Separations and Reactions in Organic Supramolecular Chemistry

Perspectives in Supramolecular Chemistry Volume 8

Edited by

FUMIO TODA Okayama University of Science, Japan

AND

ROGER BISHOP University of New South Wales, Sydney, Australia



Separations and Reactions in Organic Supramolecular Chemistry

Editorial Board

Founding Editor

J.-M. Lehn, Collège de France, Chimie des Interactions Moléculaires, 11 Place Marcelin Berthelot, 75005 Paris, France

Editors

C.J. Burrows, Office 3152 HEB, Department of Chemistry, University of Utah, 315 S. 1400 East, RM Dock, Salt Lake City, UT 84112, Utah, USA

G.R. Desiraju, University of Hyderabad, School of Chemistry, Hyderabad 500046, India

A.D. Hamilton, Yale University, Department of Chemistry, New Haven, CT 06520, USA

D. Hilvert, Laboratorium für Organische Chemie, ETH Zentrum, Universitätsstrasse 16, 8092 Zürich, Switzerland

D.N. Reinhoudt, University of Twente, Faculty of Chemical Technology, P.O. Box 217, NL-7500 AE Enschede, The Netherlands

J.-P Sauvage, Université Louis Pasteur, Institut le Bel, 4 Rue Blaise Pascal, F-67070 Strasbourg, France

Former Editors

J.-P. Behr, Faculté de Pharmacie. Université Louis Pasteur, Strasbourg, B.P. 24, F-67401 Illkirch, France

T. Kunitake, Kyushu University, Faculty of Engineering. Hakozaki, Fukuoka 812, Japan

Separations and Reactions in Organic Supramolecular Chemistry

Perspectives in Supramolecular Chemistry Volume 8

Edited by

FUMIO TODA Okayama University of Science, Japan

AND

ROGER BISHOP University of New South Wales, Sydney, Australia



Copyright © 2004	John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England
	Telephone (+44) 1243 779777
Email (for orders and orders our Home Page of the second s	customer service enquiries): cs-books@wiley.co.uk on www.wileyeurope.com or www.wiley.com
All D' 1/ D 1 N	

All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning or otherwise, except under the terms of the Copyright, Designs and Patents Act 1988 or under the terms of a licence issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1T 4LP, UK, without the permission in writing of the Publisher. Requests to the Publisher should be addressed to the Permissions Department, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England, or emailed to permreq@wiley.co.uk, or faxed to (+44) 1243 770620.

This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the Publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

Other Wiley Editorial Offices

John Wiley & Sons Inc., 111 River Street, Hoboken, NJ 07030, USA

Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons Australia Ltd, 33 Park Road, Milton, Queensland 4064, Australia

John Wiley & Sons (Asia) Pte Ltd, 2 Clementi Loop #02-01, Jin Xing Distripark, Singapore 129809

John Wiley & Sons Canada Ltd, 22 Worcester Road, Etobicoke, Ontario, Canada M9W 1L1

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Library of Congress Cataloging-in-Publication Data

Separations and reactions in organic supramolecular chemistry / edited by Fumio Toda and Roger Bishop.
p. cm. – (Perspectives in supramolecular chemistry ; v. 8)
Includes bibliographical references and indexes.
ISBN 0-470-85448-0 (cloth : alk. paper)
1. Supramolecular chemistry. 2. Chromatographic analysis. 3.
Chemical reactions. I. Toda, Fumio. II. Bishop, Roger. III. Series.
QD878 .S47 2004
547'.1226 – dc22
2003020628

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0-470-85448-0

Typeset in 10/12pt Times by Laserwords Private Limited, Chennai, India Printed and bound in Great Britain by Antony Rowe Ltd, Chippenham, Wiltshire This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

Contents

C	Contributors Preface	
Pı		
1	Inclusion Complexation as a Tool in Resolution of Racemates and Separation of Isomers Zofia Urbanczyk-Lipkowska and Fumio Toda	1
2	Enantiomer Ordering and Separation During Molecular Inclusion Roger Bishop	33
3	Molecular Recognition of Crystalline Dipeptides and Its Application to Separation Katsuyuki Ogura and Motohiro Akazome	61
4	Separation of Isomers and Enantiomers by Bile Acid Derivatives Mikiji Miyata, Nungruethai Yoswathananont, Kazunori Nakano and Kazuki Sada	87
5	Physicochemical Studies of Separation of Isomers by Supramolecular Systems Luigi R. Nassimbeni	123

Contents

6	Regioselective Synthesis of Fullerene Derivatives and Separation of Isomers of the Higher Fullerenes L. Echegoyen, M. A. Herranz, F. Diederich and C. Thilgen	137
7	Selective Reactions in Inclusion Crystals Zofia Urbanczyk-Lipkowska and Fumio Toda	173
8	Supramolecular Control of Reactivity in the Solid State Using Linear Templates Leonard R. MacGillivray	185
9	Development of a New Biocide as an Inclusion Complex Minoru Yagi, Ayako Sekikawa and Tetsuya Aoki	205
Cumulative Author Index		221
Cu	umulative Title Index	227
Inc	dex	231

Contributors

Motohiro Akazome, Department of Materials Technology, Faculty of Engineering, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263–8522, Japan

Tetsuya Aoki, Kurita Water Industries Ltd, 4-7 Nishi-Shinjuku, 3-Chome, Shinjuku-ku, Tokyo 160–8383, Japan

Roger Bishop, School of Chemical Sciences, University of New South Wales, UNSW Sydney NSW 2052, Australia

François Diederich, Laboratorium für Organische Chemie, ETH-Hönggerberg, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

Luis Echegoyen, Department of Chemistry, Clemson University, 219 Hunter Laboratories, Clemson, SC 29634-0973, USA

M A Herranz, Department of Chemistry, Clemson University, 219 Hunter Laboratories, Clemson, SC 29634-0973, USA

Leonard R MacGillivray, Department of Chemistry, University of Iowa, 323B Chemistry Building, Iowa City, IA 52242-1294, USA

Mikiji Miyata, Department of Material and Life Science, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565–0871, Japan

Kazunori Nakano, Nagoya Municipal Industrial Research Institute, 3-4-41, Rokuban, Atsuta-ku, Nagoya 456-0058, Japan

Luigi R Nassimbeni, Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa **Katsuyuki Ogura**, Department of Materials Technology, Faculty of Engineering, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263–8522, Japan

Kazuki Sada, Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812–8581, Japan

Ayako Sekikawa, Kurita Water Industries Ltd, 4-7 Nishi-Shinjuku, 3-Chome, Shinjuku-ku, Tokyo 160–8383, Japan

C Thilgen, Laboratorium für Organische Chemie, ETH-Hönggerberg, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

Fumio Toda, Department of Chemistry, Okayama University of Science, Ridaycho 1-1, Okayama, 700-0005, Japan

Zofia Urbanczyk-Lipkowska, Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka Str. 44/52, Warsaw, Poland

Minoru Yagi, Kurita Water Industries Ltd, 4-7 Nishi-Shinjuku, 3-Chome, Shinjuku-ku, Tokyo 160–8383, Japan

Nungruethai Yoswathananont, Department of Material and Life Science, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565–0871, Japan

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

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 © 2004 John Wiley & Sons, Ltd 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 $-\alpha_D$. 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 'nonsuperposable 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].



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 $3\mathbf{a}-\mathbf{c}$, 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 ($3\mathbf{c}$), 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 $O \cdots H$ distances and $OH \cdots O$ angles are in the range 1.60-1.62 Å and $165-175^{\circ}$, respectively, formation of this intramolecular Hbond 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-dioxa-spiro[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 $3\mathbf{a}-\mathbf{c}$ are not soluble in hexane and water, and therefore they have been used in suspension in order to resolve oily racemic alcohols $4\mathbf{a}-\mathbf{c}$ and $5\mathbf{a}-\mathbf{b}$.



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



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 POCl₃ 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⁻ ··· 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].



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

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 decom	position	_
25a	(−)- 25b	100	60
25b	No resolution	_	_
25c	(−) -25c	100	33
25d	No resolution	_	_

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

 $^{a}(+)$ -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).



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-2ol (**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

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	_ <i>a</i>	1:1	1:1
Cyclohexane	_a	1:1	_a

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

^aNo complex was formed.



(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 hydrogenbond 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 hydrogenbonded 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.