with the best guest compound. The thermodynamic and kinetic parameters of the host–guest complexation process can be studied using various techniques, including NMR, fluorescence and UV-titration, differential scanning calorimetry, thermogravimetry, etc. These results are usually discussed from the viewpoints of size and shape complementarity, the induced-fit concept, and cooperation between several types of weak noncovalent interactions. Therefore, X-ray diffractometry remains one of the best tools to give an insight into the solid-state structure of the hosts and their supramolecular complexes. The above studies show that, within certain host types, binding constants towards isomeric compounds can be enthalpy- or entropy-driven, and can depend on the solvent used and the ratio of the concentrations of the isomeric guests [56–58].

One of the first examples is the use of achiral 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (**1**) for resolution of a mixture of *o*-, *m*- and *p*-methylbenzaldehydes (**56–58**). It showed that an inclusion complex at a 1:1 ratio was formed selectively with the *p*-isomer **58**. The complexant was effectively separated from the complex by heating *in vacuo*, and *p*-methylbenzaldehyde was obtained at 100 % purity and 96 % yield [59].

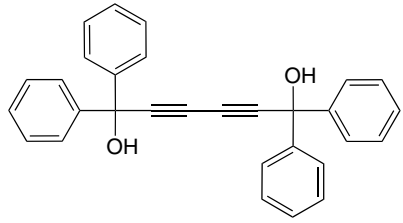


56 **57** **58**

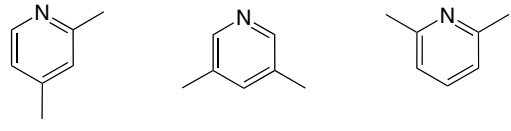
The *o*-isomer **56** was distilled off from the remaining filtrate at 99 % purity and 90 % yield. The above processes are solvent-dependent, and therefore polar

solvents like water and less polar ones, such as benzene, toluene or a mixture of ether-light benzene, etc., should be tried in every individual case. It was observed that selectivity of complexation could be changed drastically by changing the solvent [57]. The purity of the obtained guest can be significantly improved by repeating the crystallization several times.

The host compound **17** has been used for separation of alcohols or NaOH from aqueous solution [60]. One interesting application of inclusion complexation is the separation of natural compounds from natural sources, e.g. caffeine from tea leaves and nicotine from tobacco leaves – making this technique industrially feasible [61]. Similarly, host **1** was used for the separation of mono- and disubstituted naphthalenes [62]. More complete information about selectivity rules involving host **1** and isomeric 2,4-, 3,5- and 2,6-lutidines (**59–61**) was obtained in competition experiments carried out between pairs of gust compounds [63]. In these experiments, a small quantity of the host was added to 11 vials in which the molar fractions of the two isomeric complexors were varied from 0 to 1. The resulting crystalline product was analysed by gas chromatography to determine the composition of the guest compounds. The experiments were repeated for all three combinations of guests. The crystal structures of three inclusion complexes formed with the isomeric guests were analysed independently from this. For each crystal structure the lattice energy was calculated, using the atom–atom potential with coefficients given by Gavezzotti [64] and the hydrogen-bonding potential according to Vedani and Dunitz [65]. The results show that 3,5-lutidine (**60**) is selectively included in the host lattice in the presence of **59**. Competition between **59** and **61** is concentration dependent; 2,6-lutidine (**61**) is favoured when its molar fraction exceeds 0.2. Under the same conditions, **60** is favoured over **61**. In crystal structures, host **1** is always hydrogen bonded to two guest molecules. The lattice energy calculations agree with the complexation preferences.

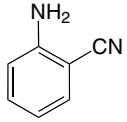


trans-**1**



59 **60** **61**

Similarly, competition experiments on the aminobenzonitrile isomers **62–64** showed **62** > **63** > **64** preferences towards host **1** [66]. In this case, complexing selectivity was also concentration dependent. Lattice energy calculations performed for the crystallographically obtained models agreed well with the results of the competition experiments. Additionally, when there were no pronounced selectivity differences, both hosts were included in the host framework.



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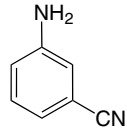
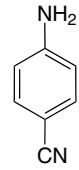
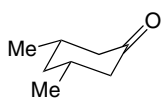


63

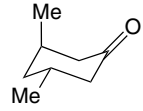


64

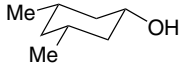
The versatility of host **1** allows discrimination not only between isomeric planar, aromatic compounds but also between quite bulky derivatives of cyclohexane. For example, host **1** will include selectively the diequatorial isomer of 3,5-dimethylcyclohexanone (**65**), but not **66** or isomer **67** from a mixture of **67–69** [67].



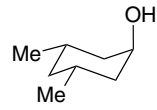
65



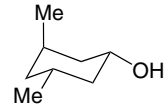
66



67

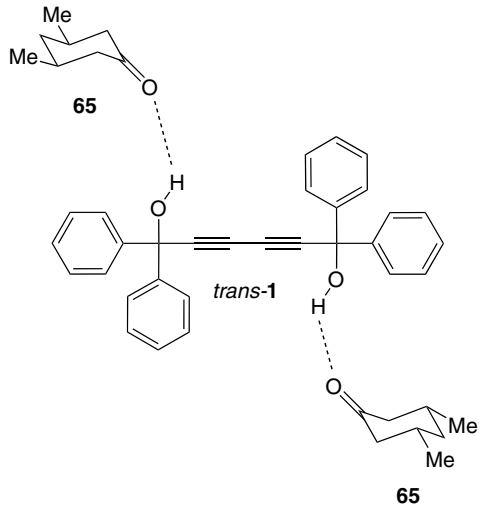


68



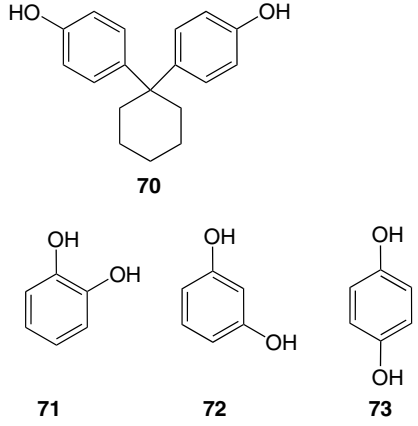
69

It can be seen from the X-ray structure of the 1:2 complex of **1** and **65** that the two hydroxyls of the hosts are hydrogen-bond donors for the two carbonyl groups of the guest. The crystal is a collection of trimeric aggregates bound via two intermolecular hydrogen bonds (Scheme 1). In the case of a 1:2 complex of **1** and **67**, two guest molecules donate their H-atoms and form intermolecular hydrogen bonds. In both cases, the isomers that were included into the host framework were those with smaller space-demands. Due to the elongated structure of these guests, hydrogen bonds formed with a sterically constrained host were more energetically favourable.



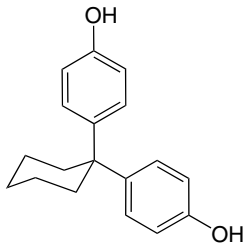
Scheme 1

Recently, an interesting example of the resolution of isomeric benzenediols **71–73** by the host **70**, performed in solution under solvent-free conditions has been reported [68]. Although in aqueous solution the *para*-isomer was strongly favoured by a suspension of powdered **70**, no complexation occurred when **70** and **73** were ground together.



Most of the isomeric guests are achiral compounds, and therefore achiral hosts with variable properties are effective enough to selectively form a molecular complex with one of these hosts. 2,2′-Dihydroxy-1,1′-binaphthyl **17**, has been found to

form inclusion complexes of various geometries with air- and moisture-sensitive alkali-metal hydroxides [60]. This organic–inorganic hybrid forms crystals with large hydrated domains made up by several water molecules (six to eight). This technique will allow separation of these hydroxides from aqueous solution. Small variations in the chemical structure of a host can change its complexing selectivity. This is observed in the case of the two hosts **74** and **75**. Whereas the latter selectively recognizes *p*-cresol and easily forms a 1:1 complex from benzene, under the same conditions the former selectively forms a 1:1 complex with *m*-cresol [69].



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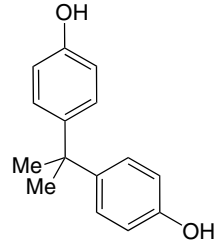

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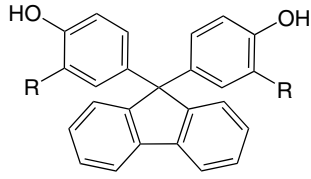


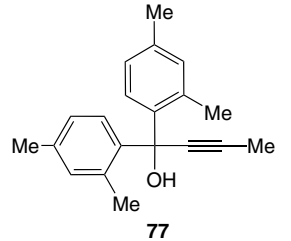
76a: R = H
b: R = Me

Further modification of **74** by introducing a bulky fluorene residue gave two compounds: **76a** and **76b** [70]. Of particular interest is host **76b**, which forms inclusion complexes with volatile guests such as MeOH, Me_2CO, MeCN, DMSO, and DMF, as well as with low-boiling-point dimethyl (bp −25 °C) and diethyl ethers (bp 35 °C). This makes it possible to store these complexes at room temperature, for easy release on heating. X-ray studies have shown markedly different construction of the host framework. Its versatility was studied using DSC measurements. It appears that the 1:1 complex of **76b** with MeCN decomposes at 95 °C, releasing a MeCN molecule (endothermic peak), then rearranges itself at 130 °C (exothermic peak), and finally melts at 225 °C.

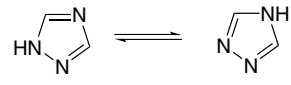
The above examples show that resolution of isomeric mixtures is possible both in solution and under solvent-free conditions. The resolution process is driven by multicentre recognition events in which solvent molecules play an important role.

6 STABILIZATION OF TAUTOMERIC FORMS BY INCLUSION COMPLEXATION

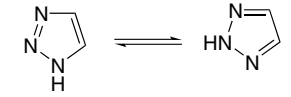
The problem of tautomeric equilibria is of general interest, because it concerns the isomeric situation in natural systems like the nucleic acid pairs in DNA and RNA, ligand–receptor interactions, and, in general, the reactivity of organic compounds [71]. This problem has been approached both experimentally in solution by ^{1}H NMR and UV spectroscopy, in the gas phase, as well as theoretically by conventional *ab initio* Hartree–Fock and density functional theory (DFT) calculations [72,73]. It has been found that, due to specific noncovalent interactions during the inclusion complexation process, a particular tautomer can be selected or even generated during crystallization [74]. For example, host **77** is extremely efficient at differentiating between tautomers of 1,2,4-triazole-**78** (a 1:1 complex between **77** and **78a**) and 1,2,3-triazole-**79** (a 1:1 complex between **77** and **79a**), whereas both tautomers of methyl 3(5)-methylpyrazole-**80** have been included into the 1:1:1 complex with host **77** [75,76].



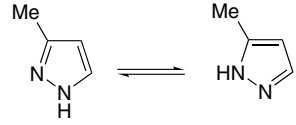
77



78a **78b**



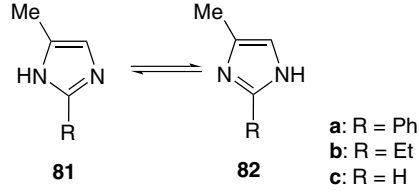
79a **79b**



80a **80b**

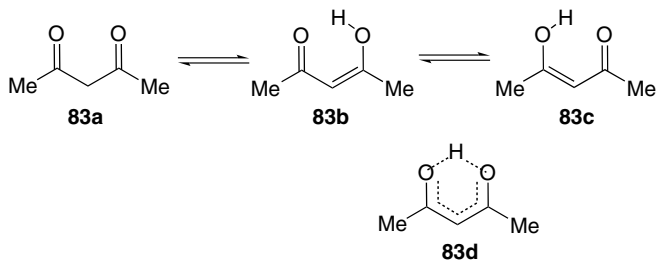
Modifications of the tautomeric equilibrium and therefore the pK_a value, through hydrogen-bond formation and the electrostatic solvation effects of imidazole, are

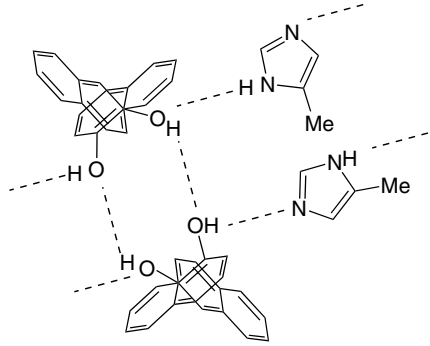
fundamental for explaining the mechanism of several biological processes involving histidine residues. As molecular recognition is solvent and host specific, co-crystallization of 2-ethyl-5-methylimidazole **81** and 2-ethyl-4-methylimidazole **82** with two other hosts – binaphthyl **17** and versatile host **1** – was attempted. In this case, recrystallization of **81b** and **1** from diethyl ether gave a 2:1:1 complex of **81b** and **17** and a solvent molecule [77].



The tautomer **82c** of 3-methylimidazole, however, was found in the 1:1 complex with *rac*-**17**. X-ray structure analysis of the above inclusion complex showed that molecules of **82c** act as hydrogen-bond donors and acceptors between two dimeric assemblies of binaphthyl molecules (Scheme 2). Methyl groups are located in the vicinity of the dimeric host. However, steric hindrance of this methyl group is less important for the energetics of crystal construction than formation of two hydrogen bonds.

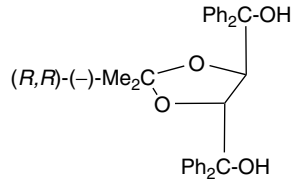
The keto–enol equilibrium of the 1,3-diketones has been the subject of intensive studies using various physical techniques and theoretical calculations [78–80]. Recently, X-ray crystal analysis of acetylacetone (**83**) was carried out at 110 K, and it was found that it exists as an equilibrium mixture of the two enol forms **83b** and **83c** [81]. Room-temperature studies show an acetylacetone molecule with the enolic H-atom centrally positioned, which can be attributed to the dynamically averaged structure **83d**. Application of a crystal engineering technique showed that a 1:1 inclusion complex of **83** can be formed with 1,1′-binaphthyl-2,2′-dicarboxylic acid in which the enol form is stabilized by a notably short intramolecular hydrogen bond [82].





Scheme 2

Another example is the 1:1:1 complex of acetylacetone with the host **74** and a water molecule in which again the enol form was observed. In the case of the 2:2 complex of acetylacetone with (*R,R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2,2′-dimethyl-1,3-dioxacyclopentane **84**; however, a crystal measured at room temperature showed a disordered enolic proton, i.e. the presence of two enol forms. The same complex measured at 100 K revealed the pure enol form for both symmetrically independent molecules of acetylacetone [83]. The geometry of the enolic molecules resembled that obtained by gas-phase electron diffraction studies at room temperature [84].



84

The above examples show that proton transfer resulting in keto-enol tautomerism cannot be studied separately from the environment. The equilibrium between keto and enol forms, both in solution and in the solid state is a derivative of numerous noncovalent interactions that can stabilize a particular isomer. In this context, host–guest chemistry can shed more light towards understanding of the proton-transfer mechanism in biological systems.

7 CONCLUSIONS

Recent interest in the preparation of enantiopure compounds both in the laboratory and on an industrial scale has created the need for new synthetic methodologies

and efficient resolution processes. In particular, the optical resolution process is currently one of the most frequently investigated. The examples presented show that supramolecular concepts of host–guest chemistry with application to solid-state techniques could be used for designing new chiral host molecules. One of the characteristic features of these chiral host compounds is the property of optical resolution of a wide range of racemic guests. The resolution process is accomplished by the formation of inclusion complexes selectively with one enantiomer of the resolved compound, followed by chemical decomposition of the complex, distillation under low pressure, or fractional distillation. Complex formation is driven mostly by construction of the hydrogen-bonding network between host and guest molecules in the solid state. There is experimental evidence that protonic solvents may strongly influence chiral selection. Investigation of the resolution process showed unexpectedly that, for the designed host compounds, chiral resolution is efficient also in the solid state or in suspension media, giving optical purity around 100 % and good yields. The rapid movement of guest molecules within the solid-state structure of the host is of particular interest. The chiral recognition process depends on the solid-state host structure, the character of the solvent used and the guest topography. Although the effective optical resolution of a new class of compounds is a matter of trial and error, there are already several versatile chiral host compounds that can be tried first. There is continuous need to design new, chiral host compounds capable of efficiently resolving racemates and isomeric mixtures of higher molecular weight compounds. As it has been shown, the chemistry of inclusion compounds also offers the opportunity of isomer separation and the generation of particular keto-enol isomers. From this perspective, it is reasonable to look for new types of versatile synthons, allowing both strong hydrogen bonding and enclathration opportunities.

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