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Design and selection of host molecules in the resolution by inclusion compound formation. Molecular recognition by Tröger's base and its derivatives

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DESIGN AND SELECTION OF HOST MOLECULES IN THE RESOLUTION BY INCLUSION COMPOUND FORMATION. MOLECULAR RECOGNITION BY TRÖGER'S BASE AND ITS DERIVATIVES

by

JIAN ZHONG QI

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirement for the degree of Doctor of Philosophy, The City University of New York

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ABSTRACT

DESIGN AND SELECTION OF HOST MOLECULES IN THE RESOLUTION BY INCLUSION COMPOUND FORMATION. MOLECULAR RECOGNITION BY TRÖGER'S BASE AND ITS DERIVATIVES

by

Jian Zhong Qi

Mentor: Professor Samuel H. Wilen

Tröger's base, **79**(TB), has been resolved by diastereomeric salt formation with a strongly acidic resolving agent, **81**. The resolution is attended by an asymmetric transformation. Enantiopure TB acts as a chiral solvating agent (CSA) in ^1H NMR toward several secondary and tertiary alcohols. The configuration of TB has been determined by X-ray crystallography on salt **82a** to be (+)-(5S, 11S) which is contrary to that previously established from the circular dichroism spectrum by the method of exciton chirality.

Enantiopure (+)-TB methosulfate **107a** formed *in situ* resolves eight out of nine selected alcohols by clathrate formation. The enantiomeric excess (ee) observed is 10-80%. In contrast, enantiopure TB does not act as a host toward racemic alcohols in resolution by inclusion compound formation.

Compound **107a** formed *in situ* acts as CSA toward all alcohols (nine) tested. Anisochrony is observed clearly by ^1H NMR in aliphatic alcohols, 2-butanol (**92**) and 4-octanol (**93**).

The chemical shift difference ($\Delta\delta$) between two sets of splitting peaks is larger in **107a** as CSA than in **79**. Inclusion phenomena have also been observed with **82a** and **114** serving as hosts.

Hydrogen bonding, aryl-aryl interaction, the ionization (onium salt formation), the size of the host lattice void, the rigid skeleta and the molecular symmetry of the host are all considered as potential contributors to the molecular recognition leading to inclusion compound formation.

Hydrogen bonds play an important role in resolution by inclusion compound formation. However, a balance of all binding forces controls the results of resolution by inclusion compound formation.

Host compounds with more O, and N atoms functional groups; rigid geometry; benzene rings and triple bonds seem favorable for inclusion compound formation and molecular recognition. Compound **107a** is considered to have a majority of these beneficial features.

To my wife and daughter

Acknowledgements

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A very special acknowledgement goes to my wife and my daughter who shared with me the joy and disappointment of my whole graduate studying and my life. My wife has been consistently supportive and warmly encouraging all these years. She contributed a great effort toward correcting and typing this thesis. My success in writing this thesis closely tied to my wife's constant love and support.

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Chapter I

Optical Resolution through Inclusion Compound Formation

1.1 Introduction & Historical Background

Inclusion compounds have been described as combinations of complete organic molecules that are united spatially, leaving unaffected the bonding systems of the components.[1] Actually, inclusion is believed to be the result of the ability of one compound, because of its peculiar stereochemical properties and possibly its polarity, to enclose a second molecule spatially. The inclusion compound which forms will have a stability largely attributable to the way in which the molecules involved fit together in space. When inclusion occurs, the host and guest molecules must be properly oriented with respect to one another.

In recent years, more and more research activity has been directed to understanding the nature of what is called "weak intermolecular interaction" in a broad sense. This refers to weak noncovalent bonds involving neutral organic molecules. Chemists, in fact, no longer just aim at the synthesis of compounds via ionic, covalent, coordinate covalent linkage or the clarification of chemical reaction mechanism, but have been inspired to search for artificial host mimics possessing specific weak interactions.

The chemistry of inclusion compounds has a long history.[2] Confirmed accounts of the preparation of such chemical species date back to the beginning of the nineteenth century. At that early time chlorine clathrate hydrate was first reported as an inorganic inclusion compound by Davy in 1811.[2] The formation of organic clathrate inclusion compounds was first discovered in the middle of the past century.[3, 4]

Inclusion phenomena are central to biological processes. Enzymic catalysis and inhibition,[5, 6] immunological response, storage and retrieval of genetic information, replication, biological regulatory function, drug action, and ion transfer[7] are all based on structure recognition taking place when dissimilar molecules interact without forming covalent bonds. For instance, transfer of one carbon involves this structural recognition, such as the transfer[7] of a methyl group to homocysteine from N^5-methylterahydrofolate can be generated in a reaction catalyzed by homocysteine methyltransferase.[8] In the chemotherapeutic treatment of cancer, for example, the replication of DNA is inhibited, in part, by intercalative binding of drugs.[9]

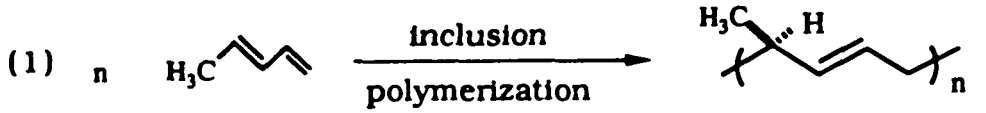
The structures of compounds originating in nature have long inspired and challenged organic chemists to develop laboratory syntheses of analogs, e.g., a newer challenge provided by the biotic world is the design and synthesis of new compounds that mimic some of the properties of biotic systems. Any response to this challenge depends directly on an understanding of structural recognition in inclusion compound formation. The potential fruits of the

development of a field of synthetic organic inclusion compounds are obvious.

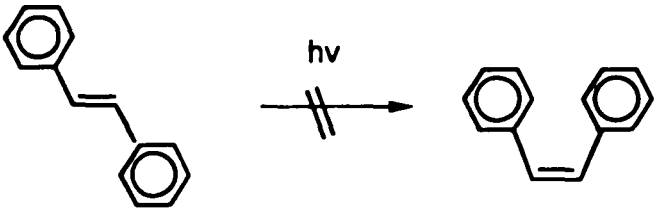
An enormous amount of work done by chemists in the field of inclusion compound formation has resulted in a wide range of applications. For instance, host-guest interactions permit the separation of mixtures of substances according to the molecular shape and size using reversible crystallization-solution processes,[10] chromatographic procedures,[11] or suspension methods.[12] Host-guest selectivities are able to separate aromatic compounds from other compounds in multicomponent hydrocarbon mixtures,[10] to separate branched from normal hydrocarbons,[13] and to fractionate geometrical isomers[14] and isotopomers.[15] There is a large body of literature devoted to the application of inclusion compounds to the storage and handling of toxic, radioactive, or explosive substances,[16] to the stabilization of sensitive substances and unusual conformations of molecules,[17] to the detoxification of contaminated systems, to promote phase transfer of sparingly soluble hydrophobic or hydrophilic compounds,[18, 19] and to act as chemical reagents or specific catalysts.[20]

Reporting the current state of knowledge in this area is very desirable, especially in the context of the research project described in this dissertation. Lattice-type molecular inclusion compounds, or clathrates, are the subject of this research. Clathrates are inclusion compounds which refer to the guest species that are enclosed by channels or cages in a given host lattice.

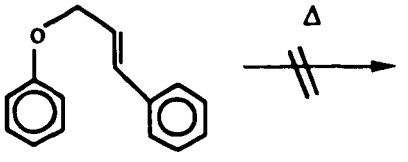
The characteristic of crystal lattices is a strict periodic succession of structurally identical molecular units, and in the sense of inclusion lattices, also of holes, channels, layers, etc., which may include guest molecules in an organized and oriented fashion. This organizing principle makes the topochemistry of Eq. **1**, the inclusion polymerization of dienes in channels of urea to stereoregular polymers, possible.[21] Equations **2** and **3** [22, 23] show altered chemical reactivity due to the presence of conformations different from substrate molecules free of constraints of the lattice environment. In formed inclusion compound, the host lattice serves a protective function, the reactivity of an included molecule being drastically reduced. For example, in this way guest molecules are protected against the influence of light and heat. Equation **4** shows a regioselective and stereospecific hydroxylation reaction under host oriented conditions.[24]

(1) 

(included in urea)

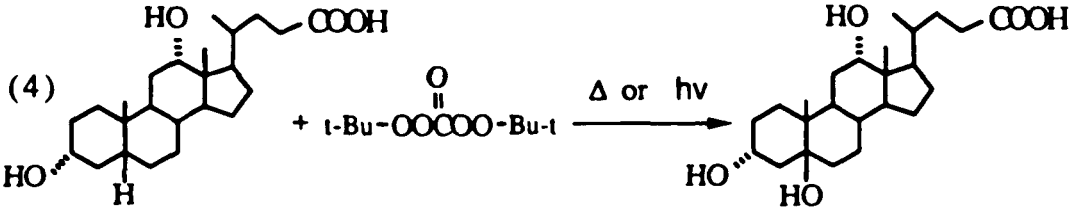
(2) 

E (included in Tri-o-thymotide) Z

(3) 

no Claisen Rearrangement products

(included in 4,4'-dinitrobiphenyl)

(4) 

M (included in M)

More enantioselective photochemical reacations in crystaline inclusion compounds were reported recently.[25] Our research has focussed quite simply on the resolution of enantiomers by inclusion compound formation. Production of enantiomerically pure substances has importance far beyond mere academic interest. Industrial objectives include chemical analysis and molecular separation

processes. The industrial production of large amounts of optically pure compounds has significant economic value, e.g., in the development of chemicals and drugs. Selective inclusion of guest molecules in crystal lattices of inclusion compound, taking advantage of the size, the shape, and the chemical nature of the surfaces of holes generated in inclusion lattices, has significant industrial potential. More enantiomer drugs can be made commercially available more cheaply using this approach.

An inclusion compound will have a stability attributable to the way in which the molecules involved fit together in space. If inclusion compound formation is to occur, the host and guest molecules must be properly oriented with respect to one another, whereupon weak intermolecular interactions drive host and guest to form an easily isolable inclusion compound. Many hosts and guests can be recovered in good yield from crystalline inclusion compounds and afford considerable enantiomer enrichment. Toda, et al., have reported many examples of resolution by inclusion compound formation in high yield and with recovery of enantiopure (100% ee) products.[26]

Our interest in these resolutions by inclusion compound formation is broad, in both theoretical and practical senses, ranging from the direct selection or synthesis of new host molecules to the investigation of selective inclusion properties, molecular recognition, receptor-substrate analogy, X-ray crystallography, chemical analysis, molecular separation and other applications of potential industrial value. At the beginning of this project, it was our hope that new, and more specific host compounds would be identified, leading to greater

ease of enantiomer differentiation and to the practical resolution of (racemic) neutral guest substances in a predictable way.

1.2 Classification and Nomenclature of Inclusion Compound

1.2.1 Classification and Nomenclature of Host and Guest Type Compounds

There is much confusion in the literature over the terminology used for the description of inclusion compounds.[27] Over the years, a large number of terms have been used to describe host and guest types of compounds,[28] for example: addition compound, cage compound, clathrate complex, donor-acceptor complex, clathrate hydrate, clathrate, inclusion compound, host-guest complex, molecular compound, and so on. The term *intercalation* has sometimes been replaced by *insertion* and has even been interchanged with *inclusion*. [28] Newly-coined terms, such as *cascade complex, supermolecular complex, molecular complex associate, speleate* [29] plus other terms mentioned by Davies et al.[30] add to the present confusion.

Because of the growing interest in the chemistry of "weak interactions",[2] a large increase in the number of new host molecular structures is expected.[30] The characterization of these host molecular structures by the present system of naming[31] will become more and more difficult. In response, Weber, E. et al., have drawn up a new system of classification and naming, which is applicable not only to the

presently-known types of host-guest compounds, but also to future possible types.[32]

1.2.2 Classification and Nomenclature of Inclusion Compounds

Weber, E. et al., take two main criteria for advancing the new classification system: (a) the host-guest interaction type and (b) the topology of the host-guest aggregate.

Regarding criterion (a), a division is made into *complex* and *clathrate* (Fig. **1**). They defined that the complexes are those aggregates which are derived from a coordination between host and guest components with coordinative interaction. The complexes retain their identity in solution. Metal ion complexes of crown ethers and cryptands are typical examples of complexes.

The term "clathrate" is reserved to host-guest aggregates where the guest is retained by steric barriers formed by the host crystal lattice (lattice barrier interaction). Clathrates normally decompose on dissolution. Typical examples of this host-guest relationship are the inclusion compounds formed by urea and graphite with guests such as hydrocarbons, alcohols, ketones, halides and so on.[20, 33-35]

Weber, E. et al., distinguish two topological aspects of inclusion: intramolecular host-guest aggregation and extramolecular aggregation. The former includes use of any sort of host cavity, and leads to compounds that are named monomolecular inclusion compounds, or

cavitates. During dissolution, cavitates have an inclination for keeping host and guest together in solution. In contrast, extramolecular aggregates operate via lattice voids, and are called multimolecular inclusion compounds, or *clathrates*. Clathrates readily decompose on dissolution as mentioned above.

Since all host-guest aggregates cannot be classified as either complexes or clathrates, the borderline cases must be treated as complex-clathrate hybrids. Consequently, Weber, E. et al. introduced two other classes (Fig. **1**):

1) coordinatoclathrates, which demonstrate a certain degree of coordinative participation, but have a dominant clathrate character, and

2) clathratocomplexes, that are the lattice complexes, where the influence of coordination is weaker than in complexes, but is dominant in the aggregate.

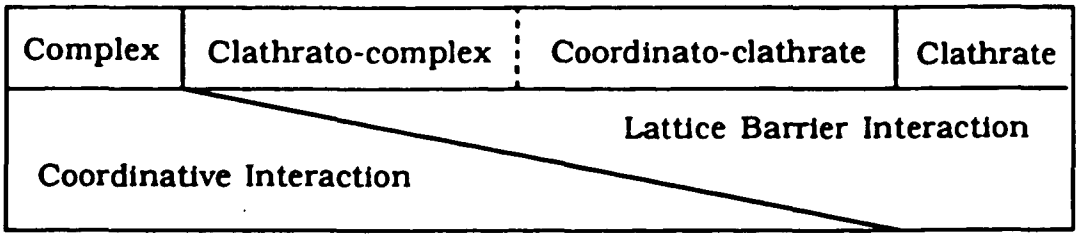


Fig. 1 Assignment of complex/clathrate hybrids.[32]

1.3 Resolution by Inclusion Compound Formation

Optical resolution by inclusion compound formation takes place when the host compound is optically active and one enantiomer of the guest compound is included selectively. In other words, if an optically active guest molecule selectively forms a crystalline inclusion compound with one enantiomer of the host compound, the host compound accomplishes a resolution. This can be demonstrated as follows:

$$\left.\begin{array}{l}\text{(R)-host + (R)-guest} \longrightarrow \text{(R)-host} \cdot \text{(R)-guest} \\ \text{(R)-host + (S)-guest} \longrightarrow \text{(R)-host} \cdot \text{(S)-guest}\end{array}\right\} \text{diasteromeric crystal lattices}$$

An essential feature of inclusion compound formation is that the host and guest molecules are bound together by noncovalent forces. It is very basic that no covalent bonds are formed between host and guest molecules, as e.g., when diastereomeric crystal lattices are used for separation. In the case of chiral host and guest molecules, the "chiral spatial environment" of the crystal, or of the interior of the host molecule, effects the differentiation of the enantiomers. The type and strength of the bonding between host and guest molecules depends on a variety of forces,[36] including hydrogen bonding, ion-ion interactions, ion-dipole interactions, dipole-dipole interactions, dipole-induced dipole interactions, dispersion and electron donor-acceptor interactions, π-acid to π-base interactions, and van der Waals interactions. Diastereomeric host-guest inclusion compounds with

differing energy summations result in different solubilities, leading to isolation of one of the enantiomers during crystallization.

1.3.1 Optical Resolution

Examples of hosts applied to resolution by inclusion compound formation are urea, tri-o-thymotide (TOT), cyclodextrins, binaphthyl derivatives such as 2,2'-dihydroxy-1,1'-binaphthyl, alkaloids, e.g. brucine and sparteine, 1,6-diphenyl-1,6-di(o-chlorophenyl)hexa-2,4-diyne-1,6-diol, chiral onium compounds, e.g., enantiopure quaternized quinine. Of these, TOT, cyclodextrins and brucine are the hosts most applied in resolution by inclusion compound formation.

1.3.1.1 Urea

Resolution of racemates by inclusion compound formation began early in 1954. Urea **1** (NH_2CONH_2) as the clathrate former is the first known example.[37] Although the urea molecule is not chiral, it forms chiral helical lattices.[38] These can be compared to left-and right-handed screws. Long chiral guest molecules can be differentiated inside 5.5 Å wide channel-type cavity lattice of urea when stretched. If the crystallization of an enantiomorphic crystal is favored in the channel-type cavity lattice of urea, only this species will crystallize from the solution and hence can be separated from the racemate.

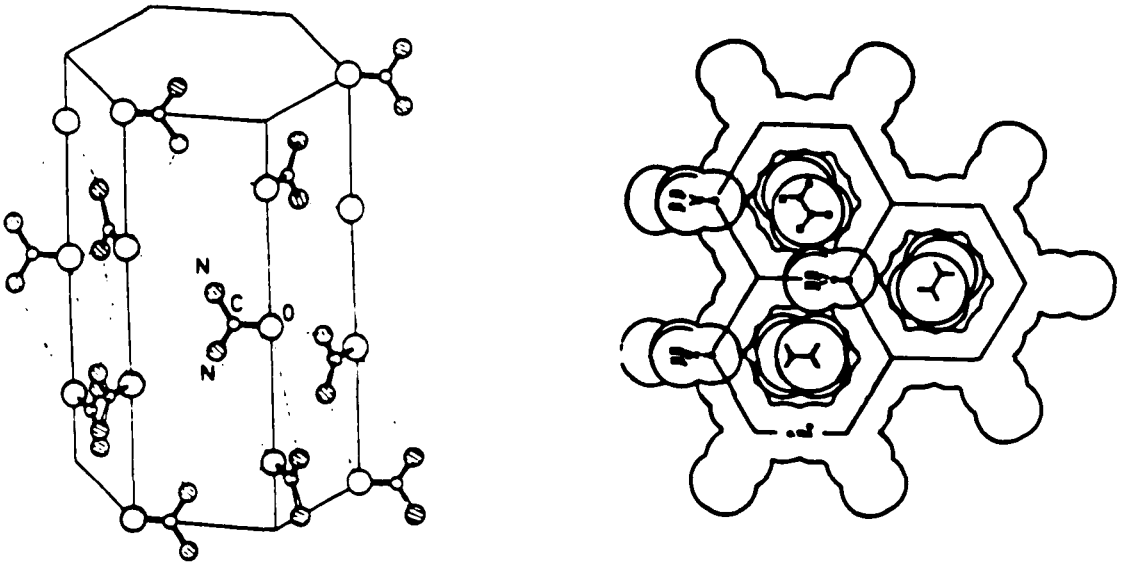


Fig. 2 The H-bonded hexagonal channel network of urea typical for a n-hydrocarbon inclusion compound (H-bonds as dotted lines)[39] (left). Cross section of the urea-n-hydrocarbon complex[40] (right).

Unfortunately, the enantiomer enrichment in resolution by clathrate formation with urea usually is not very high (ca. 5-15% ee).[36, 37a] The slight difference between the lattice energies of the diastereomeric urea clathrates leads to low ee values and renders control of the recrystallization difficult.

Figure **2** illustrates schematically the arrangement of hydrogen bonds between the NH_2 groups and the oxygen of adjacent urea molecules which account for the stability of the inclusion compound

formation. The channel formed by van der Waals' radii of the atoms of the urea molecules is indicated.

1.3.1.2 Tri-o-thymotide (TOT)

As a resolving agent, tri-o-thymotide (TOT) **2** has attracted attention since the original report of Powell on the inclusion of 2-bromobutane.[41] It has become known as a versatile clathrate former.[42, 43, 44] If TOT crystallizes with inclusion of guest substances, in other words as a clathrate, even with achiral solvent molecules, spontaneous racemate resolution usually results, i.e., the TOT crystallizes as a conglomerate. It is TOT's propensity to enclose a wide variety of guest molecules on crystallization that makes it so interesting.

In absence of appropriate guest molecules, TOT crystallizes in an achiral crystal lattice that contains molecules of P-(+) and M-(-) helical configuration (Fig. **3**) which rapidly convert into each other (ΔG 88 KJ/mol) in solution at room temperature.[42, 43]

Single clathrate crystals consist of P- or M-host molecules, respectively (formation of a conglomerate). The three-blade propeller-shaped TOT molecule (Fig. **3**) is constrained to adop dissymmetric conformation owing to the action of crystal packing forces, which leads to one of the enantiomers of chiral guest molecules enclosed preferentially in the cavity or channel-like chiral void of the host lattice. The crystallization of TOT clathrate allows the resolution of racemic guest molecules under appropriate conditions. The guest

compound is easily isolated from these single crystals by warming in vacuum.

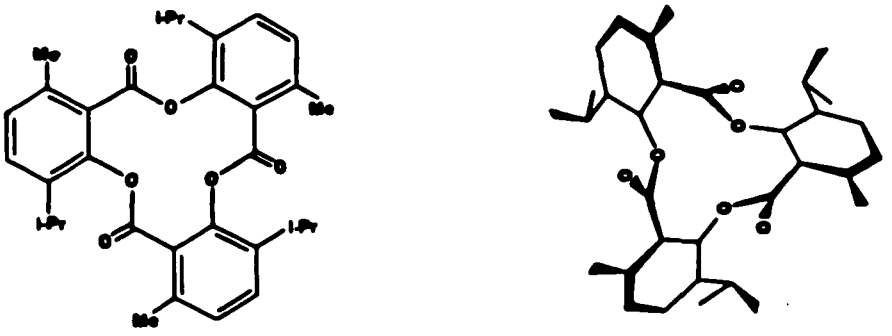


Fig. 3 Tri-o-thymotide **2**. Constitution (left) and idealized view of the (M)-(-)-configuration (right).[45].

Depending on the shape of the guest molecules, TOT can form cage as well as channel type inclusion compounds. In cage type clathrates small guest molecules are enclosed in discrete closed cavities (2:1 TOT/guest) and are not in mutual contact. The application of TOT clathrates to the separation of enantiomers is assumed to rely upon a good "fit" of the guest molecular shape to the cavity within the host lattice. With TOT, this type of complementarity offers two advantages:

a) the quasi invariance of the cavity (for a given clathrate type) with regard to varying guest structures may facilitate the rationalization of the phenomenon of stereospecificity.

b) only non-bonded functional interactions come into play, consequently guests with different shape and size, but with other similar physico-chemical properties are potentially separable;

The cage-type inclusion gives rise to the $P3_121$ space group. This is the most extensively studied type of TOT clathrate. The presence of dissymmetric cavities provides a chiral environment around the trapped molecule and can give rise to the preferential inclusion of one the enantiomers of the racemic mixture.

A measure of the cavity enantioselectivity is given by the *enantiomeric excess* (e.e.) of the guest in a single TOT crystal of a given handedness. The percentage of enantiomeric excess (e.e.) equals the percentage of the major enantiomer minus the percentage of the minor enantiomer. Figures ranging from 2 to 83% have been observed for the e.e. in TOT cage-type clathrates depending on the nature of the included molecule.[46]

Enantiomeric excesses have been determined by various methods: Polarimetric measurements of the residual optical activity of clathrates solutions after TOT racemization for (TOT rapidly converts P- and M- configurations in solution at room temperature); VPC

analysis on enantioselective stationary phases,[47] and NMR analysis using chiral shift reagents.

Another mainly type of TOT clathrate is channel-type inclusion compounds, which have space group $P6_1$. Longer molecules insert in channels with variable stoichiometry as a function of the size of the guest molecule. The extracted guest from single crystals of a channel-type inclusion compound has uniformly low, but significant, enantiomeric excess values of about 5% [48].

TOT analogs, in which the three oxygen atoms in the macrocyclic ring are substituted, for instance, by nitrogen atoms, also show spontaneous racemate resolution combined with clathrate formation.[42a] These host compounds and the TOT molecule itself possess a three-fold axis of symmetry, which is encountered remarkably often with good clathrate formers, such as cyclophosphazenes,[49] perhydrotriphenylene,[50] and hexa hosts.[51]

The host-guest stereospecific interaction is the summation of the physical-chemical events that allow the mutual recognition of two molecular species, leading to a specific association. The nature of the forces that maintain the active conformation of the macromolecular receptor are involved in the binding of the substrate and are fairly well known qualitatively: van der Waals repulsion and dispersion forces, Coulombic forces, interactions with solvation shells in various

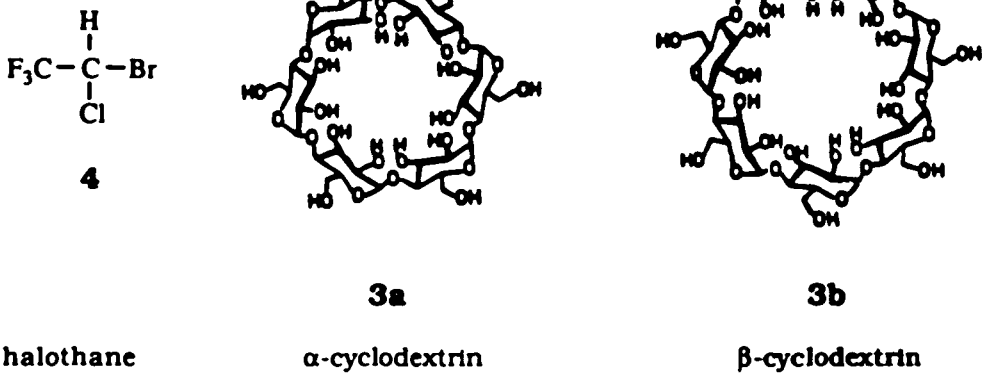
environments, and hydrogen bonding. However, the balanced contribution of these forces to the overall inclusion compound formation appears extremely intricate in spite of the fact that complete three-dimentional structures of several enzymes, established by X-ray diffraction, serve as models.[52]

1.3.1.3 Cyclodextrins

The optically active cyclodextrins **3** (Fig. **4**), available from the chiral pool, are able to differentiate chiral guests within their intramolecular cavity. Cyclodextrin inclusion compounds are quite different from those formed by urea and TOT. Urea and TOT inclusion compounds are formed by the chiral crystal lattice of the achiral or racemic host, respectively. In the terminology of Weber, they are clathrates. However, cyclodextrins do not necessarily form lattice inclusion compounds. If the guest fits into the cavity of a specific cyclodextrin molecule according to its size and shape, the guest is encapsulated while it is in solution. According to Weber, the host-guest compound is a complex.

This complex inclusion compound formed properly allows application of the cyclodextrins as chiral materials for chromatographic resolution of racemates.[53] Apart from the topological (static) conditions, the dynamic processes of inclusion formation and inclusion dissociation also play a part in the host-guest interactions and are therefore important in imparting efficiency to the separation.

α-Cyclodextrin **3a** (Fig. 4) effects the optical enrichment of halothane, $CF_3CHBrCl$ **4**.[54] Complete optical resolution of **4** on per-n-pentylated **3a** has been achieved. The inclusion method is one strategy for racemate resolution of this substance. It is a good example demonstrating the independence of the inclusion method from the presence of functional groups.



4 **3a** **3b**

halothane α-cyclodextrin β-cyclodextrin

Fig. 4 α-Cyclodextrin and β-cyclodextrin structures, which are composed of 6 and 7 glucoside units, respectively. γ-Cyclodextrin is composed of 8 glucoside units.

1.3.1.4 Binaphthyl and Biphenyl Derivatives

The binaphthyl hinge, as the well known 1,1'-binaphthyl chiral carbon skeleton is designated by Pummerer et. al.,[55] has been introduced into asymmetric synthesis and resolution of racemates in the form of the derivatives of 2,2'-dihydroxy-1,1'-binaphthyl, **5**.

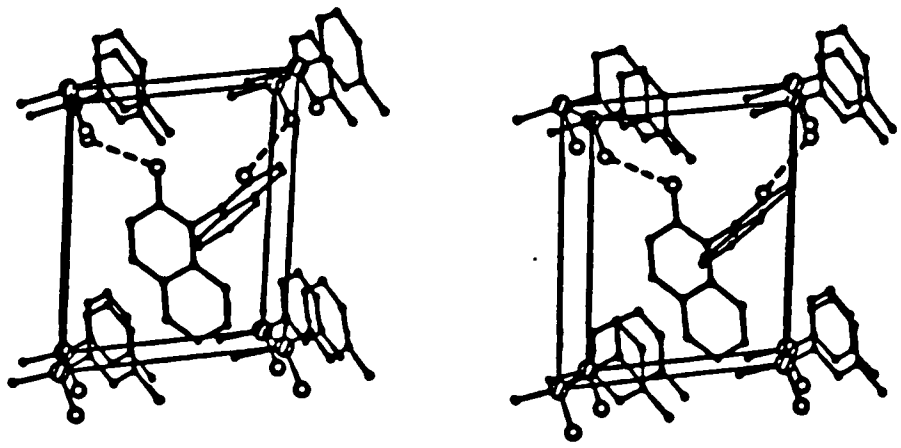
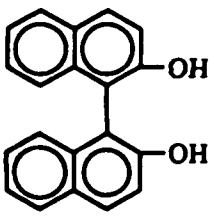


Fig. 5 Stereodrawing of the 1 : 2 methyl sulfoxide (**9a** , m-$CH_3C_6H_4SOCH_3$) crystal inclusion of (R)-(+)-**5** (broken lines represent H-bond contacts; O atoms as circles, C atoms as bold, S atoms hatched).[56]

Crystalline inclusion compounds containing chiral organic sulfoxides as guests are formed with binaphthol **5**, and with the spiro compound **6**. These hosts have been used to separate enantiomers of sulfoxide guest compounds.[26b, 57] Moreover, the reciprocal process, optical enrichment of racemic binaphthols using enantiopure sulfoxides has also been successfully carried out. Figure **5** illustrates such a reciprocal resolution. [26b]



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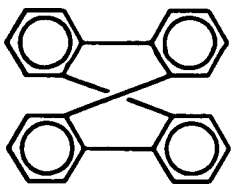

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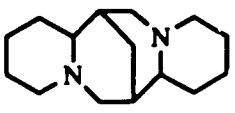

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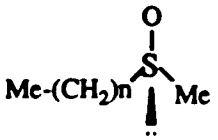
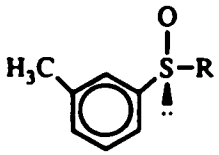


a n=6 d n=3
b n=5 e n=2
c n=4

8



a R=Me
b R=Et
c R=CH=CH$_2$

9

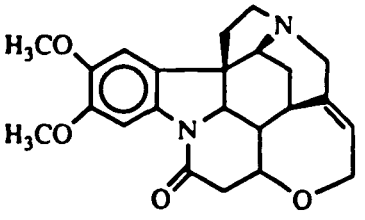
Optically active **5** is very effective in the resolution of sulfoxides **8** with relatively short alkyl chains, such as **8d-e**, and for *m*-tolyl alkyl sulfoxides **9**. The results are as follows: 100% e.e. of (+)-**8d** [α]$_D^{25}$ +111 (c 1.0, MeOH)], of (+)-**8e** ([α]$_D^{25}$ +123), of (+)-**9a** ([α]$_D^{25}$ +140), of (+)-**9b** ([α]$_D^{25}$ +199), and of (+)-**9c** ([α]$_D^{25}$ +486) were obtained in good yields. [26b] The *m*-methyl group of **9** seems important for the resolution, since neither the *o*-nor the *p*-tolyl-analogs of the 1 : 1 inclusion compounds of (+)-**5** with (+)-**9a** are effective. In contrast, the *m*-methyl isomer (**9a**) is nicely accommodated in the host lattice of the inclusion compound (Fig. **5**).[58]

1.3.1 5 Alkaloids

The classical and still widely applied method of resolution by means of diastereomeric salt formation involves the combination of an alkaloid base and a racemic organic acid. Though this method has given satisfactory results in many cases, it has the disadvantage of depending on functional groups (acids and bases). Beside salt formation, and in some cases, formation of clathrates of alkaloids plays a role in racemate resolution processes. As an example, the enantiomeric enrichment of bromochlorofluoromehane (CHBrClF) was achieved successfully by crystallization with brucine **10**.[59] For the

measurement of the enantiomeric excess (e.e.) of this interesting compound a specially constructed cryptophane derived from the triveratrylene skeleton and having a large cavity inside the molecule, was applied to the differentiation of the bromochlorofluoromethane enantiomers on an analytical scale.[60]

In addition, alkaloids such as sparteine **7**, brucine **10** and quinine **11**, have been used to differentiate between the enantiomers of racemic guest compounds such as prop-2-yn-1-ol derivatives by clathrate formation, either as free bases,[61, 62] or as quaternary onium salts.[63]



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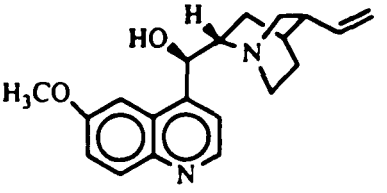

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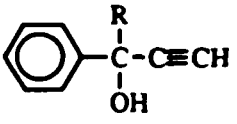


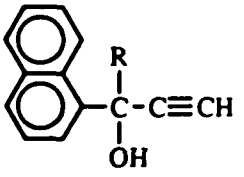
12

a R = *o*-Br-C_6H_4
b R = *o*-Cl-C_6H_4
c R = *o*-F-C_6H_4
d R = *o*-Me-C_6H_4
e R = t-Am
f R = t-Bu
g R = n-Bu
h R = n-Pr
i R = i-Pr
j R = Et
k R = CCl_3
l R = $CHCl_2$
m R = CH_2Cl

Toda, et al., found that alkaloids such as brucine **10** and sparteine **7** form channel-type inclusion compounds with some kinds of alcohols. These alcohols are easily resolved by inclusion compound formation. They also found that sparteine can be resolved by inclusion

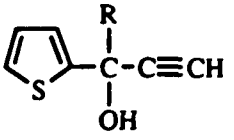
formation with an optically active tertiary acetylenic alcohol with resultant very high ee.

For example, when a solution of racemic **12f** (8.12 g, 43.2 mmol) and **10** (17.0 g, 43.2 mmol) in acetone (260 ml) was kept at room temperature for 12 h, a 1:1 crystalline inclusion compound of (+)-**12f** and **10** (12.1 g) was obtained as colorless crystals. Decomposition of the inclusion compound with dil. HCl gave (+)-**12** (3.9 g, 96% of the (+)-enantiomer) with an ee of 71%. Upon a second crystallization with **10** the ee was raised to 100 % : (+)-**12f** (3.16g, 77%, $[\alpha]^{25}_{D}$ + 12.4) (c 1.0, MeOH). The acetone solution left after separation of the brucine inclusion compound of 71% ee of (+)-**12**, was treated as above to give (-)-**12f** (4.06 g, 100% of the (-)-enantiomer) with an ee of 66%.[64, 65] By the same procedure, **12a-e** and **12g-m** were also resolved efficiently to give enantiomers with 100% ee. Since **12** with R = Me or CF_3 is only poorly resolved by **10**, R should be a larger group than Me to make an efficient resolution possible. Compounds **13** and **14** were also easily resolved giving 100% optically pure enantiomers.



13

R = Ph, Et, CH_2Cl



14

R = n-Bu, n-Pr, i-Pr

The guest enantiomer is accommodated in the channel space formed by **10**, and two kinds of hydrogen bonds, OH···N of **10** (Fig. 6) and C≡CH···O of **12a**, play important roles in holding the guest and host components together. Replacement of the (R)-(-)-**12a** molecules in this lattice aggregate by the other guest enantiomer, (S)-(+)-**12a**, would result in an unfavorable system of hydrogen bonds.

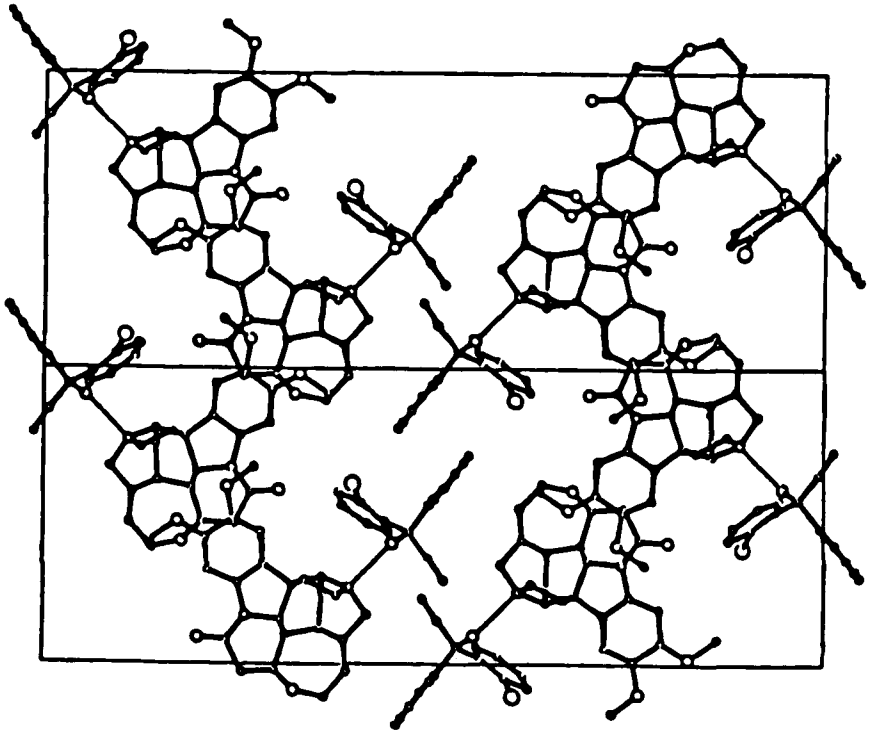
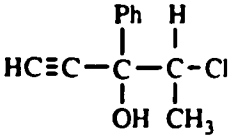


Fig. 6 Packing diagram of the 1:1 brucine crystal inclusion of (R)-(-)-**12a** (thin lines represent H-bond contacts; Br, O, N atoms represented by circles of decreasing size, in this sequence).[57]

In some cases, resolutions by sparteine **7** are much more effective than by **10**, because the sparteine inclusion compounds can be purified by recrystallization. For example, (-)-**8a** (50% e. e.), (-)-**8b**

(55% e.e.), (-)-**8c** (34% e.e.), and (-)-**8f** (59% e.e.) gave 100% optically pure enantiomers in 60%, 52%, 20% and 62% yields, respectively, with two recrystallizations of their 1:1 sparteine clathrates from acetone followed by decomposition with dil. HCl. Racemic sparteine was easily resolved by utilizing inclusion compound formation with an optically active propynol.[61b] This method can probably be applied to the resolution of many synthetic alkaloids and related compounds.

Propynols which have two stereogenic carbon atoms also form inclusion compounds with **10**, and can be resolved quite efficiently by clathrate formation. For example, **15** and **16**, are resolved perfectly (100% ee) by inclusion compounds formation with **10**.[62a]



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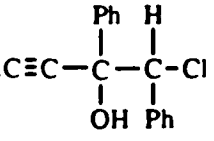
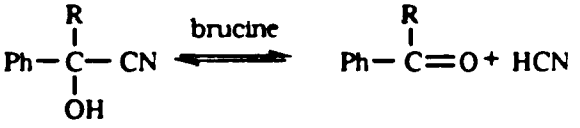


16

This resolution method was found to be applicable to some cyanohydrins **17** and to secondary alcohols **18**. Very interestingly, the racemic cyanohydrins **17** and secondary alcohols **18** were converted into a enantiopure samples in almost quantitative yield in the presence of brucine (**10**).

For example, when a solution of 1.0 g of (±)-**17a** (5.3 mmol) and 2.1 g (5.3 mmol) of brucine in 2 ml of methanol was kept in an uncapped flask for 24 h at room temperature, a brucine inclusion

compound of (+)-**17a** was obtained in quantitative yield which upon decomposition with dil. HCl gave 1.0 g of (+)-**17a** (94% ee). Repeating the inclusion of the 1.0 g of 94% ee of (+)-**17a** with 2.1 g of brucine one more time, gave 1.0 g of 100% ee of (+)-**17a** {$[\alpha]^{25}_D$ +15.9 (c 1.0, MeOH)}. The process of the complete conversion of racemic cyanohydrin to afford one enantiomer consists of racemization of the cyanohydrin through the equilibrium in Equation (**5**) and selective inclusion of only one enantiomer in brucine to form a stable brucine inclusion compound. This stable clathrate crystallizes out while the less stable inclusion compound is more soluble in solvent and dissociates to host and cyanohydrin, with the cyanohydrin racemizing in solution. It is a resolution attended by an asymmetric transformation.[57, 62b]



(5)

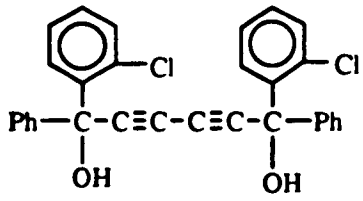
Simple secondary alcohols **18** are also easily resolved with brucine to give 100% of **18a** {$[\alpha]^{25}_D$ + 32.2 (c 1.0, MeOH)} and **18b** {$[\alpha]^{25}_D$ + 34.4 (c 1.0, MeOH)}.

17 **18**

a R = t-Bu b R = CCl_3

1.3.1.6 1,6-Diphenyl-1,6-di(*o*-chlorophenyl)hexa-2,4-diyne-1,6-diol

The chiral clathrate former 1,6-bis(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyn-1,6-diol **19**, was synthesized in optically pure form by oxidative coupling of optically pure 1-phenyl-1-(*o*-chlorophenyl) prop-2-yn-1-ol (**12b**), (itself resolved by clathrate formation with brucine).[57] Toda et al., found that **19** shows inclusion ability with numerous guest substances, e.g., cyclic ketones and lactones, which constitute important synthetic building blocks.[57, 66, 67] 2,3-Epoxycyclohexanones **20-22** were also easily resolved by inclusion compound formation with **19**. In almost every case, resolutions with very high e.e.s and good yields were obtained.[68] Racemates **8-9**, **23-46** were all resolved by inclusion formation with **19**.[69-71]



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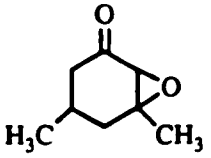

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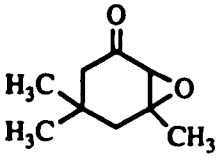

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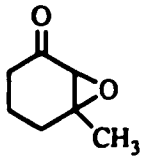

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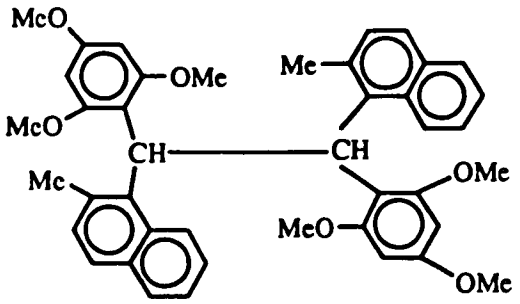

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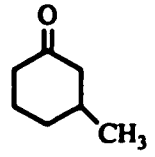

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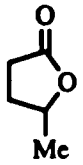

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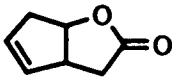

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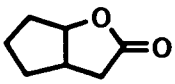

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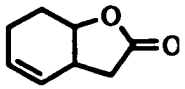

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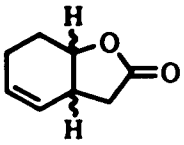

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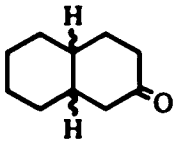
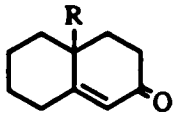


30

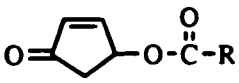
a *cis*-isomer
b *trans*-isomer



a R = H
b R = Me
c R = Et

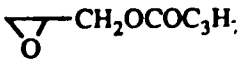
31

32



a R = n-Pr
b R = n-Bu
c R = t-Bu

33



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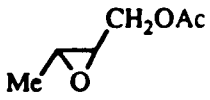

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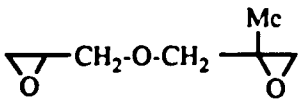

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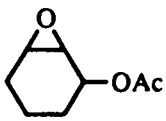

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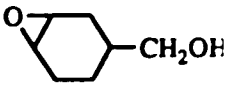

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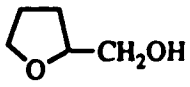

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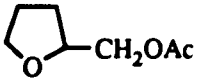

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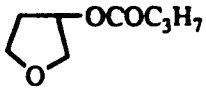

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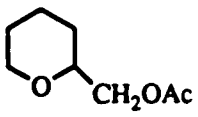

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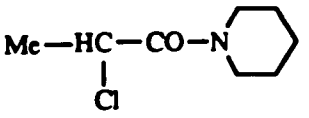

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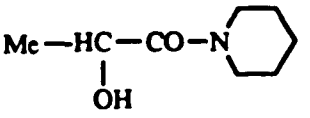

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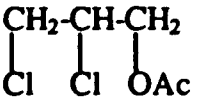

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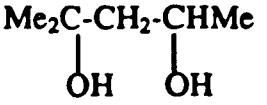

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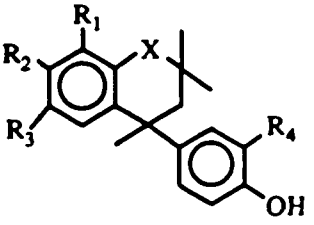


47

a X = O, R_1-R_4 = H
b X = O, R_1-R_3 = H, R_4 = CH_3
c X = S, R_1-R_4 = H
e X = S, R_1 = CH_3, R_2-R_4 = H

1.3.1.7 Chiral Onium Host Compounds

The use of clathrate chemistry to effect precise, crystalline, chiroselective guest inclusion is still in its infancy. Numerous chiral clathrates are unable to resolve enantiomers. In fact, some hosts even lose their inclusion ability in pure enantiomeric form. For example, 3'-methyl-substituted Dianin's analogue (**47**, R_4 = CH_3; Sec. 1.4) causes a complete loss of the original clathrate activity.[72, 73, 74]

It has been long recognized that host-guest interactions involving organic onium compounds as hosts are important in biological processes. The interaction between enzymes and substrates or inhibitors, antibodies and antigens, ionophores and metal ions,

receptors and drugs, which participate in the most basic and important biological processes, are all the interaction of complexing partners, in other words, these biological processes are the interactions between host and guest. As for many of presently known clathrate systems, the discovery of the family of onium clathrate hosts was due to a chance observation.[75] The structural features of the chiral onium compounds are bulkiness and limited conformational flexibility. Exploring chiral onium compounds as hosts to resolve racemate guests is interesting.

The inclusion capacity of organic onium salts has been shown for numerous representatives of this family of host compounds [67, 75-79] However, resolution by inclusion compound formation with chiral onium host is still seldom found. It is possible that optically pure onium salts, preferably taken from the chiral pool, may be promising inclusion hosts and resolving agents.

1.3.2 Conclusion and Outlook

There still are many other examples of racemates that have been resolved by complexation with host compounds through formation of chiral crystal lattices.[80, 81, 82] However, the examples of optical resolution by inclusion compound formation illustrated here sufficiently reveal the many ways in which host compounds can be applied in this branch of chemistry. Actually, many clathrates have been found by chance or in the course of large series of experiments.

Attention by chemists has been mainly focussed on the experimental and theoretical aspects of inclusion compound formation. However, much work remains to be done in this branch of chemistry. The non-covalent bond interaction between host and guest, the correlation of the absolute configurations of host and the preferentially included guest, the function of "rigidity" of the cavity, the symmetry relationships between the cavity and the included reactant, and so on, all are important factors for chiral recognition between host and guest. And all these factors are incompletly understood. A better understanding of these factors will not only develop the study of resolutions, but also contribute to the understanding of biological processes.

1. 4 Selection and Design of Host Compounds

Most of the classical clathrate hosts[35, 83-85] were discovered by accident and were not chosen by design.[86] Considering the efficient resolution by inclusion compound formation, where hosts form stable crystalline clathrates and improve the selective complexation with potential guests, it would be very desirable to construct guidelines for host compound selection and design.[2, 87]

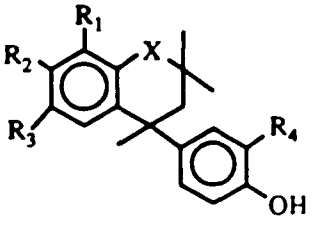
How can we achieve host selection or design? There is a great deal of successful research on inclusion phenomena by molecular recognition. Yet it is still not clear why some hosts are very efficient in the inclusion of guests and others not? What is the significance of molecular type, shape and complementarity in inclusion compound

formation? The following questions should be asked and understood: What are the structural characteristics of good inclusion hosts, common or special? What are the hosts' important "functional groups"? What kind of molecular shapes and sizes make for "good" hosts? What is the most important interaction between host and guest, or which interactions are more important? What are the functions of these interactions? For good inclusion compound formation and molecular recognition, what is the relationship between the host intramolecular microenvironment and host-guest interaction? We can not answer all these questions now, but we can at least summarize some generalizations to guide our research.

1.4.1 Hydrogen Bonding in Inclusion Compound Formation

Until quite recently, a general way of looking at clathrates and their molecular construction principles came from Powell's fundamental crystallographic work. Powell pointed out that the hydrogen bond between an OH group and other OH groups, or oxygen atoms, or nitrogen atoms, appropriate to neither a covalent bond nor a van der Waal's contact but intermediate between them, provided an additional element in the cohesion of crystals. In particular, hydrogen bonds bound together molecules which might otherwise have been expected to cohere through van der Waals forces alone[88, 89] The phenolic hydroxyl function, e.g., as present in different quinols or in Dianin's compound (Fig.**7**) is a structural prerequisite certain to be favorable to formation of a host lattice.[84]

The first true rational design of a new clathrate family came from MacNicol[90] and is based on the so-called "hexahosts", a class of compounds featuring a hexa-substituted benzene constitution[91, 92] The original idea behind this strategy is derived from a close analogy between the hexa-substituted benzene ring and the hydrogen-bonded hexamer unit present in the clathrates of most phenol-type hosts (Dianin's compound included), bearing in mind that the O···O spacing (in the hydrogen-bonded hexagon) is similar to the distance where the atoms of a hexa-host bend off from the central unit (Fig. **7a** and **7b**).



47

a X = O, R_1-R_4 = H
b X = O, R_1-R_3 = H, R_4 = CH_3
c X = S, R_1-R_4 = H
e X = S, R_1 = CH_3, R_2-R_4 = H

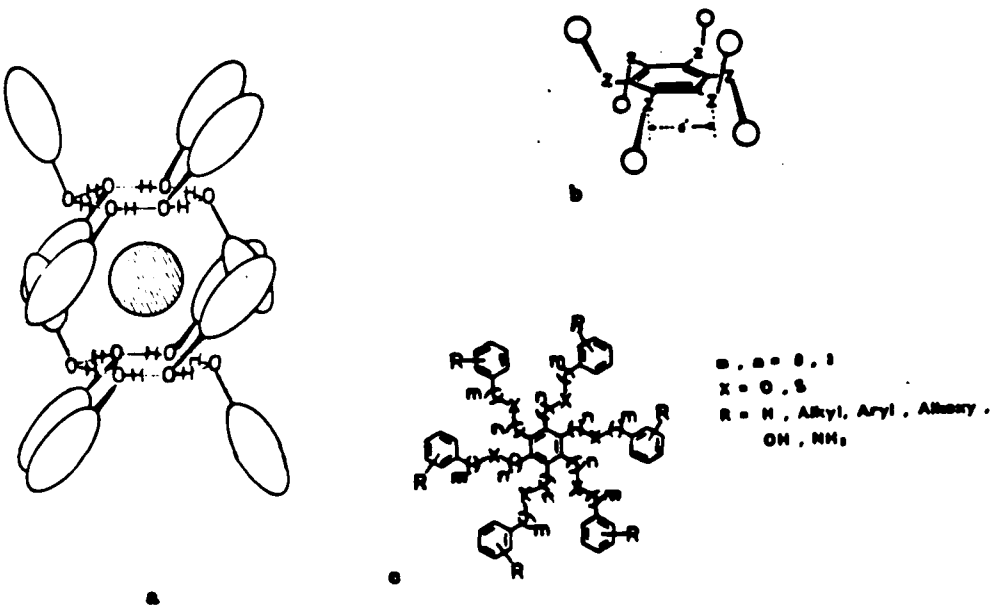
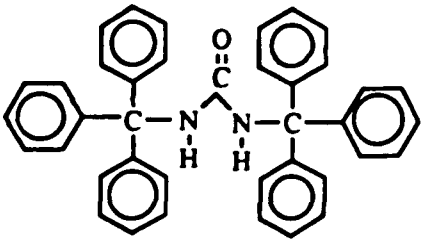


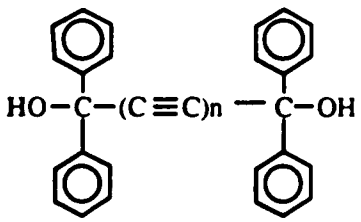
Fig. 7 (a) Inclusion matrix of Dianin's compound. Individual Dianin molecules are represented by a specified hydroxy group attached to an ellipsoid. The characteristic hydrogen bridge networks are indicated by the shaded hexagons (H-bonds in dotted lines). The hatched sphere in the center of the cavity pictures an included guest molecule, e.g. chloroform; (b) a hexasubstituted benzene analogue (follow the shaded hexagons); (c) characteristic constitution of "hexa-host" molecules.[93, 94]



69

Choosing suitable substituents might increase the possibility of forming non-close-packed structures on crystallization (Fig. **7c**). Many of the Dianin's compounds **47**, follow this strategy, and exhibit distinct inclusion ability.[92] Goldberg and Hart have applied the very same

structural principle to bulky ureas such as **69** (Sec. 1.4.3)[92, 95] which provide a polar region along the central axis which is involved in H-bonding with the guest. The original linear acetylenic hosts **48** reported by Toda[96] differ from those of Hart due to the presence of hydroxyl groups,[97] e.g., **49**. As a consequence of H-bonding, compounds **48** may also contribute to inclusion compound formation, e.g., in host-guest binding, where feasible. A further kind of hydroxylic host which has hydroxyl groups in its molecule, **65** and **66** that are unrelated to the propargylic alcohol type of compound, has also been applied successfully by Toda.[98] Strong hydrogen bonding between hosts and guests was observed in many of the studies of resolution by inclusion compound formation.[99, 100] The data suggest once again (cf. classic phenol hosts, Fig. **7a**) that hydroxyl and carbonyl oxygens both play an important role in hydrogen bonding. Hydrogen bonding is an essential part of the lattice build-up and may also contribute to clathrate formation, e.g., in host-guest binding, if feasible.[100b, 101]



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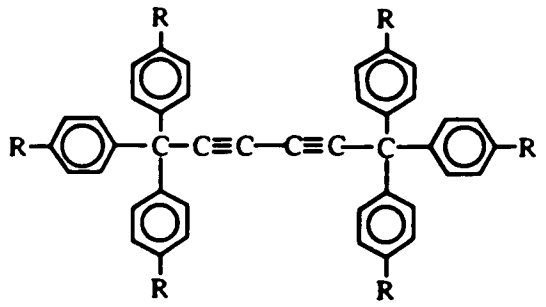
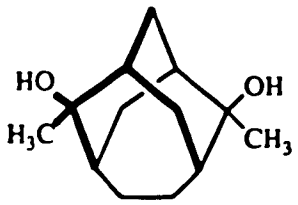


49

In 1979, Bishop and Dance discovered that rigid bicyclic aliphatic diol **50** crystallizes in a new H-bonded channel inclusion

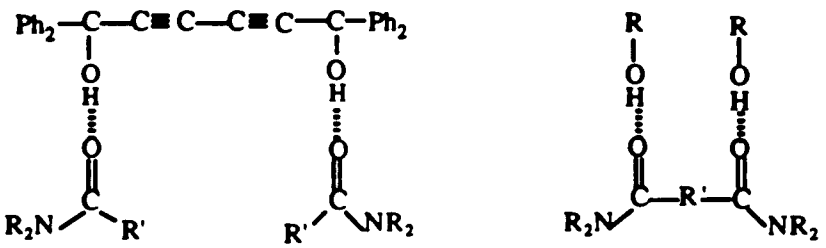
network[102], and they expanded their studies to include a whole series of compounds similar to **51**.[103] As their results show, a suitable interplay of structural features is involved in constructing an efficient host molecule related to the general skeleton **50**. For instance, both alcohol functions must be tertiary with an α-methyl group, and the molecule must have a C_2 rotation axis as the only molecular symmetry element. Some other structural restrictions were specified such as host molecule orientation and lattice dimensions in the crystalline clathrate. The main principle of this particular host design combines a rigid skeleton with two appropriately syn-positioned hydroxyls which stabilize a hydrogen-bonded channel matrix.

50



51

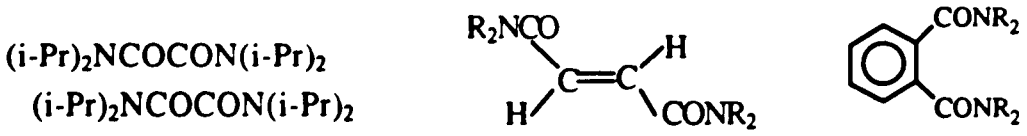
Amides form stable hydrogen-bonded inclusion compounds with **48a** as depicted in Fig. **8**, I[96] This suggested that a diamide might possibly serve as a good host molecule for alcohols (Fig. **8**, II). Toda, et al., designed several diamides: **52-55** and **59-61**, triamides **56** and **57**, and a tetraamide **58**, some of which exhibit C_2 symmetry, and found them to be good hosts for alcohols but also for other guest compounds.



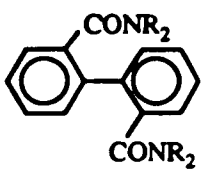
I II

Fig. 8 Suggested binding modes of carbonamide alcohol crystal inclusions (mutual recognition).

Toda has used alkaloids such as brucine (**10**) and sparteine (**7**), to enantioselectively enclathrate chiral propargylic alcohols.[61b, 64] Hydrogen bonding contributes to the lattice build-up and contributes as well to host-guest binding between N of host and OH of guest. Both kinds of hydrogen bonding are responsible for the success of resolutions. In view of the large pool of natural alkaloids, the potential of this method is obvious.



52 **53** **54**



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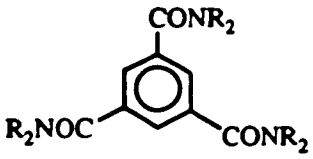

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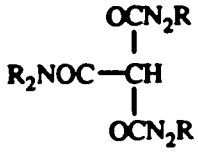

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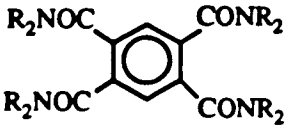

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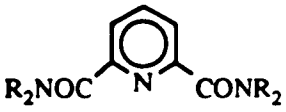

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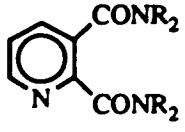

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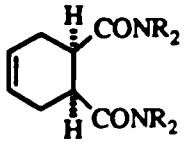


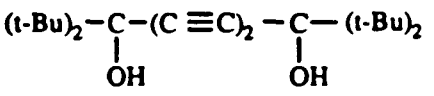
61

1.4.2 Rigid Skeleta in Inclusion Compound Formation

Bishop discovered some rigid compounds with inclusion ability due not only to their hydrogen bonding abilities, but also to their rigid skeleta as mentioned above. Weber, et al. called that a combination of specific polar binding subunits connected by rigid apolar shaping components was an effective principle for the design of new highly selective host molecules.[104]

Toda, also understood that the rigidity of the molecular structures of **48** and **62** also constitute an important factor for their excellent clathrate formation ability. However, (E,E)-1,1,6,6-tetraphenylhexa-2,4-diene-1,6-diol **63** is relatively flexible, so it includes only a few types of guest compounds in the crystal. Furthermore, 1,1,6,6-tetraphenylhexane **64** does not form any inclusion compound at all, for its freely rotating C-C bonds provide no

rigidity at all to the molecule. Accordingly, using a rigid molecule which has an anti-diol function and some bulky hydrophobic group such as phenyl, Toda, used binaphthol **5** and designed **65** and **66**, and found them to be good inclusion hosts.[105]



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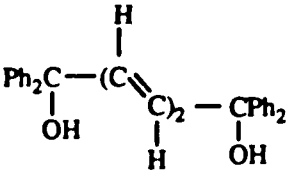

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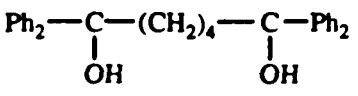

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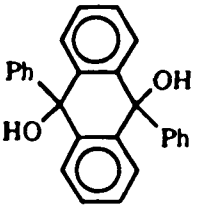

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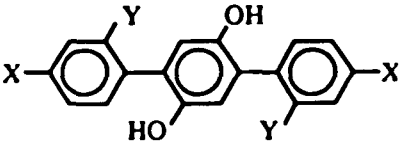
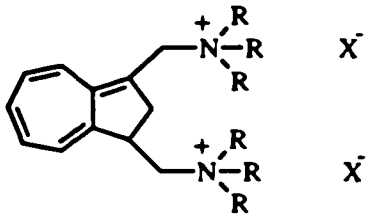


66

Due to a chance observation, Vögtle discovered[75] that a certain type of organic onium compound with limited molecular flexibility, e.g., **67** and **68**, is a rich source of clathrate formers.[78] The stability of the ionic host lattice is certainly of significance for this particular clathrate design. The strategy of using ionic forces to create a crystal lattice has also been extended to chiral hosts,[79] e.g., quaternized alkaloid bases which allow enantioselective recognition upon inclusion compound formation.[66, 106] The (-)-N-methyl-and (-)-N-benzylquininium salts, respectively, form inclusion compounds with a chiral species (2-butanol). The (-)-*N*-methylquininum salts gave (+)-(*S*)-2-butanol (16% ee), and the (-)-*N*-benzylquininium salt gave (-)-

(*R*)-butanol (25% ee). Kikuchi, et al., recently designed a host molecule, which recognized anionic guests with hydrophobic character, was of the specific structural rigidity of the steroid moieties.[107]



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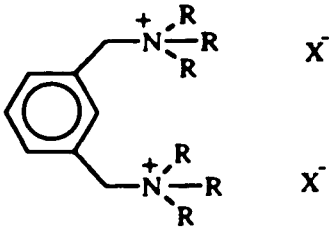
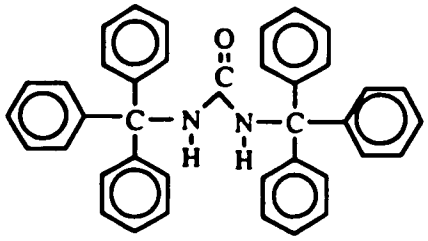


68

1.4.3 The Molecular Shape of Hosts in Resolution by Inclusion Compound Formation

Early in 1968, Toda[96] and 16 years later Hart[97] designed the host which is spoken of pictorially as the "wheel-and-axle". Such hosts contain a long molecular axis made up of several sp hybridized carbons with sp^3 carbons at each end that bear large, relatively rigid groups (e. g. **48**, **49**, Sec. 1.4.1). The large end groups act as "spacers" which prevent the host molecules from forming a close packed structure in the crystal, hence substantial lattice voids are created. The lattices are well prepared to accommodate guests such as aromatic hydrocarbons of varying sizes and geometry. Control of the lattice dimensions is practicable by shortening, lengthening or bending the molecular axis. Using more than one sp carbon pair or incorporating sp^2 and sp^3 carbons, e.g., **48a** instead of **48b** and using **69**, causing the molecular

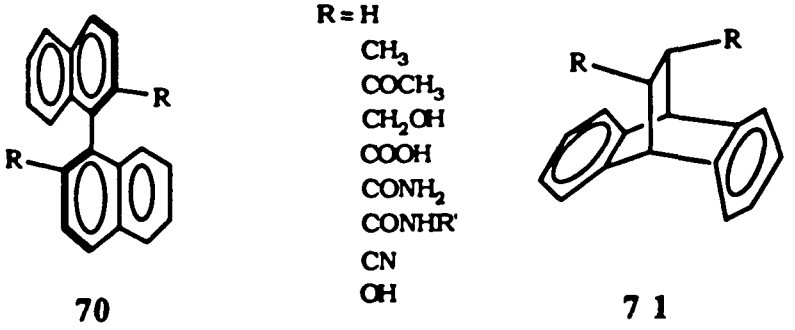
axis to be lengthened or bent led to host molecule lattice dimensions more suitable for guest inclusion.



69

X-ray crystal structural studies of the inclusion compounds of hosts **65**,[108-110] **62b**[109] and **5**,[58] demonstrated the presence of a twisted relationship between two aryl groups in all these cases. In some cases, two aromatic groups are almost perpendicular to each other. Compounds **65** and **66**, have also two hydroxyl groups in an anti-relationship, which is supposed to be a prerequisite for hydrogen bonding and inclusion compound formation. In accord with this observation, Toda designed host compounds with aromatic moieties in a twisted relationship and provided with two hydroxyl groups, and obtained satisfactory results.[57]

Hosts of scissor-like and roof-shaped appearance, e.g., **70** and **71** having attached carboxylic groups (Fig. **9**), are the most impressive in respect to the formation of selective and stable crystal inclusion compounds.[111] Now V-shaped,[112] Basket-shaped,[113] Roof-shaped,[114] and other moleculas having particular shaps,[115] have been applied in the design of hosts.



70 71

Fig. 9 The structure of a scissor-like coordinatoclathrate host (**70**); roof-shaped host (**71**).

1.4.4 The Formation of "Coordinatoclathrates" in Host-Guest Interaction

A new strategy, the formation of "coordinatoclathrates"[116] has been developed. The new principle deals with the concerted action of van der Waals non-polar steric shielding and polar Coulomb attractions or hydrogen bonding. A typical host design involves two main building elements: (1) a bulky basic skeleton providing the lattice voids characteristic of a clathrate matrix, and (2) appended functional groups (sensor groups) that take an active part in the coordinative host-guest interaction.

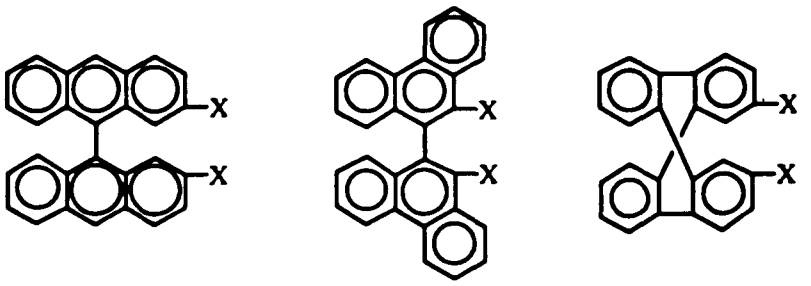
This inclusion strategy seems to be the most universal up to the present since it is independent of an overall molecular shape, e.g., as structural aspects of the above mentioned hosts. The geometric as well as the chemical host-guest fit may be controlled by selection of appropriate building elements. Beside selectivity, coordination-assisted host-guest binding is also likely to be stronger which will lead

to more stable inclusion compounds than with van der Waals attraction alone.

a n=2
b n=1
c n=0

48 **72**

Here, Toda, gives very interesting examples. In his research on hydrocarbon host compounds, the *p*-xylene inclusion compound of **48c** showed that the guest molecules were fixed by the surrounding phenyl groups of **48c** only. From X-ray data, he drew the conclusion that hydrogen bonding played no role.[117] This prompted the design of new hosts without hydroxyl groups, in which the hydroxyl groups of **48a,b,c** were replaced by hydrogen, giving the corresponding hydrocarbon hosts, 1,1,6,6-tetraphenylhexa-2,4-diyne **72a**, 1,1,4,4-tetraphenylbut-2-yne **72b**, and 1,1,2,2-tetraphenylethane **72c**. The same idea was applied to **73a**, **74a** and **75a**. These hosts also allowed clathrate formation with some guest compounds such as cyclopentanone, benzene, tetrahydrofuran and pyridine.[57] These results were also observed in 9,9'-bianthryl **73b**, 9,9'-biphenanthryl **74b**, and 9,9'-spirobifluorene **75b** as hosts, in which the hydrogen groups (X = H) of **73a**, **74a** and **75a** were replaced by methyl groups.



a: X = H; b: X = Me; c: X = Cl

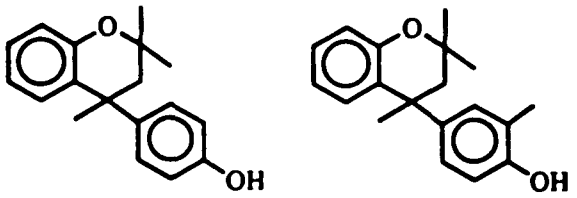
73 **74** **75**

Similar results can be observed with Toda's amide host compounds. In all of the newly designed amide host compounds **52-61**, R should be larger than i-Pr, preferably cyclohexyl, since large R groups in the amide hosts would make it easier to surround the guest molecule in a crystalline lattice.

1.4.5 Modification of Host Compounds

Efforts have been made to create new host compounds simply by altering an individual section of a known host constitution. On the one hand, it is possible to vary the cavity size being formed in the crystal lattice and the bonding forces in a very special way via modifications of molecular segments, e.g., Dianin's compound **47c** and **47d**. These have quite different cavity size and inclusion ability [74] in such a way that it leads to an increase in the ability of the hosts to form clathrates and to increase guest molecule selectivity. On the other hand, modification of host compounds can lead to loss of the original clathrate activity; for instance, changing the structure of Dianin's compound **47a** to the 3'-

methyl-substituted analogue **47b** causes a complete loss of the original inclusion ability.[74]



47a **47b**

A special merit of Dianin's compound is that the inclusion cavity could be easily tuned to the geometric and steric requirements of the guest by altering the bulk of the side arms. However, host structures tunable specifically to different classes of guest compounds, i.e. chemoselectivity control in inclusion, is not yet feasible in a significant way.

The method of modifying an individual segment of a classical host molecule does not solve the real problem of directed host design. Directed design of a host compound, to be exact, means the synthesis of new clathrate hosts unrelated to any known host lattice but which would be expected to act as a host lattice. The situation in this field is not satisfactory now. There still is a lot of work yet to do.

However, the stabilization of an ionic host lattice by molecular modification is certainly a significant mode of host molecule design. This strategy has been extended to chiral hosts[79] by using ionic forces to create a non-close-packed crystal lattice, i.e., quaternized alkaloid

bases which allow enantioselective recognition on clathrate.[66] An example was given in Sec. 1.4.2.

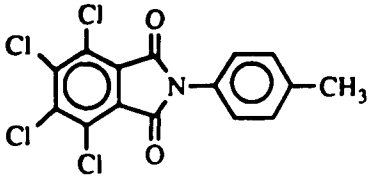
1.4.6 Symmetry Relations in Directed Clathrate Formation

The importance of symmetry relationships has been noticed by different research groups as a further variable in directed clathrate formation, primarily the presence of a C_2 or C_3 rotation axis [66, 74, 103a, 118,.119] Host molecules with a three-fold axis of symmetry are encountered remarkably often among good clathrate formers, such as TOT, in cyclophosphazenes,[45] in perhydrotriphenylene[46, 120] the hexahosts described on Sec. 1.4.1[47a, b, 121] and the cage of Dianin's compounds.[122]

In the multimolecular inclusion compounds formed by these hosts, the surrounding lattice is normally consolidated by van der Waals forces alone, and not by hydrogen-bonding. But, the individual host molecule does not always attain exact crystallographic three-fold symmetry in its adducts. It seems that characteristic conformational deviations from the ideal C_3 symmetry are exhibited in each of the space groups so far investigated. However, a trigonal lattice symmetry is quite often encountered.[123] Consequently, according to MacNicol "it appeared very attractive to incorporate trigonal symmetry as a key design element in the synthesis of new host molecules".[92] Examples of systems of this trigonal symmetry type are not only the above mentioned, but also include triphenylmethane,[124] cyclotriveratrylene,[125] tri-o-thymotide,[126] tri(o-phenylenedioxy)

cyclotriphosphazene.[127] These compounds are often applied as hosts in resolution by clathrate formation.

C_2 symmetry also correlates satisfactorily with clathrate formation ability in some host compounds, such as N-(*p*-tolyl) tetrachlorophthalimide **77** (TTP),[128] tetraphenylene **78**[129] and **19**, **23**, **50**, **57**, **65-75**. C_2 symmetric hosts are wide spreadly used for enantioselective recognition of guests bearing single asymmetric centers.[130]



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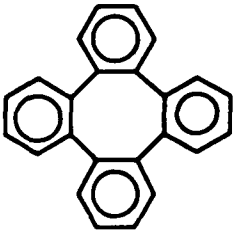


78

1.4.7 Conclusion

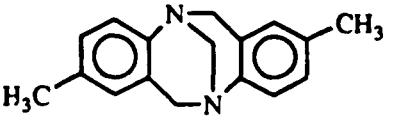
Evidently, the very recent past has made us a present of different profitable design strategies for new clathrate hosts. Individual design elements involve molecular bulkiness,[131] rigidity[132, 133], hydrogen bonding,[131-137] Coulomb attraction,[138, 139] as well as the use of specific geometrical arrangements, including "wheel-and-axle", "roof", "scissor" or "spider" structures[140] as well as certain symmetry relationships[74, 103a, 141] .

Nevertheless, rummaging about in the literature might also be a promising method of rediscovering "new" clathrate formers, e.g., *o*-tetraphenylene,[142] or extending the application of known lattice hosts, such as tri-o-thymotide **2**,[143] trimesic acid,[144] Heilbron "complexes" etc.[145] which are full of exciting results.

Summing up, we now have the beginnings of a reasonable number of principles which can be used to find or to design an appropriate host for a given guest.

1.5 The Properties of Tröger's Base

Tröger's base,[146] 2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f]diazocine **79** (TB), is a product of the acid-promoted condensation of toluidine and formaldehyde. It is a chiral heterocyclic diamine whose chirality is solely due to the presence of two stereogenic nitrogen atoms. It was the first amine proven to have a rate of configurational inversion so slow as to allow resolution of the synthetic material into its enantiomeric components. The chiral nature of TB was first recognized by Prelog and Wieland in 1944.[147]



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There is something of a resurgence of interest in TB and its analogues due in large measure to the sharply folded geometry of the molecule. The angle formed by the least-squares planes containing the two aryl rings varies, depending on the ring substituents, but ranges from 92° to 104°.[148] Obviously two cup-shaped molecules joined in this manner would form a substantial concave surface and define an interesting new binding site. The structure is therefore ideally suited to the preparation of clathrates.

Tröger's base is a relatively rigid molecule. Derivatives of TB are also relatively rigid molecules, and have proven useful in the efforts to construct biomimetic systems and specific functional group arrays.[148a, 149]

Natural receptors are often described as clefts, grooves, or depressions on protein, membrane, or polynucleotide surfaces. The essential characteristic of small molecule receptor is concavity.[150] The great majority of synthetic receptors have used macrocyclic rings to enforce the formation of concave surfaces.[151] Interesting examples of nonmacrocyclic hosts are appearing at an accelerating rate.[152] Analogues of TB contain a deep cleft or a groove large enough to bind small organic molecules, and find use in biomimetic, enzyme catalysis, and molecular recognition studies.

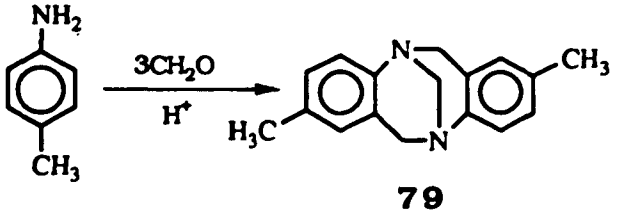
Could we not use TB and its analogues as hosts to recognize different enantiomers? Toda, et al., found that tertiary acetylenic alcohols could be resolved efficiently by inclusion compound formation

with (-)-sparteine (7) which, like brucine, can be used for optical resolution by inclusion compound formation.[61b] TB has some similarity in structure to sparteine as it does to the rigid diol **50**. Moreover, the two aryl rings of TB may increase the efficiency of stereoisomer recognition relative to sparteine by the interaction of the π-electrons of the host and guest molecules. TB's rigid chiral armatures, substantial cleft, the roof shaped geometry of the molecule and its C_2 symmetry all suggest that it may be a good candidate substance for studies of optical resolution by inclusion compound formation.

Following trials of resolution by clathrate formation with enantiopure TB, it might be possible to answer the questions on Sec. 1.4. This was our intent and goal at the start of our research.

1.6 Synthesis and Resolution of Tröger's Base

The synthesis of TB was first reported in 1887[146] and it was studied in detail by Spielman in 1935.[153] Such molecules are readily prepared from aniline derivatives and formaldehyde. (Eq. **6**) More efficient syntheses of TB and analogues have been described in the recent literature.[148a, 149]

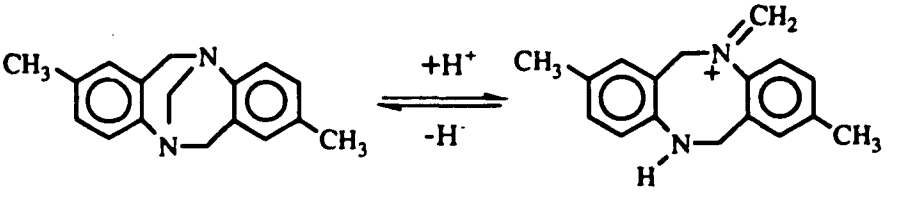


79 (6)

Eq. 6 The synthesis of Tröger's base.

TB was first resolved into its enantiomeric forms by Prelog and Wieland.[147] Resolution of racemic TB with acidic resolving agents, e.g., 10-camphorsulfonic acid, led to the finding that partially resolved samples undergo racemization in acid medium. In order to circumvent the racemization, TB was subjected to resolution by chromatography on an enantioselective stationary phase (lactose).[147] All subsequent reports of resolution of TB up to 1991 have been of chromatographic resolutions[154, 155] with the consequence that only small amounts of optically active TB have been available for study or evaluation of properties. Moreover, it has been asserted that resolution of TB through formation of diastereomeric salts is not feasible.[156]

Prelog and Wieland implicitly assumed early in 1944 that, in dilute hydrochloric acid, TB formed a monohydrochloride. Simultaneously the aminal bridge between the two nitrogens broke to form iminium ion **80**, **80**, a flexible intermediate easily able to achieve planarity. Since bonding of the methylene group to the protonated nitrogen can take place with equal ease from either side of the eight membered ring "plane," restoration of the methylene bridge leads to racemic TB.[154]



79 **80**

In a recent study, Greenberg, et al.,[157] sought evidence for iminium ion **80** suggested by Prelog and Wieland as being the intermediate responsible for the racemization of TB. They synthesized Tröger's base and its monohydrochloride to analyse these two compounds by ^{1}H NMR and UV. They found that an iminium was not present in significant concentration in dil. HCl; however the anilinium ion did not change in its NMR spectrum up to 180 °C when TB was dissolved in concentrated HCl. Although Greenberg's investigations did not uncover evidence for such an intermediate by NMR and UV analysis, their study implied that racemization might not be as facile in concentrated acid as it is in dilute acid. Their study encouraged us to consider whether a diastereomer-mediated resolution might be feasible after all with a strongly acidic resolving agent.

1.7 Tröger's Base DSC, CD, and UV Analyses

Although Tröger's base was studied in detail as early as 1935, the study of its physical properties was still fragmentary at the beginning of this study. We were interested in using Tröger's base in a study of molecular recognition phenomena. A study of the properties of racemic and especially of enantiomercally pure Tröger's base was a desirable adjunct to its application in the aforementioned phenomena.

1.7.1 Binary Melting Point Phase Diagrams

The utility and importance of binary melting point phase diagrams in resolutions and in the determination of enantiomer composition has been detailed by Jacques, et al.[158] Three fundamental types of enantiomer mixtures may be characterized by their melting point (fusion) diagrams : (a) conglomerates. These are equimolecular mixtures of two crystalline enantiomers that are, in principle, mechanically separable. These 1:1 mixtures melt as if they are pure substances and thus fit the definition of an eutectic; (b) racemic compounds, which are characterized by a crystal form in which the two enantiomers coexist in the same unit cell; (c) solid solutions, in which the two enantiomers of a given compound form mixed crystals. These fusion diagrams are illustrated in Fig. **10.**

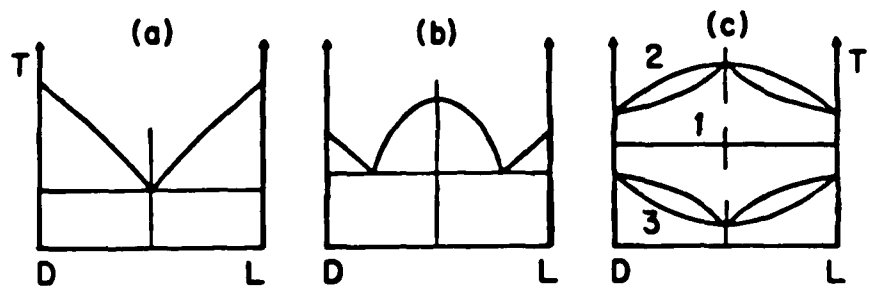


Fig. 10 Binary phase diagrams illustrating the three fundamental types of crystalline racemates (a) conglomerate (b) racemic compound (c) solid solution: 1, ideal; 2, with a maximum; 3, with a minimum.[157]

The techniques best adapted to the construction of phase diagrams are differential scanning calorimetry (DSC) and differential thermal analysis (DTA).[158]

1.7.1.1 Differential Scanning Calorimetric (DSC) Analysis

Differential scanning calorimetry (DSC) is a sophisticated instrumental technique for the measurement and characterization of the thermal properties of materials. Most crystalline or semicrystalline materials undergo melting. Exceptions occur if the material sublimes or decomposes prior to reaching the melting temperature. Melting is, however, the most commonly encountered thermal behavior and is generally observed as a rather sharp endothermic peak on a DSC trace. The area under the melting peak is a direct measure of the heat of fusion for the material and the melting point temperature is recorded simultaneously.

1.7.1.2 Theoretical Phase Diagram of Tröger's Base

Schröder, Van Laar, and Le Chatelier almost simultaneously proposed an equation relating the composition of mixtures to their melting points or, more precisely, to the termination of fusion, T^f. For the case of enantiomer mixtures, the Schröder-Van Laar equation may be written as follows (Eq. 7).[158]

$$\ln x = \frac{\Delta H^f_R}{R}\left(\frac{1}{T^f_R} - \frac{1}{T^f}\right) - \frac{C^l - C^s_R}{R}\left(\ln\frac{T^f_R}{T^f} + 1 - \frac{T^f_R}{T^f}\right) \qquad (7)$$

In this equation, x is the mole fraction of the more abundant enantiomer ($0.5 \leq x \leq 1$) of a mixture whose melting terminates at T^f (in degrees K); ΔH^f_A (in cal.mol^{-1}) and T^f_A (also in degrees K) are the

enthalpy of fusion and melting point of the pure enantiomers, respectively; C^l and C^s_A (in cal. mol^{-1}. K^{-1}) are the specific heats of the liquid and of the solid enantiomer respectively, while R is the gas constant (R = 1.9869 $cal.mol^{-1}.K^{-1}$)

The second term of Eq. 7 containing the specific heats is generally negligible relative to the first term. Equation 8 is always employed in its simplified form.[158]

$$\ln x = \frac{\Delta H^f_A}{R}\left(\frac{1}{T^f_A} - \frac{1}{T}\right) \qquad (8)$$

The equation of Schröder-Van Laar not only permits the calculation of the liquids curve from the melting point and the enthalpy of fusion of a pure enantiomer, in the case of a conglomerate, but also for the racemic compound enantiomer branch, that is curve $T^f_A E_D$ (and $T^f_A E_L$) in Fig. 11.

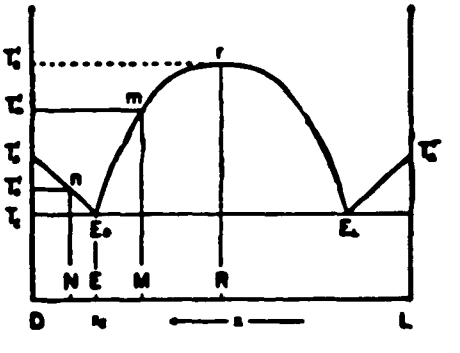


Fig. 11 Common melting point diagram of enantiomers forming a racemic compound .[157]

The $E_D rE_L$ part of the curve, the racemic compound branch, can be calculated by means of the Prigogine and Defay equation (Eq. **9**):

$$\ln 4x(1-x) = \frac{2\Delta H^f_R}{R}\left(\frac{1}{T^f_R} - \frac{1}{T^f}\right) \qquad (9)$$

in which x represents the mole fraction of one of the enantiomers in the mixture whose melting point (end of fusion) is T^f (in degrees K); T^f_R (also in degrees K) and ΔH^f_R (cal. mol^{-1}) are, respectively, the melting point and the enthalpy of fusion of the racemic compound; and R (1.9869 cal. $mol^{-1}.K^{-1}$) is the gas constant.[158]

1.7.1.3 Circular Dichroism (CD) and UV Analysis of TB

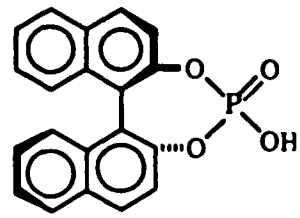
Circular dichroism (CD) has been applied to the determination of the configuration of TB.[159]

In TB, two identical aniline chromophores exhibiting strong π-π^* absorption are located asymmetrically with respect to each other. The exciton interaction between the two chromophores splits the excited state into two energy levels, which generate Cotton effects of mutually opposite signs. This leads to a two component CD spectrum separated by the energy gap $\Delta\lambda$ (Davydov Splitting). Summation of the component Cotton effects results in the solid curve having two extrema, respectively, the first Cotton effect and the second Cotton effect. Positive chirality corresponds to positive first and negative

second CD Cotton effects at longer and shorter wavelengths respectively, while negative chirality corresponds to negative first and positive second Cotton effects at shorter and longer wavelengths respectively.[160] These signed properties can be linked to the sample's configuration in empirical ways as well as through theoretically based models.

1.8 Determination the Configuration of TB

The correct structure of Tröger's base was established by Spielman in 1935, and the base was first resolved into its enantiomeric forms by Prelog and Spielman.[153] The configurational assignment of Tröger's base was carried out in 1967 by Mason, et al., who measured the UV absorption and the circular dichroism spectra of the (+)- and (-)-isomers of Tröger's base. The spectra were analyzed by means of the coupled dipole model, in which the excitation moments of the two aniline chromophores interact to give helical charge displacements responsible for the optical rotatory power of the corresponding absorption bands. Based on exciton chirality (coupled oscillators) calculations,[159] the configuration of (+)-Tröger's base was deduced to be 5*R*, 11*R* and has been so cited in the literature since 1967.



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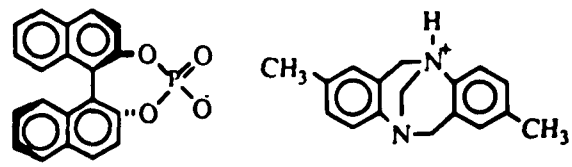
In our resolution of Tröger's base, nice crystals of salt **82a** were obtained [(+)-**79**·(-)-**81**] [(-)-Binaphthylphosphoric Acid: (-)-BNP = (-)-**81**] [**82b**: (-)-**79**·(+)-**81**]. This made it possible for Prof. Paul Williard (Brown University) to undertake an X-ray structural analysis (Fig. **27**) and to thereby determine independently the absolute configuration of Tröger's base. The results are shown in Figures **24**-**26**. Conclusions are made in Chapter III.



82a

1.9 Application of Tröger's Base as an NMR Chiral Solvating Agent (CSA)

Chemists have long appreciated that, in principle, a chiral environment might dissimilarly perturb the properties of enantiomeric molecules, alter the stereochemical course of reactions, or imbue otherwise achiral molecules with chiral properties. This principle has been embodied in many forms in the practical applications of selectively preparing, separating, and determining the absolute configuration and enantiomeric purity of optical isomers.

NMR spectroscopy is a sensitive probe for the occurrence of solvent-solute and solute-solute interactions, and it has provided some of the most detailed information concerning the nature of these interactions. Chiral solvating agents (CSA),[161] such as 2,2,2-trifluoro-1-(9-anthryl) ethanol (TFAE), or 1-phenylethylamine (PEA),[162] attractively interact with appropriate enantiomeric solutes, engendering different spatial environments for their nuclei measurable by NMR methods. Here, the "solute" refers to a substance which may be racemic, enantiomerically enriched, or even a single enantiomer, such as many racemic alcohols in this dissertation. In all CSA-solute combination cases, the CSA and the solute have the common feature of complementary functionality, which permits their interaction. Both are in general hydrogen bond donors or acceptors such as amines, alcohols, sulfoxides, cyclodextrins, crown ethers, or peptides, which interact with appropriate enantiomeric solutes. For example, TFAE incorporates a relatively acidic hydroxyl group and interacts strongly with solutes having one or more basic sites. The result is that the chirality of CSA influences solute spectral behavior. The different average spatial environments of solute nuclei induced by CSA correspond to different magnetic environments that in turn lead to nonequivalence in the spectra of two enantiomers measurable by NMR.

TB's special characteristic of structure[163] make it especially suited to incorporation in molecular systems. Enantiopure TB should be considered as a good candidate substance for application as an NMR

chiral solvating agent (CSA). The mechanism of CSA will be discussed in Chapter III. All results are summarized in Table 18.

1.10 Resolution of Alcohols by Inclusion Compound Formation with Tröger's Base

Enantiopure TB was considered as a possible inclusion host for resolution for the following reasons:

1) Toda's very successful resolution of compounds **12a-m**, **13** and **14** by inclusion compound formation with brucine. All samples recovered from the inclusion compounds attained 100% ee.[64, 65] However, Toda pointed out that, in some cases, resolution with sparteine as host is much more effective than with brucine, since sparteine inclusion compounds can be purified by recrystallization.[61b] This is in addition to the apparent lower toxicity of sparteine relative to brucine.

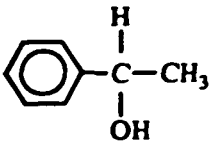
Tertiary acetylenic alcohols can be resolved very efficiently by inclusion compound formation with (-)-sparteine.[61b, 64, 65] The structure of TB is analogous to that of sparteine. Moreover, being synthetic, both enantiomers of TB were likely to be available. With both enantiomers of a resolving agent available, one can obtain both enantiomers of a (racemic) resolution substrate whereas with the natural product sparteine, resolution will easily provide only one enantiomer in a resolution.

Furthermore, there are two aromatic rings in TB's structure, each of which bears a methyl group. This is possible to synthesize varied derivatives of TB.[164] It is thus reasonably chosen as a potential host resolving agent.

2) TB's sharply folded geometry, relatively rigid structure, two aromatic ring armature, and C_2 symmetry let us believe that enantiopure TB in the crystal form might incorporate channels or cavities permitting inclusion compound formation.

3) It is evident that enantiopure TB can serve as a chiral solvating agent.[163] The results encouraged us to believe that enantiopure TB might act as a resolving host in inclusion compound formation.

Considering the importance of hydrogen bonding in inclusion compound formation, the following alcohols and other compounds were selected as candidates in the study of resolution by inclusion compound formation with Tröger's base:



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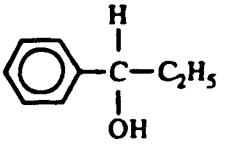

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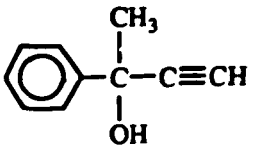

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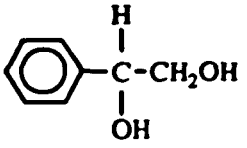

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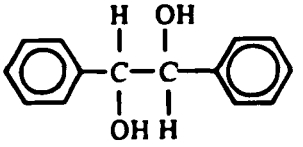

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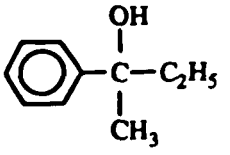

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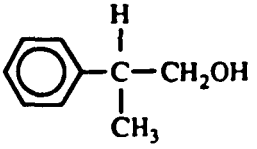

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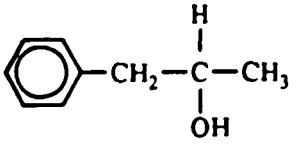

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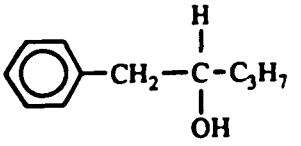

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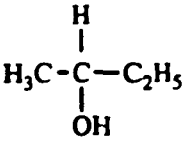

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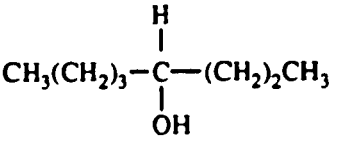

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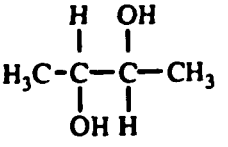

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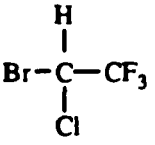

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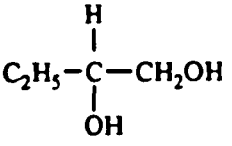

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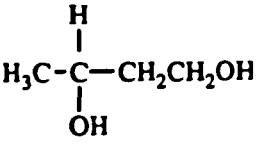

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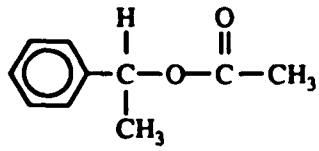

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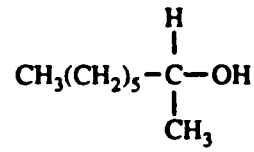

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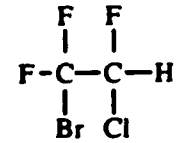

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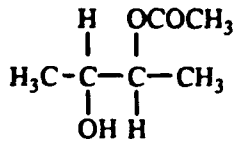

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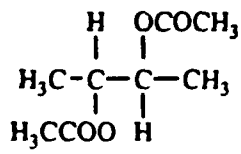

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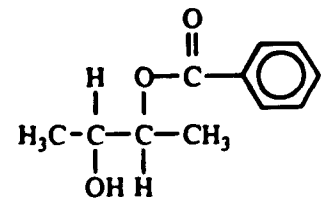

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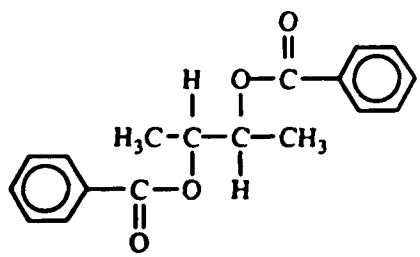

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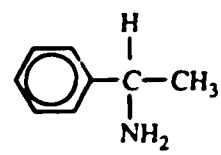

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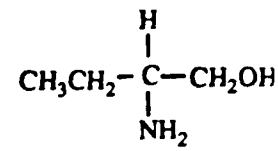

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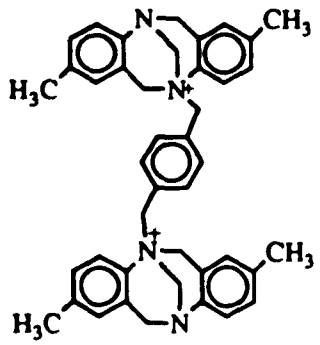
1.11 Quaternary Onium Salts Derived from Tröger's Base as Inclusion Hosts.

Vögtle, et al. have described numerous organic onium compounds that serve as hosts for inclusion compound formation, with, among others, alcohols.[67, 165] These onium hosts have a remarkable ability to include a variety of neutral compounds having a wide range of sizes and geometries.

Moreover, Weber, et al.[79] found that quaternary salts derived from racemic Tröger's base (**107a/b-110**) may act as inclusion hosts. They made several racemic quaternary Tröger's base salts (**111-112a/b**) by common alkylation methods.[166] These products are all mono-quaternary salts. No bis-quaternary products of Tröger's base are found under their reaction conditions. Although all of these salts are derived from racemic Tröger's base, it is noteworthy that all these host molecules are chiral.

As a general outcome of the clathrate study, Weber, et al., observed that all quaternary Tröger's base salts investigated showed inclusion properties with numerous aromatic guest solvents (Table 1).



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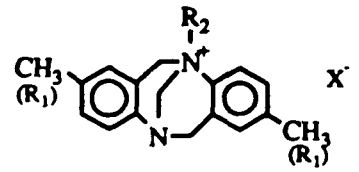
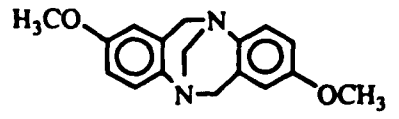


107a/b-109



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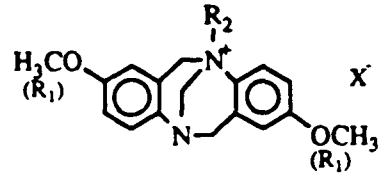


112a/b-113

Chiral onium salts **107a/b-109**, **110**, **112a/b-113**

No.	R_1	R_2	X
107a/b	CH_3	CH_3	CH_3SO_4 /I*
108	CH_3	CH_2-CH=CH_2	Br
109	CH_3	CH_2-(p-C_6H_4)-CH_3	Br
112a/b	OCH_3	CH_3	CH_3SO_4 /I
113	OCH_3	CH_2-(p-C_6H_4)-CH_3	Br

* **a** = CH_3SO_4 **b** = I

Table 1. Clathrates Formed with Host Compounds 107a/b-110 and 112a/b-113[167]

Onium Salt	Molar Ratio (host : guest)	Guest Molecules
107a/b, 108, 112a/b	1:1	benzyl alcohol
	2:1	dioxane, benzene, toluene, ethylbenzene chlorobenzene, *o*-, *m*-, *p*-xylene, *p*-chlorotoluene, D,L-1-phenylethanol, benzaldehyde, cyclohexanone.
	3:1	mesitylene, acetophenone,
	3:2	cyclohexane,
109, 113	1:1	ethanol, benzene, dioxane, toluene,
	2:1	acetone, 1-butanol, benzene, dioxane

From the above, we may conclude that:

1) Quaternary Tröger's bases as racemates do form inclusion compounds with various solvents. X-Ray analysis of the inclusion compound, **107b**. 0.5 dioxane, clearly reveals clathrate type of inclusion.[79]

2) The inclusion selectivity of host onium salts to guest molecules depends on the host molecules structures. Host compounds with similar structures exhibit similar inclusion behavior to guest

compounds. The bigger the difference in size of R_2, the bigger the difference in guest selectivity, and also the bigger the difference in stoichiometry. Compounds (±)-**107a/b**, $R_2 = CH_3$, have more guest selectivity than does (±)-**109**, R = CH_2-(*p*-C_6H_4)-CH_3; and also (±)-**107a/b** have different stoichiometry from (±)-**109**. These are illustrated in Table 1.

3) The competition experiments showed that the certain onium salt host, at least with (±)-**107a**, exhibited selectivity for analogous guests. When (±)-**107a** was recrystallized from 1:1:1 mixture of dioxane, benzene and toluene, dioxane is selectively incorporated into crystals of (±)-**107a** from mixtures, benzene being preferred over toluene.[79]

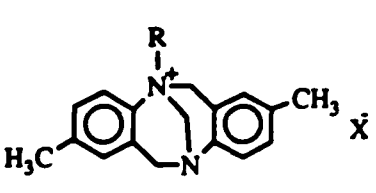
Finally, we found that when we synthesized enantiopure Tröger's base methosulfate (see Chapter III) in different solvents, such as benzene, dichloromethane and ethanol, the NMR spectra always showed these solvents to be included in the onium salt. Moreover, ethanol is indeed included in the (+)TB·(-)BNP salt as observed by X-ray analysis (Fig. **27**). This phenomenon was never observed by NMR when enantiopure Tröger's base was crystallized from these solvents, even though very nice crystals of enantiopure TB were obtained. It would appear that quaternary Tröger's bases have more power for inclusion compound formation than Tröger's base alone.

1.12 Resolution of Alcohols with Enantiopure Tröger's Base Onium Salts

The importance of organic onium compounds for host-guest interaction in biological processes has been long recognized, for instance in the electrostatic binding of biologically active substances to receptors or of substrates to enzymes.[168] In contrast, the versatility of synthetic onium compounds as host molecules in abiotic chemistry has only been investigated in detail for the last few years. The use of clathrate chemistry to induce precise, and chiroselective guest inclusion in crystals is still in its infancy. The basic prerequisite is the inclusion of chiral species in chiral crystal cavities.[72, 73]

The above mentioned reports of inclusion compound formation and selectivities of TB onium salts encouraged us to consider whether enantiopure TB onium salts might not be better hosts for the resolution of chiral alcohols than enantiopure TB itself.

Enantiopure TB salts, **82a** and **107a**, were prepared for trial as an inclusion hosts. Other onium salts, such as **114**, **115** and **116**, were also selected as possible inclusion hosts in resolution of alcohols. The results are described in Sec. 3.1.3 & 3.1.4.



114 R = H_3CO-C$_6$H$_4$-CH_2 X = Cl

115 R = H_3C-C$_6$H$_4$-CH_2 X = Br

116 R = C$_6$H$_5$-CH_2CH_2 X = Cl

1.13. Brucine as a Host for Exploratory Resolutions by Inclusion Compound Formation

Brucine is known to resolve not only polar compounds, such as chiral acids, but also neutral compounds, such as (±)-2,3-dibromobutane,[169, 106] bromochlorofluoromethane,[59] and some of the prop-2-yn-1-ol derivatives **12**, **13**, **14**. All of these are now understood to occur by inclusion compound formation with brucine serving as host.[64, 61b, 65] By the same method, the cyanohydrin **17**[57] and the simple secondary alcohols **18**[170] were also easily resolved by brucine.

At the very beginning of our research project, we attempted resolution by inclusion compound formation with brucine as host. We did this not only to help us to get experience in resolution by inclusion compound formation, but also to help us to begin thinking about and understanding the nature of the nonbonded interaction between host and guest, and about the function of shape and size of the host and guest in inclusion compound formation. The analysis of the inclusion compounds, the recovery of host and guest, ee measurement of the enantiomer composition of the resolved compounds, are all essential in the study of resolutions by inclusion compound formation.

Chapter II

Experimental

2.1 General Methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on Bruker NR/300 (300 MHz) or Bruker NR/200 (200 MHz) FT spectrometers, and deuterium was used as an internal lock. Tetramethylsilane (δ 0 ppm), chloroform $CDCl_3$ (δ 7.26 ppm), DMSO-d_6 (δ 2.49 ppm) or acetone-d_6 (δ 2.04 ppm) were used as internal standard references. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker NR/300 (300 MHz) spectrometer using a deuterium lock and deuterochloroform as internal standard (δ 77.0). Chemical shifts (δ) are reported in both ^{1}H and ^{13}C NMR spectra in ppm downfield from tetramethylsilane. The NMR data of guest compounds are reported as underlined values. FT infrared spectra were measured on a BIO-RAD Digilab FTS 40 spectrometer. Mass spectra were obtained on a Finnigan MAT SSQ-70 GC-MS Quadrupole system. The molecular ion peak is labeled as (M^+).

Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory (Woodside, New York). Melting points (uncorrected) were determined on a Thomas-Hoover Unimelt capillary melting point apparatus or Fisher-Johns melting point apparatus. Microweighing was done on a Cahn 26 Automatic

Electrobalance (Cahn Instruments, Inc.) and semi-micro weighing on an Oertling balance. Differential Scanning Calorimetry (DSC) thermal scans were obtained on a Perkin-Elmer Model DSC-2 Differential Scanning Calorimeter. Ultraviolet Visible (UV) spectra were obtained using an AVIV Ultraviolet-Visible Spectrophotometer, Model 14 DC UV-VIS (AVIV Associates, Inc.). Circular Dichroism (CD) spectra were obtained on an AVIV Circular Dichroism Spectropolarimeter Model 60DS. (AVIV Associates, Inc.). Optical rotations were measured on a Perkin-Elmer 141 polarimeter, in a 1 decimeter microcell fitted with a water jacket. The cell temperature was maintained at 25±0.1 °C by means of a Forma-Scientific circulating bath. Gas Chromatography (GC) was performed on a Hewlett-Packard 5890A Gas Chromatograph fitted with a flame ionization detector.

Flash chromatography was carried out with Merck 230-400 mesh ASTM silica gel.

Analytical TLC was performed using Merck 250 mM silica gel plates with gypsum binder and fluorescent indicator.

Preparative TLC was performed using Analtech and Merck silica plates (2 mm thickness) containing a fluorescent indicator. Visualization was effected normally with iodine or ultraviolet light.

Dichloromethane, acetone, hexane, carbon tetrachloride and chloroform were dried over 4 Å molecular sieves. New 4 Å molecular

sieves were activated and dried at 310 °C for 12 h. Used 4 Å molecular sieves were dried at 310 °C for 3 h.

Abbreviations: br= broad, s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet.

2.2 Starting Materials

p-Toluidine was purchased from Lancaster Synthesis Ltd., brucine from SIGMA Chemical Company, (±)-binaphthylphoshoric acid (BNP) and (+)-10-camphorsulfonic acid from Aldrich Chemical Co., and (+)-cinchonine from Eastman Chemical Company. A sample of (-)-1,3-dioxaphosphorinane-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-2-oxide (DOPO) was generously provided by Andeno, BV, Venlo, the Netherlands.

2.3 Experimental

2.3.1 Purification of *p*-Toluidine

To a stirred mixture of 150.0 g of impure black *p*-toluidine (mp 42-44 °C) and 200 mL of ethanol (100%) was added 15 g of activated carbon and the solution was boiled for 10 min. The solution was filtered immediately and was cooled to 0 °C. It was kept at 0 °C for 2 h, the brown crystals which formed were filtered, washed with cold ethanol and dried in vacuum (2 mm Hg) at room temperature, to give

123.1 g of p-toluidine, mp 43-45 °C. Two spots were observed by TLC (eluant: acetone : ether = 3 : 2).

To a stirred mixture of 123.1 g of this first crop of *p*-toluidine and 200 mL of acetone was added 12.3 g of activated carbon and the solution was boiled for 10 min. The solution was filtered immediately and was cooled to 0 °C. It was kept at 0 °C for 2 h, and brownish crystals which formed were filtered, washed with cold acetone and dried in vacuum (2 mm Hg) at room temperature, to give 65.2 g of *p*-toluidine, mp 44-46 °C. Two spots were observed by TLC. (eluant: acetone : ether = 3 : 2)

To a stirred mixture of 65.2 g of the second crop of *p*-toluidine and 120 mL of ethanol was added 7.0 g of activated carbon and the solution was boiled 10 min. The solution was filtered immediately and was cooled to 0 °C. The solution was kept at 0 °C for 2 h, very brownish crystals were filtered, washed with cold ethanol and dried in vacuo (2 mm Hg) at room temperature, to give 47.1 g, (31.4%) of p-toluidine, mp 45-46.5 °C (lit.: mp 45-47 °C).[171] One spot was observed by TLC. (eluant: acetone : ether = 3 : 2)

2.3.2 Synthesis of Tröger's Base

2.3.2.1 Synthesis of Tröger's Base[164]

To an ice cooled solution of 30.0 g (0.280 mol) of *p*-toluidine in 300 mL of 95% of ethanol, was added 135 mL (1.67 mol) of formalin.

The solution became milky. Then, 114 mL (1.3651 mol) of concentrated HCl was added slowly. The color of the solution changed in order from white to orange to red to deep red. The reaction solution was then stirred at room temperature under nitrogen gas for 24 h, giving a clear and deep red color. The volatile components of the reaction mixture were removed under reduced pressure at 40-50 °C until one-half of the original volume remained. The residue was poured into a 2L separatory funnel containing 1300 mL of H_2O and 300 mL of concentrated NH_4OH. The solution became yellowish and milk like, and yellow crystals appeared. The resulting mixture was then extracted three times with 100 mL of CH_2Cl_2. The combined organic phases were washed twice with 150 mL of saturated aqueous $NaHCO_3$ and with 200 mL of saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and filtered. The CH_2Cl_2 was then removed under reduced pressure, giving 39.2 g of crude product.

2.3.2.2 Purification of Tröger's Base by Flash Chromatography

Crude TB (47.4 g) was purified by flash chromatography (50 × 800 mm column, 124 g of silica gel, 1200 mL of eluant: AcOEt : CH_2Cl_2 = 2 : 3) to give a total of 28.4 g of TB which showed two spots on TLC (mp 124-126 °C) and 16.7 g of TB which showed five spots on TLC (mp 112-116 °C) (eluant: AcOEt: CH_2Cl_2 = 7 : 1).

28.4 g of the first product and 16.7 g of the second product were purified by flash chromatography separately (50 × 800 mm column, 124 g of silica gel, 1200 mL of eluant: AcOEt : CH_2Cl_2 = 7 : 1)

to give a total of 19.0 g (54.3%) (based on 0.28 mole of toluidine) of TB as white, wooly crystals, mp 138-139 °C, which showed one spot on TLC. (lit. mp 125-128 °C).[164]

2.3.2.3 Purification of Tröger's Base by Crystallization

Crude TB (39.2 g) was dissolved in the minimum amount of hot AcOEt and CH_2Cl_2 (7 : 1). Yellow crystals appeared when the solution was cooled to 0 °C. After being washed with cold solvent, the crystals were dried and then recrystallized four times from the same solvent, giving 11.2 g (mp 139 °C) of white crystals. TLC revealed one spot.

The residue was a sticky and deep red solution after keeping at 0 °C overnight. Yellow crystals (7.5 g) were obtained by crystallization; these crystals were recrystallized three further times to give 3.9 g (mp 139 °C) of pure white TB. The combined residues were purified by flash chromatography (50 × 800 mm column, 124 g of silica gel, 1200 mL of eluant: AcOEt : CH_2Cl_2 = 7 : 1), giving two product fractions, I and II. Fraction I was purer than II.

Fraction II was recrystallized from hot AcOEt. Cooling to 0 °C gave crystals which were washed and dried to give 4.8 g of TB (III). TB III was combined with TB I, and recrystallized from AcOEt : CH_2Cl_2 (7 : 1) three times to obtain 3.2 g of pure TB (mp 139 °C).

Total pure solid = 18.3 g (52.2%). (based on 0.28 mole of toluidine)

^1H NMR ($CDCl_3$): δ 2.20 (s, 6 H), 4.29 (s, 2 H), 4.37 (q, AB, J = 16.5 Hz, 4 H), 6.69 (s, 2 H), 6.93 (br d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H).

^{13}C NMR ($CDCl_3$): δ 20.7, 58.7, 67.1, 124.7, 127.3, 127.6, 128.1, 133.2, 145.6

IR (KBr): 2930, 1490, 1320, 1300, 1205, 1185, 960, 950, 895, 825 cm^{-1}.

MS: 251.3 (base), 250.3 (M^+).

2.3.3 Resolution of Binaphthylphosphoric Acid (BNP) with Cinchonine[172]

2.3.3.1 BNP Salt Formation with Cinchonine

To a stirred mixture of 63.4 g (215.3 mmol) of cinchonine and 780 mL of MeOH was added 75.0 g (215.3 mmol) of (±)-binaphthylphosphoric acid (BNP). The mixture was heated until solution of all solids was achieved, and 330 mL of water was added dropwise during 20 min with vigorous stirring, while the temperature was maintained at 70-80 °C.

When addition of the water was complete, the solution was allowed to cool slowly to room temperature with stirring.

Crystallization started at approximately 65 °C. Stirring was continued until the solution attained room temperature. Crystals were collected by filtration, washed with three 18 mL portions of a mixture of MeOH : H_2O (2 : 1) and air dried to afford 67.0 g of (+)-BNP· cinchonine salt, $[\alpha]^{25}_D$ +400.2 (c 1.0, MeOH).

The mother liquid was concentrated to dryness by rotary evaporation giving 66.7 g of salt of (-)-BNP· cinchonine.

2.3.3.2 Isolation of Enantiopure BNP from the Salt of Cinchonine Binaphthyl Phosphate

A stirred mixture of 67.0 g of (+)-BNP· cinchonine salt and 440 mL of EtOH (100%) was heated to obtain a clear solution at reflux. To this was added 580 mL of 6N HCl during 30 min. with vigorous stirring while the temperature was maintained at about 80 °C. Greenish crystals appeared when 580 mL of 70% HCl was added. The solution was stirred at room temperature for an additional 2.5-3.0 h.

The solid which precipitated was collected, washed with three 30 mL portions of water and air dried to afford 28.9 g (77.1%) of little greenish crystals of (+)-BNP, $[\alpha]^{25}_D$ +623.5 (c 1.0, MeOH) $[\alpha]^{25}_{546}$ + 717 (c 1.1, MeOH) (lit. $[\alpha]^{25}_{546}$ + 712) (c 0.98, MeOH).[172]

The (-)-BNP· cinchonine salt (66.7g) was added to 440 mL of EtOH and 580 mL of 6N HCl to similarly give 28.9 g (77.0%) of

(-)-BNP, $[\alpha]^{25}_{D}$ -618.2 (c 1.1, MeOH) $[\alpha]^{25}_{546}$ -716 (c 1.0, MeOH) (lit $[\alpha]^{25}_{546}$ - 717) (c 1.0, MeOH).[172]

2.3.4 Resolution of Tröger's Base with (+)-Binaphthylphosphoric Acid

2.3.4.1 Salt Formation with Tröger's Base and (+)-Binaphthylphosphoric Acid

To a stirred mixture of 12.5 g (50 mmol) of TB and 260 mL of absolute EtOH was added 17.4 g (50 mmol) of (+)-BNP. The solution was immediately heated to reflux, stirred at reflux for 1 h, cooled during 1 h to room temperature, then stirred at 0 °C for 1 h. Crystals were collected by filtering, then washed at 0 °C with EtOH, and dried, giving 25.9 g of (-)-TB·(+)-BNP·EtOH salt (**82b**), mp 161-162 °C, $[\alpha]^{25}_{D}$ +336.9 (c 1.0, MeOH). The mother liquid was combined with the crystal wash and concentrated by rotary evaporator to 100 mL. After one week at room temperature 4.0 g, mp 161.5-162.0 °C, $[\alpha]^{25}_{D}$ +354.2 (c 0.98, MeOH), of nice crystals of (-)-TB·(+)-BNP·EtOH salt were collected.

*^{1}H NMR ($CDCl_3$): δ <u>1.10 (t, J = 6.0 Hz, 3 H)</u>, 3.17 (s, 6 H), <u>3.54 (q, J = 6.0 Hz, 2H)</u>, <u>3.85 (br s, 1 H)</u>, 4.31 (q, AB, J = 15.0 Hz, 4H), 4.37 (s, 2H), 6.99 (d, J = 3.0 Hz, 2H), 7.14 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 7.49-8.02 (m, 12H).

* Underlined signals are those of guest molecules.

Anal: Calcd. for $C_{39}H_{37}N_2O_5P$ [$(C_{17}H_{18}N_2).(C_{20}H_{13}O_4P).(C_2H_5OH]$: C, 72.65%; H, 5.79%; N, 4.35%; P, 4.80%. Found: C, 72.31%; H, 5.95%; N, 4.29%; P, 4.76%.

2.3.4.2 Isolation of Enantiopure (-)-Tröger's Base from the (-)-TB·(+)-BNP·EtOH (82b)

To a stirred mixture of 19.6 g of (-)-TB·(+)-BNP·EtOH salt in 150 mL of MeOH and 300 mL of H_2O was added 75 mL of 5% aq. NaOH at 0 °C in 15 min. After stirring the mixture for 0.5 h, 19.0 g of white crystals were collected. This material gave two spots on TLC (eluent: AcOEt : CH_2Cl_2 = 7 : 1).

The first crop (19.0 g) of white crystals was added to 60 mL of 5% aq. MeOH (w/v), and the mixture was heated to give a clear solution. The solution was slowly cooled to room temperature, then to 0 °C, and stored at 0 °C for 3 days, giving 5.6 g of (-)-TB, $[\alpha]^{25}_D$ -282.4 (c 0.29, hexane). During the determination of [α] in hexane, it was found that the product did not completely dissolve. It is possible that there were some sodium BNP salts admixed with the (-)-TB.

Recrystallization of 5.6 g of crude (-)-TB in 20 mL of methanol gave 4.8 g (60%) of nice crystals of (-)-TB, mp 131-131.5 °C (lit. 127-128 °C),[153] $[\alpha]^{25}_{589}$ -313.6 (c 0.31, hexane). [lit $[\alpha]^{25}_{589}$ +287±7 (c 0.281, hexane)][153] [(+)-TB(Fluka): $[\alpha]^{25}_{585}$ +283±1.2 (c 0.30, hexane)]

The combined mother liquors and wash liquids were concentrated (rotary evaporator) to about 32 mL. This solution was kept at 0 °C one week, and gave 0.4 g of nice TB crystals, mp 130.5-131.0 °C, $[\alpha]^{25}_D$ -286.0 (c 0.3, hexane). From the mother liquor of this material, 2.5 g of crude TB was obtained by flash chromatography: 50 × 800 mm column, 124 g of silica gel, 1000 ml of eluant: AcOEt : CH_2Cl_2 = 7 : 1. This crude (-)-TB was recrystallized from 12 ml of methanol, giving 2.1 g of (-)-TB, mp 130.5-131.0 °C, $[\alpha]^{25}_D$ -286.8 (c 0.29, hexane). The total yield amounted to 7.3 g (91%).

^1H NMR ($CDCl_3$): δ 2.20 (s, 6 H), 4.30 (s, 2 H), 4.37 (q, AB, J = 16.5 Hz, 4 H), 6.69 (s, 2 H), 6.92 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H).

2.3.4.3 Recovery of the Resolving Agent, (+)-Binaphthylphosphoric Acid

The silica column used to isolate the last crop of TB from the combined mother liquors was stirred vigorously with 500 mL of boiling MeOH. The mixture was filtered and the extraction with hot MeOH was repeated twice more. All MeOH solutions were combined and concentrated to 250 mL (rotary evaporator).

The mother liquor of the first crop of (-)-TB (above) and 80 mL of 3.3N HCl were added to the 250 mL of concentrate with stirring. White crystals formed and were filtered and washed with three 10 mL portions of water. The crystals were recrystallized from a hot mixture

of 60 mL of methanol and 80 mL of H_2O. Cooling to 0 °C for 1 h gave crystals of (+)-BNP. The crystals were washed and dried, affording 10.0 g of (+)-BNP with $[\alpha]^{25}_D$ +588.6 (c 1.0, MeOH). This material was recrystallized from a hot mixture of 90 mL of MeOH and 45 mL of H_2O, giving (+)-BNP 7.4 g (63%), $[\alpha]^{25}_D$ +618.0 (c 1.0, MeOH).($[\alpha]^{25}_{546}$ + 715 (c 1.0, MeOH)(lit $[\alpha]^{25}_{546}$ + 712) (c 0.98, MeOH).[172]

2.3.5 Resolution of Tröger's Base with (-)-Binaphthylphosphoric Acid

2.3.5.1 Resolution of Tröger's Base with (-)-Binaphthylphosphoric Acid

To a stirred mixture of 2.5 g (10 mmol) of TB and 58 mL of absolute EtOH was added 3.5 g (10 mmol) of (-)-BNP. The mixture was refluxed for 1 h, then cooled gradually during 1 h to room temperature, then kept at 0 °C for 1 h. The crystals which formed were filtered, washed with cold EtOH and dried, giving 5.2 g of (+)-TB·(-)-BNP·EtOH salt, mp 161-162 °C, $[\alpha]^{25}_D$ -339.3 (c 1.0, MeOH).

The mother liquor was combined with the wash liquid and concentrated to 20 mL. This was kept at room temperature one week, giving 0.8 g of nice crystals of (+)-TB·(-)-BNP·EtOH salt, mp 161-162 °C, $[\alpha]^{25}_D$ -341.4 (c 1.0, MeOH).

^{1}H NMR ($CDCl_3$): δ 1.11 (t, J = 6.0 Hz, 3 H), 3.17 (s, 6 H), 3.52 (q, J = 6.0 Hz, 2H), 3.85 (br s, 1 H), 4.31 (q, AB, J = 15.0 Hz, 4H), 4.39 (s, 2H), 7 00 (d, J = 3.0 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 7.50-8.03 (m, 12H).

2.3.5.2 Release of Enantiopure (+)-Tröger's Base from the (+)-TB·(-)-BNP·EtOH Salt

To a stirred solution of 6.0 g of (+)-TB·(-)-BNP·EtOH salt in 40 mL of MeOH and 80 mL of H_2O was added 20 mL of 5% aq. NaOH at 0 °C in 15 min. Stirring was continued for 0.5 h. White crystals were obtained, 5.8 g. TLC of the crystals gave two spots (eluant: AcOEt: CH_2Cl_2 = 7 : 1).

The white crystals (5.8 g) were dissolved in 15 mL of hot MeOH. The solution was slowly cooled to room temperature, and then to 0 °C, and kept at 0 °C for 3 days, yielding 1.8 g of crystals, $[\alpha]^{25}_D$ +276.7 (c 0.3, hexane).

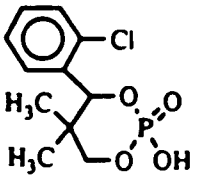
Recrystallization of 1.8 g of the above (+)-TB with 6 mL of methanol gave 1.5 g (60%) of nice crystals of (+)-TB, mp. 131-132 °C, (lit. 127-128 °C)[154] $[\alpha]^{25}_{589}$ +309.0 (c 0.31, hexane). [lit $[\alpha]^{25}_{589}$ +287±7 (c 0.281, hexane)].[154]

The mother liquors from the two recrystallizations and the wash liquids were concentrated to about 8 mL. The solution was kept at 0 °C one week and gave 0.2 g of nice TB crystals, $[\alpha]^{25}_D$ +311.1 (c 0.31 hexane). The mother liquor of this material was purified by flash chromatography (30 × 450 mm column, 42 g of silica gel, 200 mL of eluant: AcOEt : CH_2Cl_2 = 7 : 1), giving 1.1 g of crude (+)-TB. This was recrystallized from 4.5 ml of methanol, giving 0.6 g of (+)-TB, mp 131-

132 °C, $[\alpha]^{25}_D$ +299.4 (c 0.28, hexane). Yield of combined crystals: 2.3 g (92%).

^{1}H NMR ($CDCl_3$): δ 2.20 (s, 6 H), 4.29 (s, 2 H), 4.36 (q, AB, J = 16.5 Hz, 4 H), 6.70 (s, 2 H), 6.93 (br d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H).

2.3.6 Resolution of Tröger's Base with (-)-1,3-Dioxaphosphorinane-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-2-oxide (DOPO)



117 (DOPO)

2.3.6.1 Salt Formation between *rac*-Tröger's Base and (-)-1,3-Dioxaphosphorinane-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-2-oxide (DOPO)

To a stirred solution of 304.3 mg (1.1 mmol) of DOPO in 5 mL of aqueous ethanol (EtOH: H_2O = 2:1) was added 250.0 mg (1 mmol) of racemic TB. The mixture was heated until the solids dissolved, and then stoppered and cooled to room temperature gradually. After 3 days at room temperature no crystals were observed, nor after 3 days at 0 °C. The flask was opened, kept at 0 °C. and by the fourth day, a few crystal appeared. On the sixth day, 130.3 mg of crystals, mp 171-173 °C, $[\alpha]^{25}_D$ -132.4 (c 1.0, MeOH), were collected.

2.3.6.2 Isolation of (-)-Tröger's Base from the (-)-TB·(-)-DOPO Salt

To a stirred mixture of 120.0 mg of (-)-TB·(-)-DOPO salt, 1 mL of MeOH and 1.5 mL of H_2O, was added 0.5 mL of 5% aq. NaOH at 0 °C in 5 min. The mixture was stirred for 1 h, filtered, washed and dried, giving 43.5 mg (34.8%) of (-)-TB, mp 133.5-135.0 °C, $[\alpha]^{25}_D$ - 81.1 (c 0.30, Hexane) (26% ee based on our own resolved enantiopure (-)-TB as reference)

2.3.7 Resolution of Tröger's Base with (R)-(-)-10-Camphorsulfonic Acid

2.3.7.1 Salt Formation between Tröger's Base and (R)-(-)-10-Camphorsulfonic Acid

To a stirred mixture of 256.0 mg (1.1 mmol) of (R)-(-)-10-camphorsulfonic acid and 5 mL of MeOH was added 250.0 mg (1.0 mmol) of racemic TB. The mixture was heated until solution was achieved then cooled to room temperature gradually. After 3 days at room temperature, no crystals were observed, nor after 3 days at 0 °C. The flask was opened and kept at 0 °C. After one week, 71.1 mg, of crystals of TB-camphorsulfonic acid salt, mp 147-149 °C, $[\alpha]^{25}_D$ -25.5 ±0.2, (c 1.1, MeOH) were collected.

2.3.7.2 Isolation of (-)-Tröger's Base from the (-)-TB-(R)-(-)-10-Camphorsulfonic Salt

To a stirred mixture of 65.0 mg of (-)-TB · (R)-(-)-10-camphorsulfonic salt, and 0.5 mL of MeOH and 1.0 mL of H_2O, was

added 0.3 mL of 5% aq. NaOH at 0 °C. Stirring was continued for 20 min.

The solid was filtered, washed, and dried, giving 12.6 mg (10.1%) of (-)-TB, mp 138-139 °C, $[\alpha]^{25}_{D}$ -14.2 ±0.4, (c 0.29, Hexane) (4.5% ee based on our own resolved enantiopure (-)-TB as standard reference).

2.3.7.3 Salt Formation between Tröger's Base and (R)-(-)-10-Camphorsulfonic Acid and Hydrochloric Acid

To a stirred mixture of 128.0 mg (0.55 mmol) of (R)-(-)-10-camphorsulfonic acid, 45.8 ml of 3 N aq. HCl (0.55 mmol) and 5 mL of MeOH, was added 250.0 mg (1.0 mmol) of racemic TB. The mixture was heated until solution was achieved then cooled to room temperature gradually. After 3 days at room temperature, no crystals were observed, nor after 3 days at 0 °C. The flask was opened and kept at 0 °C. After one week, 56.7 mg, mp 146-148 °C, $[\alpha]^{25}_{D}$ -50.3 ±0.7, (c 1.0, MeOH) were collected.

2.3.7.4 Isolation of (-)-Tröger's Base from the Mixed Salt of Section 2.3.7.3

To a stirred mixture of 50.0 mg of (-)-TB·(R)-(-)-10-camphorsulfonic salt, 0.3 mL of MeOH and 1.0 mL of H_2O, was added 0.3 mL of 5% aq. NaOH at 0 °C. Stirring was continued for 20 min, then solid was filtered, washed, and dried, giving 7.2 mg (5.8%) of

(-)-TB, mp 137-138 °C, $[\alpha]^{25}_{D}$ -45.9 ±0.1, (c 0.29, Hexane) (14.6% based on our own resolved enantiopure (-)-TB as standard reference).

2.3.8 Differential Scanning Calorimetry (DSC), Ultraviolet Visible (UV) and Circular Dichroism (CD) Spectra of TB

2.3.8.1 Measurement of Enthalpies and Melting Points of Enantiopure and Racemic TB by DSC

About 2.0 mg each of enantiopure (+)-TB, of Fluka sample and of racemic TB were accurately weighed. The scan rate was selected as 10.0 deg/min, giving the following data which are the average of duplicate experiments (Table 2):

Table 2 **Enthalpies of Fusion and Melting Points of Optically Active TB and Racemic TB**

TB Sample	ΔH (cal/g)	ΔH (kcal/mol)	mp (K)	mp (°C)
(±)-TB (Sec. 2.3.2.3)	23.7	5.9	409.7±0.0	136.7±0.0
(+)-TB (Fluka)	17.3	4.3	403.3±0.1	130.3±0.1
(+)-TB* (Sec. 2.3.5.2)	19.0	4.8	403.9±0.1	130.9±0.1

* (+)-TB was resolved by us. Its rotation is higher than that of Fluka TB.

2.3.8.2 Measurement of Melting Points of Mixtures of the TB Enantiomers by DSC

Mixtures of (+)-and (-)-TB of different enantiomer purities were prepared by dissolving appropriate amounts of (+)-TB (sample of Sec. 2.3.5.2) and (±)-TB (sample of Sec. 2.3.2.3) each in 1 mL of CH_2Cl_2 and evaporating the solutions to dryness. The following samples were obtained: 56.7, 60.8, 67.2, 77.2, 86.5, 91.3, 92.8. (weight %) with (+)-TB in excess. About 2.0 mg of each sample was accurately weighed and loaded in small aluminum pans (sealed). Scan rate (DSC) was selected as 10.0 deg/min. The following data were obtained averagely from duplicate experiments (Table 3):

Table 3 **Melting Points of TB as a Function of Enantiomer Composition by DSC, and Melting Points of the Eutectic Mixture.**

(±)-TB (mg)	(+)-TB (mg)	Enantiomer Composition (weight % of (+)-TB)	Experimental mp (K)[a] Rac. or Enant.[b]	Eutectic
		50.0	409.7	
10.1	1.6	56.7	409.2	392.0
10.0	2.8	60.9	408.4	392.8
9.9	5.2	67.2	406.2	391.8
10.2	12.1	77.2	399.7	392.1
3.8	10.3	86.5	394.3	390.3
2.0	9.8	91.3	397.8	392.4
1.7	10.2	92.8	398.9	392.2
				(391.9)[c]

a. Experimental melting points were measured by DSC.
b. Melting point of racemate or enantiomer.
c. Average mp of eutectic.

2.3.8.3 Determination of TB Enantiomer Purity (% ee) of nearly Enantiopure TB by Differential Scanning Calorimetry (DSC)

Table 4 **Composition of Samples of (+)- and (±)-TB of High e.e. for Determination of the Limits of the DSC Method for Nearly Enantiopure Samples.**

	Sample Number									
TB[a]	1	2	3	4	5	6	7	8	9	10
(+)-TB[b]	8.624	8.700	9.120	9.240	9.621	9.846	10.09	10.44	10.10	11.20
(±)-TB[b]	0.463	0.344	0.292	0.276	0.247	0.221	0.186	0.108	0.081	0.056
(+)-TB%[c]	97.45	98.10	98.45	98.55	98.75	98.90	99.09	99.49	99.60	99.75
%ee	94.90	96.20	96.90	97.10	97.50	97.80	98.20	99.00	99.20	99.50

a. Here the selected solvent is CH_2Cl_2 which gives the nicest crystals.
b. Weighing unit: mg.
c. Weight % (+)-TB.

Mixtures of (+)-and (-)-TB of different enantiomeric purities were prepared by weighing appropriate amounts of (+)-TB and (±)-TB (Table 4) each dissolved in 1 mL CH_2Cl_2. The solutions were evaporated to dryness (pumping at 2 mm for 5 min.). The dry samples (about 2.0 mg each) were scanned with the differential scanning calorimeter in sealed aluminum pans. The scan rate selected for good sensitivity was 1.25 deg/min. Two peaks, melting of the eutectic and of the enantiomer, were observed in DSC scans from samples **1** to **9**. The peak of the eutectic became smaller and smaller going from sample **1** to **9**. There was only an enantiomer peak in the DSC scan of

sample **10**. This means that the minimum % of one enantiomer of TB detectable by DSC is less than 0.5%.

2.3.8.4 Measurement of Ultraviolet Visible (UV) and Circular Dichroism (CD) Spectra of TB

(+)-TB (12.5) mg was dissolved in 10 ml of absolute ethanol. The CD spectrum of (+)-TB was measured in ethanol from 210 to 320 nm. Similarly, the UV spectrum of (+)-TB was measured with the same solution λ_{max} = 220 nm, (ε_{max} = 5170). The results are shown in Figs. **24-25**. Our CD and UV spectra match those recorded by Mason, et al. (Fig. **26**).[159]

2.3.9 Enantiopure TB as NMR Chiral Solvating Agent

2.3.9.1 The Effect of (+)-TB on the NMR Spectra of Various Alcohols at 25 °C

^{1}H NMR spectra (300 MHz) of solutions containing 25.0 mg (0.10 mmol) of (+)-TB (Sec. 2.3.5.2) and 0.10 mmol each of racemic alcohols **83-91**, **93-95**, **98-106** in 0.5 mL of $CDCl_3$ (0.2 M) were run at 25 °C. These spectra were compared to those of the corresponding racemic alcohols (0.2 M in $CDCl_3$) also recorded at 25 °C.

Anisochrony was observed for some groups in the spectra of compounds **83** and **85-87** (0.20 M) in the presence of (+)-TB. However, when a couple of drops of acetone-d_6 were added to the

solutions in the NMR tubes, no anisochrony was observed in **83**, and reduced anisochronous signals were observed in **85-87**. When acetone-d_6 was used instead of $CDCl_3$, no anisochrony was observed in **83**, **85**, **86**. For **87**, $\Delta\delta$ (δ_B-δ_A, see Table 24) was reduced to 0.01 ppm. When a couple of drops methanol were added instead, no anisochrony was observed in all above compounds.

Solutions of **86** and **87** (in presence of (+)-TB) still exhibited anisochrony when their solutions were diluted to 0.15 M. When the alcohol solutions were diluted to 0.10 M with $CDCl_3$, anisochrony completely disappeared in the case of all the alcohols (Table 5).

Table 5 The Effect of the Concentration of Enantiopure TB on the Observation of Anisochrony

Alcohol (in $CDCl_3$)	**83**	**85**	**86**	**87**
0.20 M	+[a]	+	+	+
0.15 M	-[b]	-	+	+
0.10 M	-	-	-	-

a. Anisochrony is exhibited by ^1H NMR.
b. Anisochrony disappeared in diluted solution.

Anisochrony was not clearly evident for the following alcohols: **88**, **90**. When solutions containing 50.0 mg (0.20 mmol) of (+)-TB and 0.10 mmol of racemic alcohol **84**, **88**, and **90** were dissolved in 0.5 mL of $CDCl_3$, respectively (mol. ratio: (+)-TB : (±)-alcohol = 2:1), **84**

exhibited anisochrony in the methyl group signal, but **88** and **90** were still unaffected.

No anisochrony was observed for any of the racemic alcohols in ^{13}C NMR spectra in the presence of (+)-TB.

2.3.9.2 Enantiopure TB as NMR Chiral Solvating Agent at -30 °C

^{1}H NMR spectra (200MHz) of alcohols **84**, **88**, **90** in the presence of (+)-TB (Sec. 2.3.5.2) (mole ratio: (+)-TB : alcohol = 1 : 1) were observed at -10 °C, -20 °C, -30 °C, and -50 °C. None of these alcohols exhibited anisochronous signals.

^{1}H NMR spectra (200 MHz) of **88**, **90** in the presence of (+)-TB were also recorded with a mole ratio: (+)-TB : alcohol = 2 : 1 at -20 °C, -30 °C, and -50 °C. Neither of these alcohols exhibited anisochronous signals under these conditions.

2.3.9.3 Enantiomer Composition (e.e.) of α-Methylbenzyl Alcohol with (+)-TB as Chiral Solvating Agent at -30 °C

2.3.9.3.1 Isolation of α-Methylbenzyl Alcohol from α-Methylbenzyl Hydrogen Phthalate

To a stirred solution of 20% NaOH (10 mL) was added 270 mg (1.0 mmol) of α-methylbenzyl hydrogen phthalate. [This was a sample from the collection of Prof. Wilen[173] $[\alpha]_D^{25}$ +31.3 (c 2.4, EtOH)]

prepared by the method of Downer and Kenyon [lit. $[\alpha]_D^{25}$ +36.5 (c 2.4, EtOH)].[174] The ee of the α-methylbenzyl hydrogen phthalate sample was 85.8% based on the rotation reported by Downer and Kenyon. After being stirred 30 min with base, the α-methylbenzyl alcohol was extracted with three 8 mL portions of CH_2Cl_2. The combined CH_2Cl_2 layers were concentrated (rotary evaporator), leaving crude α-methylbenzyl alcohol, which gave 41.0 mg (33.6%) of **83** after flash chromatographic purification (eluent: AcOEt : CH_2Cl_2 = 3 : 7)

2.3.9.3.2 Measurement of Enantiomeric Excess of Partially Resolved 89 with (+)-TB as CSA at -30 °C

A solution was prepared containing 25.0 mg (0.10 mmol) of (+)-TB, and 12.3 mg (0.10 mmol) of the recovered **83** in 0.5 mL of $CDCl_3$. The observed anisochrony in the ^1H NMR spectrum of this solution at room temperature was insufficient for determination of the ee. At -30 °C, splitting in the CH group was sufficient for determination of the enantiomer ratio. 87.6% ee was calculated by ^1H NMR integration. The ee measurement by ^1H NMR was in good agreement with the polarimetric optical purity.

In a decoupling experiment (irradiation of the methyl group of **83** at room temperature) the CH group became a singlet, and the peaks of the CH groups of the two enantiomers of **83** no longer overlapped. Result: 86.4% ee, hence good agreement with the above data. The decoupling technique seems easier and more efficient in this case than low temperature NMR.

2.3.10 Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with Enantiopure TB.

2.3.10.1 Crystallization from Solutions Containing TB

A hot solution containing 0.10 mmol of a racemic alcohol, 25.0 mg (0.10 mmol) of (+)-TB and 1.5 mL of solvent was cooled to 0 °C. A piece of cotton thread was added as seed, and the solution was kept 15 days at 0 °C. Small amounts of crystals appeared in a few cases. Crystals were very carefully collected by filtration, washing, and drying. The melting point and specific rotation were measured for all crystals. TB was the only compound observed by ^{1}H NMR examination of the crystals. All crystals had average mp 131 °C; $[\alpha]^{25}_D$ + 313.0 (c 0.31, hexane).

The results are listed in Table 8.

2.3.10.2 Crystallization from Sonicated Solutions

A solution containing of 0.10 mmol of racemic alcohol, 25.0 mg (0.10 mmol) of (+)-TB and 1.5 mL of a solvent, was sonicated for 20 min., then cooled to 0 °C. A piece of cotton thread was added as seed, and the solution was kept 15 days at 0 °C.

Small amounts of crystals appeared in a few cases. Crystals were very carefully collected by filtration, washing, and drying. The melting point and specific rotation were measured. TB was the only compound

observed by examination of the crystals by ^1H NMR. All crystals had average mp 131 °C; $[\alpha]^{25}_D$ + 308.0 (c 0.30, hexane).

The results are listed in Table 9.

2.3.11 Attempted Resolution of Racemic Alcohols by Inclusion Formation with (+)-TB·(-)-BNP

2.3.11.1 Crystal Formation with Racemic Alcohols in Presence of (+)-TB·(-)-BNP.

A solution of 0.10 mmol of racemic alcohol, 2-5 mL of solvent and 59.9 mg (0.10 mmol) of (+)-TB·(-)-BNP (**82**) was boiled for 1 h, then cooled to 0 °C and kept 15 days at 0 °C.

Small amounts of crystals appeared in some cases. Crystals were very carefully collected by filtration, washing, and drying. Salt **82** itself was observed by ^1H NMR in many cases. In a very few cases, the crystals were found by ^1H NMR (in DMSO-d_6 or acetone-d_6) to contain alcohol. In no case was anisochrony observed in the NMR spectra. The alcohols were not further investigated.

The results are listed in Table 10.

2.3.11.2 Crystal Formation with Racemic Alcohols in Presence of (+)-TB·(-)-BNP. Effect of Sonication

A solution of 0.10 mmol of racemic alcohol, 2-5 mL of solvent, and 59.9 mg (0.10 mmol) of (+)-TB·(-)-BNP (**82a**) was sonicated for 20 min., then cooled to 0 °C, and kept 15 days at 0 °C.

In many cases crystals appeared in good yield. The crystals were very carefully collected by filtration, washing, and drying. Salt **82a** itself was observed by ^{1}H NMR examination of the crystals in many cases. In very few cases the crystals were found by ^{1}H NMR to contain alcohol. No anisochrony was observed in any of NMR spectra. The alcohols were not further investigated.

The results are listed in Table 11.

2.3.12 Synthesis of Enantiopure Tröger's Base Methosulfate 107a[174]

To a solution of 250.0 mg (1.00 mmol) of (+)-TB dissolved in 5.0 mL of dried CH_2Cl_2 was added 114 µl (151.2 mg; 1.20 mmol) of dimethyl sulfate in portions under nitrogen. The solution was refluxed for 1 h, stirred at room temperature for 2 h, then stirred at 0 °C for 0.5 h. Crystals were collected, washed. Then recrystalized from ethanol, dried under vacuum (25 °C/2mm) for 30 min, giving 270.0 mg (71%) of white crystals, mp 117-9 °C, $[\alpha]_D^{25}$ +684.2±0.3 (c 0.19, CH_2Cl_2) [lit. (±)-TB-methosulfate mp 126 °C).[175]

^{1}H NMR (Acetone-d_6): δ 1.10 (t, J = 6.9 Hz, 3H), 2.21 (s, 3H), 2.26 (s, 3H), 2.90 (s, 1H), 3.43 (s, 3H), 3.55 (q, J = 6.9 Hz, 2H), 3.90 (s, 3H), 4.66 (q, AB, J = 17.1 Hz, 2H), 5.15 (q, J_1 = 11.4 Hz, J_2 = 17.4 Hz, J_3 = 15.6 Hz, 2H), 5.49 (q, AB, J = 15.6 Hz, 2H), 6.92-8.08 (m, 6H).

2.3.13 Resolution of Racemic Alcohols by Inclusion Compound Formation with Enantiopure Tröger's Base Methosulfate 107a

2.3.13.1 Attempted Resolution of Racemic Alcohols by 107a in Different Hot Solvents

A solution of 37.6 mg (0.10 mmol) of (+)-TB·$(CH_3)_2SO_4$, 1-3 mL of solvent and 0.10 mmol of racemic alcohol was boiled for 1 h, cooled and kept at 0 °C for one month. Small amounts of crystals were collected in a few cases. Solvent was detected by ^{1}H NMR examination of the crystals, except those crystals formed from **107a** and alcohol **92** in Me_2CO. Here only **92** was observed in the ^{1}H NMR spectrum, but without anisochrony.

The Results are listed in Table 12.

2.3.13.2 Attempted Resolution of Racemic Alcohols by 107a in Sonication

A solution of 37.6 mg (0.1 mmol) of (+)-TB·$(CH_3)_2SO_4$, 1-3 mL solvent, and 0.1 mmol of alcohol was sonicated for 20 min., then kept at 0 °C for one month. More crystals were collected than under

thermal treatment. Racemic alcohols were observed in six crystals by ^1H NMR, without anisochrony.

The Results are listed on the Table 13.

2.3.13.3 Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with TB Methosulfate Formed *in situ*. [mole ratio: (+)-TB : $(CH_3)_2SO_4$ = 1 : 1]

To 25.0 mg (0.10 mmol) of (+)-TB and 0.10 mmol of alcohol in 1-3 mL solvent was added 9.5 µL (12.6 mg, 0.10 mmol) of $(CH_3)_2SO_4$ in portions under N_2. The resulting solution was boiled for 1 h, then cooled and kept at 0 °C for one month.

More crystals were collected than is described in section 2.3.13.1 and 2.3.13.2 (above). However, the ^1H NMR spectra gave evidence only of formation of TB-methosulfate, and solvent was observed in the majority of the crystal samples. Two alcohols were also observed in the crystal samples by ^1H NMR, but without anisochrony.The alcohols were not further investigated.

The results are listed in Table 14.

2.3.13.4 Attempted Resolution of Racemic Alcohols by Inclusion Formation with TB Methosulate Formed *in situ* [mole ratio: (+)-TB : $(CH_3)_2SO_4$ = 1 : 2]

To 25.0 mg (0.10 mmol) of (+)-TB and 0.10 mmol of alcohol in 1-3 mL solvent was added 19.0 μL (25.2 mg, 0.20 mmol) of $(CH_3)_2SO_4$ in portions under N_2. The solution was boiled for 1 h, then cooled and kept at 0 °C for one month. Crystals were formed and were collected. Racemic alcohols were detected by ^1H NMR in almost half of the crystals. No anisochrony was observed.

The results were obtained in Table 15.

2.3.13.5 Attempted Resolution of Racemic α-Methylbenzyl Alcohol (83) by Inclusion Compound Formation with TB Methosulfate Formed *in situ* in Absence of Solvent [mole ratio: (+)-TB : $(CH_3)_2SO_4$ = 1 : 1.6]

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.5 mL of **83**, was added 15 μL (20.2 mg, 0.16 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was heated for 1 h at 70 °C. Excess **83** and $(CH_3)_2SO_4$ were pumped off at 60± 2 °C/0.1 mm for 15 min. Sticky crystals remained. These were washed with cold ether 3 times, and then pumped dry at 35-40 °C/2 mm for 15 min.

^1H NMR analysis of the sticky white residual crystals (50.2 mg) (83%), mp 36-38 °C, showed the quaternary TB : $MeSO_4^-$: **83** ratio to be 1 : 1 : 2, and the alcohol exhibited a 10% enantiomeric excess (from the anisochrony of the CH group).

^{1}H NMR (DMSO-d_6) δ: 1.37, 1.40 (d, J = 6.3 Hz, 3H), 2.20 (s, 3H), 2.24 (s, 3H), 3.36 (s, 3H), 3.63 (s, 3H), 3.88 (s, 1H), 4.70, 5.18 (q, AB, J = 6.3 Hz, 1H), 4.72 (q, AB, J = 16.8 Hz, 2H), 4.78 (q, J_1 = 7.5 Hz, J_2 = 7.8 Hz, J_3 = 9.3 Hz, 2H), 5.17 (q, AB, J = 11.1 Hz, 2H), 6.89-7.38 (m, 6H, 5H).

2.3.13.6 Attempted Resolution of (±)-1-Phenyl-1-propanol (84)

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.3 mL of **84** was added 15 µL (20.2 mg 0.16 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was heated 50 min at 70-80 °C and 15 min at 80-90 °C. It was then pumped at 60 °C /0.08 mm for 5 min. The sticky crystals that remained were washed with cold ether 3 times, then pumped at 40 °C/2mm for 15 min.

White sticky crystals were obtained, 50.0 mg (77%). Examination of the crystals by ^{1}H NMR showed the quaternary TB : $MeSO_4^-$: **84** = 1 : 1 : 2, and the alcohol exhibited a 18% enantiomeric excess (from the anisochrony of the CH_3 group).

^{1}H NMR (DMSO-d_6) δ: 0.72, 0.80 (t, J = 7.5 Hz, 3H), 1.59, 1.72 (m, 2H), 2.20 (s, 3H), 2.24 (s, 3H), 3.36 (s, 3H), 3.63 (s, 3H), 3.78 (s, 1H), 4.42, 4.92 (t, J = 6.3 Hz, 1H), 4.72 (q, AB, J = 16.5 Hz, 2H), 4.78 (q, J_1 = 6.9 Hz, J_2 = 8.4 Hz, J_3 = 9.0 Hz, 2H), 5.17 (q, AB, J = 11.1 Hz, 2H), 6.89-7.35 (m, 6H, 5H).

2.3.13.7 Attempted Resolution of (±)-2-Phenyl-2-butanol (88)

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.3 mL of **88** was added 19 μL (25.2 mg, 0.20 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was heated 20 min at 60 °C and 15 min at 70-78 °C. It was then pumped at 52 °C /0.1 mm for 5 min. The remaining sticky crystals were washed with cold ether 3 times, then pumped at 35-7 °C/2mm for 15 min.

White sticky crystals were obtained, 52.0 mg (77%). Examination of the crystals by ^1H NMR showed the quaternary TB : $MeSO_4^-$: **88** = 1 : 1 : 2, and the alcohol exhibited a 47% enantiomeric excess (from the anisochrony of the CH_3 group).

^1H NMR (DMSO-d_6) δ: 0.65, 1.02 (t, J = 7.5 Hz, 3H), 2.19 (s, 3H), 2.23 (s, 3H), 3.36 (s, 3H), 3.50 (s, 4H), 3.63 (s, 3H), 4.71 (q, AB, J = 17.1 Hz, 2H), 4.78 (q, J_1 = 7.5 Hz, J_2 = 8.1 Hz, J_3 = 9.3 Hz, 2H), 5.06, 5.86 (q, AB, J = 6.9 Hz, 2H), 5.16 (q, AB, J = 11.1 Hz, 2H), 7.02-7.93 (m, 6H, 5H).

2.3.13.8 Attempted Resolution of (±)-1-Phenyl-2-pentanol (91)

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.3 mL of **91**, was added 19 μL (25.2 mg, 0.20 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was heated 10 min at 70-80 °C and 30 min at 80 °C. It was then pumped at 60-70 °C /0.1 mm for 15 min. The remaining sticky crystals were washed with cold ether 3 times, then pumped at

35-7 °C/2mm for 15 min.

Yellowish sticky crystals were obtained, 49.7 mg (37%). Examination of the crystals by ^1H NMR showed the quaternary TB : $MeSO_4^-$: **91** = 1 : 1 : 6, and the alcohol exhibited an 54% enantiomeric excess (from the anisochrony of the CH_3 group).

^1H NMR (DMSO-d_6) δ: 0.75, 0.82 (t, J = 6.3 Hz, 3H), 1.30 (s, 1H), 1.27, 1.41 (m, 2H), 2.19 (s, 3H), 2.23 (s, 3H), 2.72, 2.75 (q, AB, J = 7.8 Hz, 2H), 3.00, 3.05 (q, AB, J = 3.9 Hz, 2H), 3.62 (s, 3H), 3.84 (s, 3H), 4.23 (m, 1H), 4.69 (q, AB, J = 16.8 Hz, 2H), 4.78 (q, J_1 = 7.8 Hz, J_2 = 8.1 Hz, J_3 = 9.3 Hz, 2H), 5.15 (q, AB, J = 12.0 Hz, 2H), 6.89-7.30 (m, 6H, 5H).

2.3.13.9 Attempted Resolution of (±)-1-Phenyl-2-propanol (90)

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.3 mL of **90**, was added 19 µL (25.2 mg, 0.20 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was heated 45 min at 75-80 °C. It was then pumped at 55-60 °C /0.1 mm for 15 min. The remaining sticky crystals were washed with cold ether 3 times, then pumped at 34-6 °C/2mm for 10 min.

White sticky crystals were obtained, 50.1 mg (42%). Examination of the crystals by ^1H NMR showed the quaternary TB : $MeSO_4^-$: **90** = 1 : 1 : 6, and the alcohol exhibited an 52% enantiomeric excess (from the anisochrony of the CH_3 group).

^{1}H NMR ($CDCl_3$) δ: 1.19, 1.25 (d, J = 6.3 Hz, 3H), 2.19 (s, 3H), 2.23 (s, 3H), 2.74, 2.76 (q, AB, J = 13.5 Hz, 2H), 2.88 (br s, 1H), 3.81 (s, 3H), 4.09, 4.13 (m, 1H), 4.49 (q, AB, J = 17.4 Hz, 2H), 4.74 (q, J = 9.0 Hz, 2H), 5.02 (q, AB, J = 15.6 Hz, 2H), 7.15-7.34 (m, 6H, 5H).

2.3.13.10 Attempted Resolution of (±)-2-Phenyl-2-propanol (89)

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.5 mL of **89**, was added 19 μL (25.2 mg, 0.20 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was kept 3 days at room temperature. It was then pumped at 90 °C /2 mm for 1 h. The remaining sticky crystals were washed with cold ether 3 times, then pumped at 25 °C/2mm for 15 min.

White sticky crystals were obtained, 50.3 mg (42%). Examination of the crystals by ^{1}H NMR showed the quaternary TB : $MeSO_4^-$: **89** = 1 : 1 : 6, and the alcohol exhibited an 60% enantiomeric excess (from the anisochrony of the CH group).

^{1}H NMR ($CDCl_3$) δ: 1.26, 1.28 (d, J = 6.6 Hz, 3H), 2.18 (s, 3H), 2.22 (s, 3H), 2.94, 3.09 (m, 1H), 3.55 (s, 3H), 3.61 (s, 3H), 3.70 (s, 1H), 4.11, 4.13 (q, AB, J = 9.0 Hz, 2H), 4.47 (q, AB, J = 16.8 Hz, 2H), 4.73 (q, J = 9.0 Hz, 2H), 5.12 (q, AB, J = 15.6 Hz, 2H), 6.76-7.34 (m, 6H, 5H).

2.3.13.11 Attempted Resolution of (±)-2.3-Butanediol (94)

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.5 mL of **94**, was added 19 µL (25.2 mg, 0.20 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was kept 1 h at 70 °C. It was then pumped at 62 °C /0.25 mm for 40 min. The remaining sticky crystals were washed with cold ether 3 times, then pumped at 25 °C/2mm for 15 min.

White sticky crystals were obtained, 47.0 mg (63%). Examination of the crystals by ^1H NMR showed the quaternary TB : $MeSO_4^-$: **94** = 1 : 1 : 4, and the alcohol exhibited an 3% enantiomeric excess (from the anisochrony of the CH group).

^1H NMR ($CDCl_3$) δ: 1.17, 1.26 (d, J = 6.0 Hz, 6H), 2.23 (s, 3H), 2.27 (s, 3H), 3.57 (s, 3H), 3.72, 4.31 (m, 2H), 3.80 (s, 3H), 4.53 (br s, 2H) 4.62 (q, AB, J = 17.1 Hz, 2H), 4.88 (q, J_1 = 8.1 Hz, J_2 = 8.7 Hz, J_3 = 7.2 Hz, 2H), 5.15 (q, AB, J = 14.4 Hz, 2H), 6.70-7.26 (m, 6H).

2.3.13.12 Attempted Resolution of (±)-2-Butanol (92)

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.5 mL of **92**, was added 19 µL (25.2 mg, 0.20 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was kept at boiling for 20 min. It was then pumped at 25 °C /3 mm for 4 min. The remaining sticky crystals were washed with cold ether 3 times, then pumped at 25 °C/2mm for 15 min.

White sticky crystals were obtained, 43.6 mg (65%). Examination of the crystals by ^1H NMR showed the quaternary TB : $MeSO_4^-$: **92** = 1 : 1 : 4, mp 27-8 °C, and the alcohol exhibited an 18.2% enantiomeric excess (from the anisochrony of the C$\underline{CH_3}$ group).

^1H NMR ($CDCl_3$) δ: 0.91, 0.93 (t, J = 7.5 Hz, 3H), 1.20, 1.30 (d, J = 6.3 Hz, 3H), 1.52, 1.67 (m, 2H), 2.22 (s, 3H), 2.27 (s, 3H), 3.77, 4.48 (m, 1H), 3.84 (s, 3H), 4.51 (q, AB, J = 17.1 Hz, 2H), 5.05 (q, J_1 = 11.4 Hz, J_2 = 9.9 Hz, J_3 = 10.2 Hz, 2H), 5.10 (q, AB, J = 15.9 Hz, 2H), 5.24 (br s, 3H, 1H), 6.86 (br d, J = 8.4 Hz, 2H), 7.25 (br d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H).

2.3.13.13 Attempted Resolution of (±)-4-Octanol (93)

To 25.0 mg (0.10 mmol) of (+)-TB dissolved in 0.5 mL of **93** was added 19 μL (25.2 mg, 0.20 mmol) of $(CH_3)_2SO_4$ under N_2. The solution was kept 40 min at 70 °C. It was then pumped at 62-3 °C /0.08mm for 5 min. The remaining sticky crystals were washed with cold ether 3 times, then pumped at 25 °C/2mm for 10 min.

White sticky crystals were obtained, 45.5 mg (72%). Examination of the crystals by ^1H NMR showed the quaternary TB : $MeSO_4^-$: **93** = 1 : 1 : 2, mp 41-2 °C, and the alcohol exhibited an 42% enantiomeric excess [from the anisochrony of the $(CH_2)_3$ (C_5-C_7) and $(CH_2)_2$ (C_2-C_3) groups].

^{1}H NMR (DMSO-d_6) δ: 0.83, 0.85 (t, J = 7.2 Hz, 6H), 1.25 (br s, 1H), 1.41 (m, 10H), 2.20 (s, 3H), 2.24 (s, 3H), 3.62 (s, 3H), 4.05 (s, 3H), 4.00 (m, 1H), 4.72 (q, AB, J = 18.0 Hz, 2H), 4.78 (q, J_1 = 6.6 Hz, J_2 = 6.9 Hz, J_3 = 7.5 Hz, 2H), 5.10 (q, AB, J = 12.0 Hz, 2H), 6.90-7.54 (m, 6H).

2.3.14 Synthesis of R-(+)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride [(+)-MTPA-Cl][176a]

(+)-MTPA [α-Methoxy-α-(trifluoromethyl)-phenylacetic Acid] (5.0 g, 21.4 mmol), 9.2 mL of thionyl chloride (0.10 mmol) and 61 mg of sodium chloride were refluxed together for 50 h under nitrogen. The excess thionyl chloride was removed by vacuum evaporation at 25 °C/0.75 mm for 1 h, and the residue was distilled at 63-66 °C/0.75 mm to give 4.15 g (73.3%), $[\alpha]_D^{25}$ 131.0±0.4 (c 5.14, CCl_4), [lit. $[\alpha]_D^{25}$ 131.0±0.4 (c 5.14, CCl_4)] of (+)-MTPA-Cl.

2.3.15 Synthesis of Mosher Esters[176b]

2.3.15.1 Mosher Esters of α-Methylbenzyl Alcohol (83)

2.3.15.1.1 Mosher Ester of *rac*-α-Methylbenzyl Alcohol (83)

Into a round-bottomed 5 mL flask (dried at 150 °C for 2-3 h) were injected with stirring under nitrogen, in order, 300 μL of dried pyridine, 26μL (35 mg, 0.14 mmol) of (+)-MTPA-Cl, 300 μL of dried carbon tetrachloride, and 12 μL (12.2 mg, 0.1 mmol) of (±)-**83**.

The reaction mixture was stirred for 2 h at room temperature, then 24 μL (20 mg, 0.2 mmol) of 3-dimethylamino-1-propylamine (Aldrich, used as received) was added. The mixture was allowed to stand for 5 min, then diluted with ether, washed with cold 3N HCl, cold saturated aqueous Na_2CO_3, and saturated aqueous NaCl, and dried with $MgSO_4$. The filtered ether solution was concentrated, carbon tetrachloride was added to the residue and the concentration was repeated a second and third time in order to remove the last traces of ether.

^1H NMR ($CDCl_3$) δ: 1.58, 1.64 (d, J = 6.6 Hz, 3H), 3.56 (s, 3H), 6.09, 6.13 (q, J = 6.6 Hz, 1H), 7.23-7.45 (m, 10H).

2.3.15.1.2 Mosher Ester of Resolved α-Methylbenzyl Alcohol (83)

Into a dried flask which contained about 50 mg (0.10 mmol) of **83** inclusion compound were injected with stirring under nitrogen, in order, 300 μL of dried pyridine, 26 μL (35 mg, 0.14 mmol) of (+)-MTPA-Cl and 300 μL of dried carbon tetrachloride.

The reaction mixture was treated as described in Sec 2.3.15.1.1. From the anisochrony observed in the CH_3 peak of the ^1H NMR spectrum (observed ratio 1:1:2). The residue exhibited a 7% ee by caculation of two sets of CH_3 peaks integrated.

^{1}H NMR ($CDCl_3$) δ: 1.58, 1.64 (d, J = 6.6 Hz, 3H), 3.56 (s, 3H), 6.08, 6.12 (q, J = 6.6 Hz, 1H), 7.24-7.45 (m, 10H).

2.3.15.2 Synthesis of Esters of Resolved 1-Phenyl-1-propanol (84), 2-Phenyl-2-butanol (88), 2-Phenyl-1-propanol (89),1-Phenyl-2-propanol (90), 1-Phenyl-2-pentanol (91), 2-Butanol (92) and 4-Octanol (93) with (+)-MTPA-Cl

The preceding procedure was repeated with both racemic and resolved alcohols **84**, and **88-93**. ^{1}H NMR spectral data are recorded below:

(±)-**84**, ^{1}H NMR ($CDCl_3$) δ: 0.84, 0.94 (t, J = 7.5 Hz, 3H), 1.87, 1.99 (m, 2H), 3.56 (s, 3H), 5.82, 5.90 (t, J = 6.9 Hz, 1H), 7.19-7.46 (m, 10H).

Resolved **84** (12% ee), ^{1}H NMR ($CDCl_3$) δ: 0.83, 0.93 (t, J = 7.5 Hz, 3H), 1.87, 1.99 (m, 2H), 3.57 (s, 3H), 5.82, 5.90 (t, J = 6.9 Hz, 1H), 7.19-7.47 (m, 10H).

(±)-**88**, ^{1}H NMR ($CDCl_3$) δ: 0.82, 0.84 (t, J = 6.9 Hz, 3H), 1.18, 1.19 (s, 3H), 2.31, 2.34 (q, J = 7.2 Hz, 2H), 3.57 (s, 3H), 7.20-7.44 (m, 10H).

Resolved **88** (ee could not be measured for peak overlap), ^{1}H NMR ($CDCl_3$) δ: 0.82, 0.84 (t, J = 6.9 Hz, 3H), 1.18, 1.19 (s, 3H), 2.31, 2.34 (q, J = 7.2 Hz, 2H), 3.57 (s, 3H), 7.21-7.45 (m, 10H).

(±)-**89**. ^{1}H NMR ($CDCl_3$) δ: 1.22, 1.30 (d, J = 6.9 Hz, 3H), 3.17, 3.19 (q, AB, J = 6.6 Hz, 2H), 3.42 (s, 3H), 4.33, 4.50 (m, 1H), 7.19-7.40 (m, 10H).

Resolved **89** (80% ee). ^{1}H NMR ($CDCl_3$) δ: 1.22, 1.30 (d, J = 6.9 Hz, 3H), 3.17, 3.19 (q, AB, J = 6.6 Hz, 2H), 3.42 (s, 3H), 4.31, 4.48 (m, 1H), 7.20-7.41 (m, 10H).

(±)-**90** ^{1}H NMR ($CDCl_3$) δ: 1.25, 1.34 (d, J = 6.6 Hz, 3H), 2.75, 2.78 (q, AB, J = 13.5 Hz, 2H), 3.53 (s, 3H), 4.06, 4.10 (m, 1H), 7.21-7.43 (m, 10H).

Resolved **90** (43% ee). ^{1}H NMR ($CDCl_3$) δ: 1.26, 1.35 (d, J = 6.6 Hz, 3H), 2.75, 2.78 (q, AB, J = 13.5 Hz, 2H), 3.53 (s, 3H), 4.06, 4.10 (m, 1H), 7.22-7.44 (m, 10H).

(±)-**92** ^{1}H NMR ($CDCl_3$) δ: 0.83, 0.94 (t, J = 8.4 Hz, 3H), 1.25, 1.33 (d, J = 6.3 Hz, 3H), 1.50-1.76 (m, 2H), 3.56 (s, 3H), 5.06-5.16 (m, 1H), 7.39-7.68 (m, 5H).

Resolved **92** (13% ee). ^{1}H NMR ($CDCl_3$) δ: 0.83, 0.94 (t, J = 8.4 Hz, 3H), 1.25, 1.33 (d, J = 6.3 Hz, 3H), 1.50-1.76 (m, 2H), 3.57 (s, 3H), 5.06-5.16 (m, 1H), 7.39-7.68 (m, 5H).

(±)-**94** ^{1}H NMR ($CDCl_3$) δ: 1.25, 1.26 (d, J = 5.7 Hz, 3H), 3.50 (s, 3H), 5.16, 5.23 (t, J = 5.4 Hz, 1H), 7.26-7.65 (m, 5H).

Resolved **94** (3% ee). ^{1}H NMR ($CDCl_3$) δ: 1.26, 1.27 (d, J = 5.7 Hz, 3H), 3.51 (s, 3H), 5.18, 5.25 (t, J = 5.4 Hz, 1H), 7.27-7.66 (m, 5H).

2.3.16. Synthesis of 2,8-Dimethyl-6H,12H-5,11-methano-5-(p-methoxyl-benzyl)-dibenzo[b,f][1,5]diazocinium chloride (114)

A solution of 250.0 mg (1.00 mmol) of (+)-TB (Sec. 2.3.5) and 154 μL (172.7 mg, 1.1 mmol) of p-methoxylbenzyl chloride (Aldrich, used as received) in 5 mL of CH_2Cl_2 was refluxed for 1.5 h, stirred at room temperature for 2 h under nitrogen, then stirred at 0 °C for 5 h. Crystals were collected, washed and dried under vacuum at 25 °C/2mm for 30 min, giving 220.2 mg (54.1%) of white crystals, mp 127-8 °C, $[\alpha]_D^{25}$ + 564 ± 2 (c 0.2, CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ: 1.33 (s, 3H), 1.35 (s, 3H), 3.36 (q, AB, J = 6.0 Hz, 2H), 3.49 (q, AB, J = 1.2 Hz, 2H), 3.73 (s, 3H), 4.37 (q, J = 11.4 Hz, 2H), 5.46 (q, AB, J = 6.0 Hz, 2H), 6.78-7.47 (m, 10H).

2.3.17 Synthesis of 2,8-Dimethyl-6H,12H-5,11-methano-5-(p-methylbenzyl)-dibenzo[b,f][1,5]diazocinium bromide (115)

A solution of 250.0 mg (1.00 mmol) of (+)-TB and 203.5 mg (1.10 mmol) of α-bromo-p-xylene (Aldrich, used as received) in 5 mL of CH_2Cl_2 was refluxed for 30 min, stirred at room temperature for

2 h, then stirred at 0 °C for 2 h. Crystals were collected, washed and dried under vacuum at 25 °C/2mm for 30 min, giving 404.6 mg (93%) of nice crystals, mp 174-5 °C, $[\alpha]_D^{25}$ + 489 ±0.5 (c 0.2, CH_2Cl_2).

^1H NMR (DMSO-d_6) δ: 2.07 (s, 3H), 2.19 (s, 3H), 2.22, (s, 3H), 3.32 (s, 2H), 4.39 (q, AB, J = 17.4 Hz, 2H), 5.04 (m, 2H), 5.32 (q, AB, J = 12.9 Hz, 2H), 6.94-7.36 (m, 10H).

2.3.18 Synthesis of 2,8-Dimethyl-6H,12H-5,11-methano-5-(ß-phenylethyl)-dibenzo[b,f]diazocinium chloride (116)

A solution of 250.0 mg (1.00 mmol) of (+)-TB and 143 µL (155.1.mg 1.10 mmol) of ß-phenethyl chloride (Aldrich, used as received) in 5 mL of CH_2Cl_2 was refluxed for 2 h, stirred at room temperature for 1 h, then stirred at 0 °C for 1.5 h. Crystals were collected, washed and dried under vacuum at 25 °C/2mm for 30 min, giving 228.3 mg (58.4%) of nice crystals, mp 136-8 °C, $[\alpha]_D^{25}$ + 610 ±1 (c 0.2, CH_2Cl_2).

^1H NMR (Acetone-d_6) δ: 2.15 (s, 3H), 2.80-2.85 (m, 4H), 4.05 (q, AB, J = 15.3 Hz, 2H), 4.19 (m, 2H), 4.56 (q, AB, J = 12.0 Hz, 2H), 6.67-6.98 (m, 11H).

2.3.19 Attempted Resolutions of Racemic Alcohols by Inclusion Compound Formation with 114

2.3.19.1 Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with 114 (Thermal Conditions)

A solution of 40.7 mg (0.10 mmol) of (+)-**114** and 0.10 mmol of a chiral alcohol in 1-3 mL of solvent was boiled 1 h, then kept at 0 °C for one month. Crystals were formed in some cases. These were collected and thoroughly washed with solvent having different polarity from the reaction solvent in order to remove unincluded alcohol (so as to clean the formed inclusion compound). Reaction solvent was observed in 5 of 8 of the crystals by ^{1}H NMR. The presence of alcohol was observed in 3 of 8 of the crystals by ^{1}H NMR, but no anisochrony was observed.

The results are listed in Table 19.

2.3.19.2 Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with 114 Using Sonication

A stirred solution of 40.7 mg (0.10 mmol) of (+)-**114**, and 0.10 mmol of alcohol in 1-3 mL of solvent was sonicated for 20 min, then kept at 0 °C for one month. More crystals formed than under thermal conditions (boiling 1 h), and were collected and washed (as above). Alcohol was observed by ^{1}H NMR in crystals produced by sonication with greater frequency than in those produced thermally, but still no anisochrony was observed.

The results are listed in Table 20.

2.3.19.3 Attempted Resolution of Racemic Alcohols by *in situ* Inclusion Compound Formation of TB with p-Methoxybenzyl chloride

(a) A stirred solution of 25.0 mg (0.10 mmol) of (+)-TB (Sec. 2.3.5), 0.10 mmol racemic of alcohol and 14 µl (15.7 mg, 0.10 mmol) of *p*-methoxylbenzyl chloride [mole ratio: (+)-TB : $CH_3OC_6H_4CH_2Cl$ = 1 : 1] in 1-3 mL of solvent was boiled for 1 h under nitrogen, then kept at 0 °C for one month. More crystals were collected than in previous attempts, and racemic alcohols were observed in three of the crystalline samples by ^1H NMR, but without observation of anisochrony.

The results are listed in Table 21.

(b) A stirred solution of 25.0 mg (0.10 mmol) of (+)-TB, 0.10 mmol of alcohol and 28 µL (31.4 mg, 0.20 mmol) of *p*-methoxylbenzyl chloride [mole ratio: (+)-TB : $CH_3OC_6H_4CH_2Cl$ = 1 : 2] in 1-3 mL of solvent was ultrasonicated for 20 min under nitrogen, then kept at 0 °C for one month.

Crystals were collected, and many racemic alcohols were observed in these crystals by ^1H NMR, but without anisochrony.

The results are listed in Table 22.

2.3.20 Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with 115

A solution of 25.0 mg (0.10 mmol) of (+)-TB, 0.10 mmol of racemic alcohols and 18.5 mg (0.10 mmol) of α-bromo-*p*-xylene in 1-3 mL of solvent was boiled 1 h, then kept at 0 °C for one month. The resolutions described in above were repeated with sonication (20 min) replacing the boiling period.

Crystals were collected in every case. Neither solvent nor alcohol was found in these crystals (^{1}H NMR).

All crystals had the same melting point: 174-5 °C. The results are listed in Table 23

2.3.21 Attempted Resolution of (±)-2-Butanol by *in situ* Inclusion Compound Formation with TB and β-Phenethyl chloride [mole ratio: (+)-TB : $C_6H_5CH_2CH_2Cl$ = 1 : 2]

Solutions of 25.0 mg (0.10 mmol) of (+)-TB, 0.10 mmol of (±)-2-butanol and 26 μL (28.2 mg, 0.20 mmol) of β-phenethyl Chloride in 3 mL of each of the following solvents (MeOH, EtOH, n-BuOH, Me_2CO, AcOEt, CH_2Cl_2, hexane) were boiled for 1 h, then kept at 0 °C for one month. No crystals were observed in any of these reaction mixtures.

2.3.22 Resolution of Racemate by Inclusion Formation with Brucine

2.3.22.1 Drying Brucine

Brucine dihydrate (50.0 mg, mp 176-178 °C; Aldrich) was pumped for 24 h at 100 °C/2mm, giving 45.8 mg (100%) of brucine anhydrate, mp 178-9 °C.

2.3.22.2 Isolation of (±)-2,3-Butanediol by Distillation

30.0 g of commercial 2,3-butanediol (Aldrich) (dl : meso = 54 : 46) was distilled two times in a spinning band column under the following distillation conditions:

Top head temperature:	61-65 °C
Vacuum	16 mm (Hg)
Reflux ratio:	1 : 40

(±)-2,3-Butanediol (7.8 g, 26%) was obtained and analyzed by GC (Column: Megabor DB-1 15m x 0.53mm I.D. J & W Scientific, Folsom, CA) under the following conditions:

Carrier:	Helium @10mL/min
Oven:	Isothermal @100 °C
Injection:	Direct, 0.25 µl in CH_2Cl_2 250 °C
Detector:	FID, 250 °C

Meso-2,3-Butanediol [retention time (meso)-TB: 4.53 (min)] was absent; only one peak was observed: retention time (±)-TB: 3.76 (min).

2.3.22.3 Synthesis of 2,3-Butanediol Monoacetate.

To a stirred solution of 9 g (0.10 mol) of (±)-2,3-butanediol in 100 mL of dichloromethane, was added one drop of concentrated sulfuric acid. To this was added a solution of 11.4 g (0.11 mol) of freshly distilled acetic anhydride in 50 mL of dichloromethane, dropwise during 1 h. The reaction mixture was kept for 2 days at room temperature, then concentrated (rotary evaporator). The residue was distilled at 60 °C/0.75mm, giving 9.8 g (74%) of (±)-2,3-butanediol monoacetate.

^{1}H NMR ($CDCl_3$) δ: 1.12 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H), 2.34 (br s, 1H), 3.56 (m, 1H), 3.68 (s, 3H), 4.80 (m, 1H).

2.3.22.4 Synthesis of 2,3-Butanediol Monobenzoate

A solution of 1.54 g (1.10 mmol) of freshly distilled benzoyl chloride in 5 mL of CH_2Cl_2, was added dropwise and under nitrogen (during 30 min) to a cold (0 °C) and stirred solution of 0.9 g (1.0 mmol) of (±)-2,3-butanediol containing 1.1 g (1.10 mmol) of triethylamine.

The mixture was stirred for 1 h at 0 °C, then 3 days at room temperature and finally washed, dried and concentrated (rotary

evaporator). The residue was purified by flash chromatography, giving 1.56 g (80.4%) of (±)-2,3-butanediol monobenzoate.

^{1}H NMR ($CDCl_3$) δ: 1.26 (d, J = 6.6 Hz, 3H), 1.36 (d, J = 6.6 Hz, 3H), 2.88 (br s, 1H), 3.92 (m, 1H), 5.04 (m, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.56 (t, J = 7.8 Hz, 1H), 8.05 (d, J = 8.4 Hz, 2H).

2.3.22.5 Synthesis of 2,3-Butanediol Diacetate

One drop of concentrated sulfuric acid was added to a cold (0 °C), stirred mixture of 9 g (0.1 mol) of (±)-2,3-butanediol and 23.4 g (0.23 mol) of freshly distilled acetic anhydride. The mixture was stirred at 0 °C for 30 min, then for 24 h at room temperature. Distillation at 55 °C/5mm afforded 12.6 g (72.4%) of 2,3-butanediol diacetate, mp 41.0-41.5 °C (lit. mp 41.0-41.5 °C).[177]

^{1}H NMR ($CDCl_3$) δ: 1.22 (d, J = 6.0 Hz, 6H), 2.07 (s, 6H), 4.97 (m, 2H).

2.3.22.6 Synthesis of 2,3-Butanediol Dibenzoate

To a stirred solution of 0.9 g (1.0 mmol) of (±)-2,3-butanediol in 3 mL dichloromethane was added 2.2 g (2.0 mmol) of triethylamine. To this was added 3.1 g (2.20 mmol) of freshly distilled benzoyl chloride dropwise, with stirring, under nitrogen at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, then at room temperature for 12 h, and then washed, dried and concentrated (rotary evaporator). The

residue was purified by flash chromatography, giving 2.65 g (89%) of 2,3-butanediol dibenzoate. (30 × 450 mm column, 42 g of silica gel, 400 mL of eluant: AcOEt : Hexane = 1 : 30)

^{1}H NMR ($CDCl_3$) δ: 1.42 (d, J = 6.0 Hz, 6H), 5.37 (m, 2H), 7.42 (t, J = 7.2 Hz, 4H), 7.54 (t, J = 7.2 Hz, 2H), 8.04 (d, J = 8.4 Hz, 4H).

2.3.22.7 Resolution of Racemates by Inclusion Compound Formation with Brucine

To a stirred solution (racemate as solvent if it is a liquid, or selected alcohol as solvent if racemate is a solid) containing 25-150 mmol of racemate was added 10-20 mmol of dried brucine. Stirring of the heterogeneous mixture was continued for 2 days at room temperature, after which the crystals were filtered, washed and dried in the air. The melting points of these crystals were measured.

Resolved compounds were obtained by steam distillation of the crystal or by flash chromatography (eluant such as AcOEt: Hexane = 1 : 4).

Specific rotations were measured. Enantiomeric excesses (ee) were calculated only for those compounds for which a specific rotation was reported in the literature.

The results are collected in Table 6.

Chapter III

Results, Discussion and Conclusion

3.1 General Results

3.1.1 Resolution of 2,3-Butanediol and Analogs with Brucine

Selecting brucine as a host in our first attempted resolution trials by clathrate formation gave us experience and provided background for the later studies of resolution by inclusion compound formation with synthetic hosts.

Accordingly, we tried to make brucine inclusion compounds in a variety of different ways as reported in the literature. In order to compare the effect of structurally different guests, we also synthesized a number of derivatives of 2,3-butanediol.

The basic ideas for selecting guests were 1) the effect of hydroxyl group in clathrate formation; 2) differences between aromatic alcohols and aliphatic alcohols in inclusion compound formation; 3) the effect of alcohol esterification on molecular recognition; 4) comparison of hydroxyl group with amino group functionalities in inclusion compound formation; 5) exploring the possibility in clathrate formation by halogen compounds.

The results of experiments described in Sec. 2.3.22.7 are given in Table 6. The following points are worth mentioning about Table 6:

Table 6 Resolution of Racemates by Inclusion in Brucine

	Recovered Alcohol from Brucine		M.P.[a]
Racemate[e]	Yield(%)[b]	$[\alpha]_D^{25}$ or ee(%)	(°C)
83	76.4	-[c]	176-7
84	52.4	$[\alpha]_D^{25}$ - 0.74 (neat)	172-3
90	67.1	$[\alpha]_D^{25}$ - 0.74 (neat)	174-5
92	34.4	6.8[f]	174-5
93	71.6	--[d]	176-7
94	42.4	22.3[f]	136-7
95	72.7	--[d]	175-6
98	16.0	21.1[f]	174-6
99	72.4	-[c]	176-7
100	68.9	-[c]	174-5
101	57.7	$[\alpha]_D^{25}$ + 0.03 (c. 0.3 EtOH)	147-8
102	65.3	--[d]	151-2
103	53.5	$[\alpha]_D^{25}$ - 0.88 (c. 0.3 EtOH)	137-8
104	29.0	--[d]	171-2
105	12.0	-[c]	175-6
106	100.0	5.6[f]	166-7

a. Melting Point of inclusion compound. (mp of brucine: 178-9 °C)
b. Yield is based on mole ratio of 1 to 1 (brucine to racemate).
c. ee is less than 2%.
d. $[\alpha]_D^{25}$ is less than + 0.03 or more than - 0.03.
e. Alcohol structures are given in Sec. 1.10.
f. $[\alpha]_D^{25}$ condition: **92**, $[\alpha]_D^{22}$ -12.8 (neat)[178a]; **94**, $[\alpha]_D^{23}$ -13.0 (neat)[178b]; **98**, $[\alpha]_D^{25}$ +0.35(c 23 CH_2CH_2)[178c]; **106**, $[\alpha]_D^{24}$ +10.0 (neat)[178d]

1) Hydrogen bonding evidently plays an important role in inclusion compound formation. Compound **94** which bears two hydroxy groups, gave the highest ee (22.3%). Hydroxyl groups facilitate inclusion compound formation.

Alcohol **92**, which bears one hydroxyl group with the same length of aliphatic chain as **94**, gave a much lower ee (6.8%).

The specific rotation changes of **101** to **102** may give further evidence that hydrogen bonding is important in inclusion compound formation. Compound **101** has one free hydroxyl group, and can form hydrogen bonds with brucine. This interaction may be weaker than in 2,3-butanediol (**94**), the recovered alcohol shows a small rotation. However, in **102** the two hydroxyl groups were esterified. Compound **102** may have no hydrogen bond forming ability with brucine, the recovered alcohol showed no rotation. Compounds **103** and **104** present a similar situation.

2) Some difference between aromatic and aliphatic groups in host selectivity is also apparent e.g., **101** vs **103**. In Table 6, two of three aromatic alcohols were observed to be partially resolved. However, only two of five aliphatic alcohols were observed to be partially resolved. Although it is not significant, but it may still tell us that aromatic rings optimize diastereomer discrimination.may play some function in it.

3) Compounds **93** and **99** are nonpolar aliphatic alcohols. Their hydroxyl groups may be less acidic than those in **94**. 2,3-butanediol is moderately well resolved by brucine. The low acidity of hydroxyl groups[179] may play an important role in **93** and **99** not being resolved by brucine.

4) Halogen compounds **95** and **100** have no good hydrogen donor group, such as OH group,[180] for making hydrogen bonds. This may be responsible for a lower ee obtained after resolution.

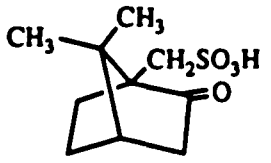
5) It is very interesting that compound **98** obtained on esterification of **83** has a higher ee than **83** after recovery from brucine. The hydroxyl group of **98** was esterified, but **98** has a higher ee. This shows that hydroxyl groups and the acidity of OH groups are not the only factors in clathrate formation. Other factors, such as molecular size (The molecular size between **83** and **98** is different.), may also play an important role in inclusion compound formation.

The above structural aspects gave us some guidelines in the following experiments to select the host and guest molecule.

3.1.2 Resolution and Asymmetric Transformation of Tröger's Base

10-Camphorsulfonic acid is the only resolving agent reported as having been tried in the resolution of racemic Tröger's Base (TB), by Prelog et al. in 1944.[154] This attempted resolution led to the finding that partially resolved samples of TB undergo racemization in acid

media. Re-exploring 10-camphorsulfonic acid as resolving agent was helpful to us in understanding the general conditions required to resolve Tröger's base, such as selection of the solvent, temperature and concentration, etc.



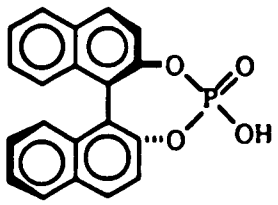
10-camphorsulfonic acid

Only partial resolution was obtained with 10-camphorsulfonic acid (CSA) as resolving agent in our study. TB with a 5% ee was obtained, and the efficiency of resolution was not improved by changing resolution conditions several times, such as concentration, temperature, resolution time and solvent. HCl is a strong acid. In order to see how an increased acidity in resolutions affects the resolution result, mixing 10-camphorsulfonic acid and HCl as resolving agent was tried. 10-camphorsulfonic acid has pK_a 2.0, and HCl has pK_a -6.1.[181] The mixture of 1 to 1 mole ratio of HCl to 10-camphorsulfonic acid should have a stronger acidity than 10-camphorsulfonic acid alone. We found that this mixture is a better resolving agent than 10-camphorsulfonic acid alone. (-)-TB with a 16.4% ee was prepared the first time in an unoptimized test, although the yield (5.8%) was lower than with CSA alone (10.1%). This finding, as well as the study of the racemization mechanism outlined in Chapter I (Sec. 1.6), encouraged us to explore other strongly acidic resolving agents.

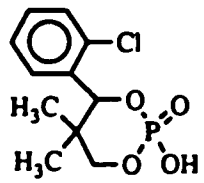
Selection of the resolving agent , although intuitive, was deliberate. We sought a strongly acidic resolving agent in order to facilitate salt formation and chose a resolving agent bearing an aromatic group to optimize diastereomer discrimination.

Few acids meet these criteria. Among them are enantiopure 1,1'-binaphthalene-2,2'-diylhydrogen phosphate (BNP, **81**) that has pK_a 2.50 (95% ethanol 10 °C),[182] and 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3-dioxaphosphorinane 2-oxide (DOPO, **117**) that is reported as a strong acid to have pK_a 2-3.[183] These acids have been reported to be excellent resolving agents for amines and amino acids through diastereoisomeric salt formation.[183, 184]

BNP and DOPO were observed to be better than 10-camphorsulfonic acid in the resolution of TB; aromatic groups may play an important function in the different interaction of these resolving agents with the two enantiomers of TB.



81 (BNP)



117 (DOPO)

From a single resolution trial, we have evidence that 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3-dioxaphosphorinane 2-oxide (DOPO)[183] is a good candidate as a resolving agent for racemic

TB (**79**). Our only attempt gave partially resolved TB with DOPO, in 34.8% yield and with 29% ee. If the resolution conditions were optimized, DOPO is likely to be an efficient resolving agent for **79**.

Reaction of racemic TB (**79**)[164] with (-)-1,1'-binaphthalene-2,2'-diylhydrogen phosphate, (-)-**81**,[172] mole ratio: (+)-BNP : TB = 2 : 1 (ratio based on the presence of two basic nitrogens on TB), in ethanol led to the following initial results: (+)-TB with 38.0% e.e., yield 36.0%. This seemed promising. When a mole ratio: (+)-BNP : TB = 1 : 1 was tried, the salt formed was (+)-**79**·(-)-**81**(**82a**), from which (+)-**79** was recovered in higher enantiomeric purity (65.0% e.e. Yield 89.0%). We subsequently established that when the crystallization was coupled to careful control of the crystallization rate, the optimal yield of salt **82a** leading to (+)-**79** is 93.0%, or 186.0% based on the amount of (+)-TB initially present in the racemate being resolved. Results are listed in the following table.

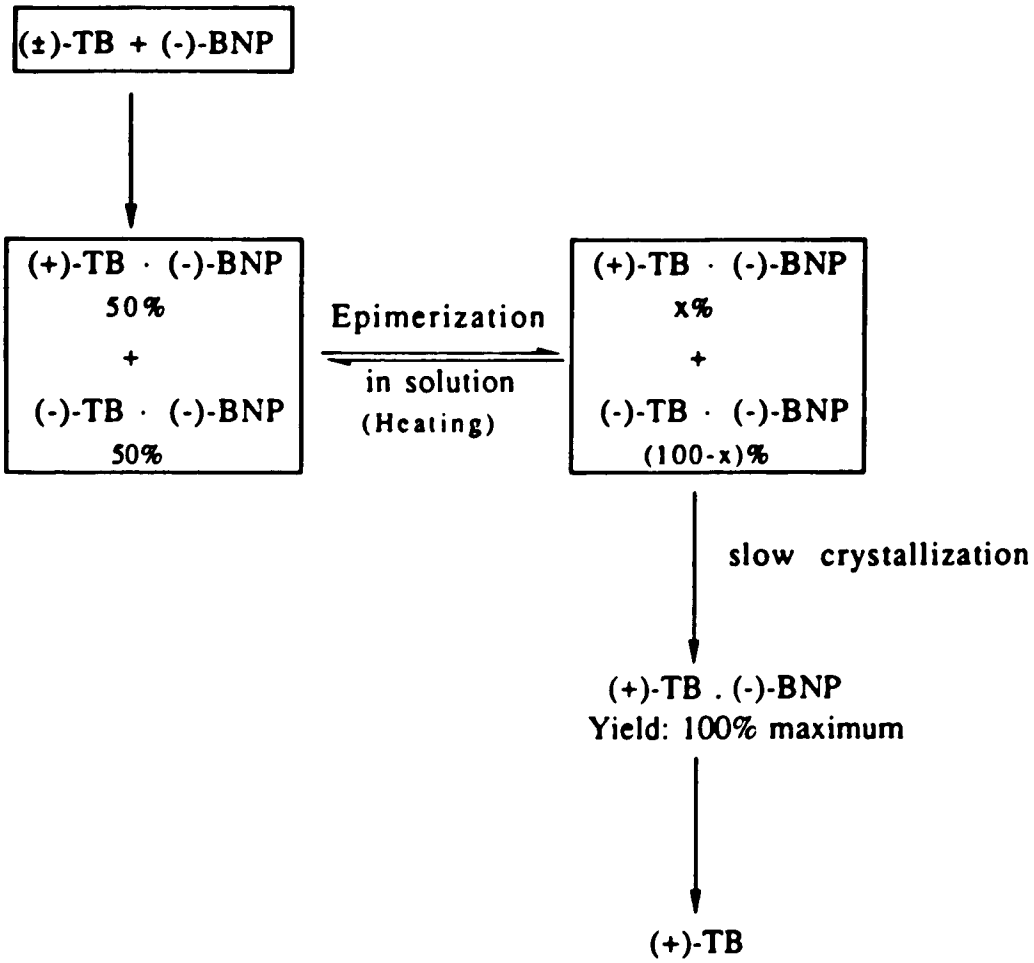
Table 7 The Results of Resolution of Tröger's Base with Enantiopure BNP

	(+)-TB[a]	(-)-TB[a]	TB[b]
$[\alpha]^{25}_D$	+293.0 ± 1.2 (c 0.28, hexane)	-313.6 ± 0.3 (c 0.29, hexane)	+287 ± 7 (c 0.28, hexane)
mp (°C)	131-132	131-132	127-128
Yield (%)	93	91.6	

a. The measurement of $[\alpha]^{25}_D$ and mp is from mixed crops of our resolved (+)-TB or (-)-TB. (-)-TB was obtained from a resolution carried out with (+)BNP.
b. Literature values [147]

The maximum yield in a resolution cannot theoretically exceed 100% (based on one enantiomer present in the racemate). "If the racemization in solution or in the molten state is facile, preferential crystallization of one of the two and displacement of the resulting equilibrium could, under some conditions, lead to a total transformation of the initial racemate into a *single* enantiomer."[158] We conclude that the yield of more than 100% is the result of an asymmetric transformation. Our findings require that, during the resolution, the (-)-**79** initially present in the racemate is converted to (+)-**79** in the precipitated diastereomeric salt. The resolution is thus attended by a crystallization-induced asymmetric transformation of salt **82a**.[185] The results are illustrated by Scheme I.

Scheme I. Crystallization-Induced Asymmetric Transformation of Tröger's Base



In a classical resolution, the two diastereomers which are formed are normally stable to interconversion under the reaction condition. Two diastereomeric salts are formed and are separated.

However, if the substrate, e.g., TB, is relatively easily racemized in the presence of optically active resolving agent, e.g., (-)-BNP, after a given length of time a solution will be obtained which contains x% of

one diastereomeric salt and (100-x)% of the other. This equilibrium corresponds to the definition of "asymmetric transformation of the first kind". If the solution is rapidly and completely crystallized, a solid mixture of the two diastereomeric salts may be obtained which reflects the proportion present at equilibrium in solution. However, on rapid crystallization only exceptionally does this asymmetric activation lead to just one of the two possible species.

As was discovered by Prelog and Wieland,[154] TB is relatively easily racemized in the presence of an optically active acid. After some time, epimerization in solution in presence of (-)-BNP affords x% of (+)-TB·(-)BNP and (100-x)% (-)-TB·(-)-BNP. On cooling, the diastereomer equilibrium is continually displaced by crystallization of the less soluble TB diastereomeric salt [(+)-TB · (-)-BNP] since the rate of crystallization of this salt is slower than the rate of equilibration of the two salts in solution. The result is crystallization of only one of the two possible diastereoisomer salts. This is called an asymmetric transformation of the second kind (This type of asymmetric transformation is better called "crystallization-induced asymmetric disequilibration".)[158] By decomposing this salt, a very high yield of enantiopure (+)-TB can be recovered. The yield exceeds the 50% (per enantiomer) that is maximal for cases in which the diastereomers (or the resolution substrates) are stable.

For the purpose of constructing a binary phase diagrams, heats of fusion (ΔH^{f}) and melting points were measured by DSC. Eutectic and enantiomeric peaks appeared in the DSC scan. This allowed us to

apply DSC to analyze the enantiomeric purity of our resolved TB. The absence of a eutectic peak in the differential scanning calorimetric trace[158] of (+)-**79**, ΔH^f_{enant}= 4.77 kcal mol^{-1}, (ΔH^f_{rac} = 5.94 kcal mol^{-1}) leads us to conclude that the enantiomeric purity is in excess of 99% (probably greater than 99.5% ee). The same sample was tested polarimetrically, whereby the optical purity of (+)-**79** was estimated to be greater than 98% based on the optical rotation. (The assessment of the sensitivity of the DSC measurement are given in Sec. 3.1.6).

Thus, contrary to the assertion that resolution of TB with an acidic resolving agent is not feasible,[156b, 159] the resolution is straightforward and multigram quantities of optically active **79** (both enantiomers) can be readily prepared by our method. The resolution by crystallization-induced asymmetric transformation of (+)-TB was also carried out on a 50 mmol scale (yield 91.4%). Our results disprove the contention that resolution of easily racemizable compounds by crystallization of diastereomers is not possible. Resolution of such compounds may actually be facilitated by an attendant crystallization-induced asymmetric transformation.

The resolving agent used, **81**, is readily available in either pure enantiomeric form[172] and it is recovered from the resolution in 79% yield.

3.1.3 Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with Enantiopure TB and Enantiopure TB Quaternary Salts 82a and 107a

3.1.3.1 Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with Enantiopure TB

Tests with fifteen different racemic alcohols and seven different solvents using different resolution conditions, thermal and ultrasonic treatment, all showed negative results (Tables 8 and 9). Almost no difference was seen in thermal versus ultrasonic conditions.

In many cases, no crystals were obtained from either resolution procedure. In those few cases where some crystals formed (Tables 8 and 9), almost the same melting point (131 °C) was obtained as that of TB (mp 131 °C; Sec. 2.3.5.2), with a maximum deviation of ±2 °C. These crystals were independently checked by ^{1}H NMR and GC for the presence of included alcohol or solvent. They had the same melting point and specific rotation as enantiopure (+)-TB (Section 2.3.10). No included solvents or racemic alcohols were observed, and the crystals were invariably only TB itself with minor impurities in a few cases.

Comparison of enantiopure (+)-TB (Section, 2.3.5.) as a host with enantiopure TB quaternary salts **82a** & **107a** in the resolution of racemic alcohols by inclusion compound formation, showed TB quaternary salts to be more efficient as hosts.

In all the following tables: "+" means that crystals formed and amounted to more than 2.0 mg after washing and drying.

Table 8. Attempted Resolution of Alcohols by Inclusion Compound Formation with Enantiopure (+)-TB as Host in Warmed Solutions[a]

Solvent Alcohol[d]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	AcOEt crystals[b,c]	CH_2Cl_2 crystals[b,c]	$CHCl_3$ crystals[b,c]
83	+	+	-	+	-	-	-
84	+	+	-	-	-	-	-
85	+	+	-	-	-	-	-
86	+	+	-	+	-	-	+
87	+	-	-	-	+	+	+
88	-	+	+	+	-	-	-
89	+	-	+	-	+	-	-
90	-	+	-	-	-	-	-
91	-	-	-	+	-	-	-
92	-	+	+	+	+	-	-
93	-	-	-	-	-	-	-
94	+	-	+	+	+	+	-
95	+	+	+	+	+	-	-
96	-	+	-	-	-	-	-
97	+	-	-	-	-	-	-

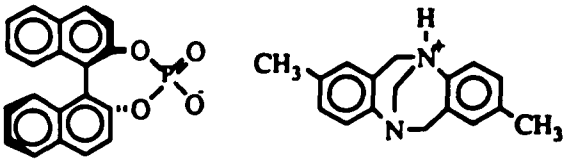
a. Mole ratio: (+)-TB : alcohol = 1: 1 (1.0 mmol of each). Resolution solutions were heated for 1 h, cooled to 0 °C, and were kept 15 days at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.10.1).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Structural formulas are given in Sec. 1.10.

Table 9. Attempted Resolution of Alcohols by Inclusion Compound Formation with Enantiopure (+)-TB as Host in Sonicated Solutions[a]

Solvent Alcohol[d]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	AcOEt crystals[b,c]	CH_2Cl_2 crystals[b,c]	$CHCl_3$ crystals[b,c]
83	+	+	-	+	-	-	-
84	+	+	+	-	-	+	-
85	+	+		-	+	-	-
86	+	+	-	+	-	-	-
87	+	+	-	-	+	-	+
88	+	-	-	+	-	-	-
89	-	+	+	+	+	+	-
90	+	+	-	-	-	-	-
91	-	-	-	-	+	-	-
92	+	-	-	-	-	+	-
93		-	-	-	-	-	-
94	+	+	-	+	-	-	-
95	+	+	+	+	+	+	+
96	-	-	+	-	-	-	-
97	-	-	+	-	-	-	-

a. Mole ratio: (+)-TB : alcohol = 1 : 1 (1.0 mmol of each). Resolution solutions were sonicated for 20', cooled to 0 °C, and were kept 15 days at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.10.2).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Structural formulas are given in Sec. 1.10.

3.1.3.2. Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with Enantiopure TB Salt 82a



82a

The first indication that enantiopure onium salts of TB might indeed serve as an inclusion host was provided by (+)TB·(-)BNP salt **82a**. X-ray structural analysis of salt **82a** reveals that there is one ethanol molecule included in the unit cell of the salt. The potential of quaternary onium salts as inclusion hosts is obvious. The negative results obtained on attempted resolution of racemic alcohols by inclusion compound formation with enantiopure TB drove us to undertake resolution trials with enantiopure TB salt **82a** as host, this compound (an intermediate in the resolution of TB) being already on hand. Moreover, on inspection of the crystal lattice of **82a**, X-ray analysis told us that there was a channel in the crystal lattice of **82a**.

However, if **82a** were to be used as an inclusion host, either (1) removal of the ethanol from this crystal lattice, and replacement of the achiral guest molecule with a chiral one would have to be achieved or (2) replacement of the included ethanol might be attempted by dissolving salt **82a** and allowing its recrystallization in the presence of an excess of a racemic alcohol, which might displace the ethanol in the **82a** crystal lattice.

An attempt was made to remove the ethanol included in the crystal lattice of **82a**. Onium salt **82a** was heated to 158 °C (mp of **82a** is 161-2 °C) under 0.1 mm vacuum for 3 h but ^{1}H NMR analysis of the resulting solid (mp 161-162 °C) showed no loss of ethanol.

Salt **82a** (containing ethanol) was then directly dissolved in a variety of solvents, excess racemic alcohol was added and the mixture was heated or sonicated. The solution was cooled and kept 15 days at 0 °C. The results are shown in Tables 10 and 11.

All samples marked "+" were analyzed by ^{1}H NMR. The overwhelming majority were recovered salt **82a** with included EtOH still present. Those containing tested alcohols **83-97** (EtOH absent) are marked "+/n" in the tables. Symbol "n" means that no anisochrony was observed.

Table 10. Attempted Resolution of Alcohols by Inclusion Compound Formation with Onium Salt 82a as Host in Warmed Solutions[a]

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	AcOEt crystals[b,c]	CH_2Cl_2 crystals[b,c]	$CHCl_3$ crystals[b,c]
83	+	+	+	+/n	-	-	-
84	+	+	+	+	-	-	-
85	+	+	-	-	-	+	+
86	+	+	-	+	+	+	-
87	+	+	-	+	-	+	+
88	+	-	-	+	-	-	+
89	+	+	+/n[d]	+/n	+	-	-
90	+	+	-	-	-	+	+
91	+	-	-	+	+	+	-
92	+	+	-	-	+	+	-
93	-	+	-	-	-	-	+
94	-	-	+	-	+	-	-
95	-	-	-	-	-	+	+
96	+	+	-	-	-	+	-
97	-	-	+	+	-	-	-

a. Mole ratio: **82**: alcohol = 1 : 1 (1.0 mmol of each). Resolution solutions were heated for 1 h, cooled to 0 °C, and were kept 15 days at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.11.1).
b. Result labelled "+ "implies that more than 2.0 mg of crystals deposited; they were characterized as **82a** with included EtOH.
c. Result labelled "- "implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

Table 11. Attempted Resolution of Alcohols by Inclusion Compound Formation with Onium Salt 82a as Host in Sonicated Solutions[a]

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	AcOEt crystals[b,c]	CH_2Cl_2 crystals[b,c]	$CHCl_3$ crystals[b,c]
83	+	+	+	-	-	-	+
84	+	-	+	+	-	-	-
85	+	+	+	-	-	+	+
86	+	+	-	-	-	+	+
87	+	+	+	-	+	+	+
88	+	-	-	+	-	+	-
89	+/n[d]	+/n	+	+	-	-	+
90	+	+	-	-	-	-	+
91	+	+	+	+	+	-	-
92	-	+	+	+	+	-	+
93	+	-	-	+	-	-	-
94	+	+/n	-	+	-	-	+
95	+	+	+	+	+	+	+
96	-	+	-	-	+	-	-
97	-	-	-	+	-	-	-

a. Mole ratio: **82**: alcohol = 1 : 1 (1.0 mmol of each). Resolution solutions were sonicated for 20", cooled to 0 °C, and were kept 15 days at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.11.2).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **82a** with included EtOH.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

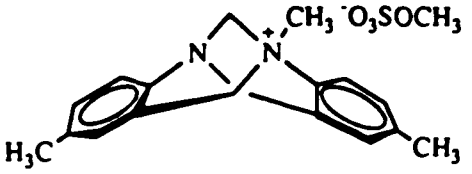
As shown in Tables 10 and 11, using (+)-TB· (-)-BNP (**82a**) as a host, the majority of alcohols tested formed crystals which were characterized by ^{1}H NMR as the onium salt **82a** itself, and one molecule of ethanol was still observed to be present. Clearly then, there was no inclusion compound formation in the majority of cases when **82a** was host. However, a few crystals had different melting points from that of **82a** (mp: 161-162 °C) such as crystals from alcohol **83** (in Me_2CO) mp: 156-7 °C; crystals from alcohol **89** (in *n*-BuOH), mp: 142-3 °C (Table 10). In these crystals, some with same melting point were obtained with the same racemic alcohol but prepared in different solvents, e.g. crystals from **89** [in MeOH and EtOH, both of mp: 141-3 °C (Table 11)]. The chiral alcohols were observed to be present in these crystals by ^{1}H NMR analysis, but without anisochrony, and by GC.

The significant finding was that in the three positive cases (**83**, **89** and **94**) ethanol had disappeared from the cavity/channel of **82a** and was replaced by these chiral alcohols, which shows that these chiral alcohols competed with ethanol to form a new inclusion compound. No anisochrony was observed meaning that the included alcohol may be racemic or enantiopure. Further study is necessary.

From Tables 10 and 11, it is evident that resolutions carried out by the two variant methods (attempted in hot solution and with sonication) lead to only small differences in inclusion compound formation. However, the few formed inclusion compounds did show

that **82a** can act as a host in inclusion compound formation with some chiral alcohols. The enantiomer recognition ability of **82a** should be further studied.

3.1.3.3 Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with Enantiopure TB Methosulfate (107a)



107a

Enantiopure TB methosulfate **107a** was prepared for trial as an inclusion host. In order to discover the best conditions for good resolution by inclusion compound formation with this quaternary salt as host, inclusion compound formation between five racemic alcohols and (+)-TB methosulfate **107a** was attempted in six solvents, with different mole ratios of host to guest and under different reaction conditions (Sec. 2.3.13.1). Selection of racemic alcohols here was based on those which exhibited discrimination in TB acting as a chiral solvating agent (CSA) in Table 24, and those which could form inclusion compounds as listed in Tables 10 and 11.

As shown in Table 12, crystals were obtained in 11/30 cases. These crystals had melting points differing from that of **107a**

(mp: 117-119 °C) (Sec. 2.3.12). One inclusion compound formed in acetone was observed by ^{1}H NMR analysis to contain tested alcohol **92**, but no anisochrony was exhibited. Other crystals were shown by ^{1}H NMR analysis to cor.tain solvent. Solvent peaks were observed more frequently in the ^{1}H NMR spectra of the crystals formed from (+)-TB methosulfate (**107a**) with racemic alcohols than was the case for host (+)-TB·BNP (Sec. 3.1.2.2).

Further, it appears that more inclusion compounds containing tested chiral alcohols are formed when the process includes sonication (Table 13). (6/30 vs 1/30). Alcohols **83** and **89** were detected by ^{1}H NMR in new crystals formed in ethanol solvent, but no anisochrony was observed. The melting points of these two new crystals were quite different from the melting point of **107a**. All melting point data of solvents included and racemic alcohols included are listed in Table 16.

It is clear that (+)-TB methosulfate (**107a**) may form inclusion compounds with some racemic alcohols when crystallization is allowed to proceed in several solvents (even in competition with alcohols solvent molecule). Although the results did not indicate that inclusion was enantioselective, the results spurred us to further study.

Table 12. Attempted Resolution of Alcohols by Inclusion Compound Formation with (+)-TB Methosulfate 107a as Host in Warmed Solutions[a]

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b,c]
83	+	+	-	+	-	-
84	+	+	-	+	-	-
89	-	-	-	-	+	+
92	-	-	-	+/n[d]	+	-
94	-	-	-	-	-	+

a. Mole ratio: **107a**: alcohol = 1 : 1 (1.0 mmol of each). Resolution solutions were heated for 1 h, cooled to 0 °C, and were kept 15 days at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.13.1).
b. Result labelled "+" implies that no crystals , or less than 2.0 mg of crystals deposited.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

Table 13. Attempted Resolution of Alcohols by Inclusion Compound Formation with (+)-TB Methosulfate 107a as Host in Sonicated Solutions[a]

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b,c]
83	-	+/n	-	-	-	+
84	+/n[d]	+	+	+	+/n	-
89	+	+/n	+/n	-	-	-
92	-	-	+/n	-	+	-
94	-	-	-	-	+	+

a. Mole ratio: **107a**: alcohol = 1 : 1 (1.0 mmol of each). Resolution solutions were sonicated for 20', cooled to 0 °C, and were kept 15 days at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.13.2).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **107a** and solvent.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

3.1.3.4 Inclusion Compound Formation Concomitant with Alkylation

Enantiopure TB, dimethyl sulfate and racemic alcohols were combined in a mole ratio of 1 : 1 : 1 or 1 : 2 : 1, respectively, in different solvents. The solutions were heated or ultrasonicated, then cooled and kept one month at 0 °C. Larger quantities of crystals were formed by this procedure than in the procedures described in Sec. 2.3.13.1 and than in Sec. 2.3.13.2. The results are listed in Tables 14 and 15.

These results did not show significant differences between thermal and ultrasonic treatments, and we will temporarily discontinue comparison of these two different treatments.

In general, the results reported in Tables 14 and 15 are better than those of Tables 12 and 13 in that more inclusion was observed, not only of solvent, but also of racemic alcohol. The crystals containing solvent showed different melting points from **107a** (Sec. 3.1.2.3). They have the same melting point as crystals obtained from preformed **107a** in inclusion trials in the identical solvents (Tables 12 and 13). Although racemic alcohols were also detected in other crystals by ^{1}H NMR (Tables 14 and 15), no anisochrony was observed. The melting points of putative inclusion compounds formed here were the same as these obtained with preformed **107a** (Tables 12 and 13). Melting points are collected in Table 16.

Table 14. Attempted Resolution of Alcohols by Inclusion Compound Formation: *In Situ* Formation of TB Methosulfate (107a) with Heating[a] [(+)TB : Dimethylsulfate : Alcohol Ratio = 1 : 1 : 1]

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b,c]
83	+	+/n[d]	-	-	+	-
84	+	+/n	+	-	+	-
89	+	+	-	+	+	-
92	-	-	+	-	+	-
94	-	-	+	-	-	-

a. Resolution solutions were heated for 30', cooled to 0 °C, and were kept one month at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.13.3).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **107a** and solvent.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

Table 15. Attempted Resolution of Alcohols by Inclusion Compound Formation: *In Situ* Formation of TB Methosulfate (107a) with Heating[a] [(+)TB : Dimethylsulfate : Alcohol Ratio = 1 : 2 : 1]

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b,c]
83	-[c]	+	+/n	+	+/n	-
84	+[b]	-	+/n	-	+/n	-
89	+/n[d]	+	-	+/n	+	-
92	-	-	+/n	+	+/n	-
94	-	+	-	-	-	-

a. Resolution solutions were heated for 30', cooled to 0 °C, and were kept one month at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.13.4).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **107a** and solvent.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

Table 16. The Melting Points of Compounds Formed by Inclusion of Solvent or Racemic Alcohols in TB Methosulfate (107a).[a,b]

Solvent	MP of Inclusion Compound (°C)	Racemic Alcohol	MP of Inclusion Compound (°C)
MeOH	97.0-98.0	**83**	147.5-150.0
EtOH	103.0-104.0	**84**	113.0-115.0
n-BuOH	95.0-96.0	**89**	132.5-136.0
Me_2CO	83.0-85.0	**92**	123.0-126.0
$CHCl_3$	87.0-88.0	**94**	____[c]
Cyclohexane	69.0-71.0		

a. All melting point listed here are averages of at least two runs.
b. The melting point of **107a** is 117-119 °C (Sec. 2.3.12). The melting point of (+)-TB is 131-132 °C (Sec. 2.3.5.2).
c. No inclusion compound formed.

Inclusion phenomena with chiral alcohols are reported more frequently in Table 15 (eight cases) than in Table 14 (two cases). The conditions of inclusion were the same, and the only difference was the larger quantity of dimethyl sulfate used in Table 15.

Summing up all the above data, TB methosulfate appears to be a more effective inclusion host than enantiopure TB. However, these results are still generally unsatisfactory. The yields of newly formed crystals in all examples above are low; anisochrony was not observed in ^1H NMR spectra and resolution by inclusion compound formation is uncertain.

In further resolution trials, in order to avoid presumed competition between solvent and racemic alcohol during inclusion compound formation, the racemic alcohol itself was used as solvent.

In the modified procedure, enantiopure TB and excess dimethyl sulfate were added to the racemic alcohol acting as solvent. The resultant solution was heated, and the excess alcohol and dimethyl sulfate were then pumped out under vacuum. In other words, in this procedure the host TB methosulfate (**107a**) was allowed to form *in situ*.

Now all methods described here have the following working scheme essentially in common:

a) Inclusion compound formation between the host compound and the guest acting as solvent. After a period of heating, excess solvent is removed by pumping under vacuum.

b) Washing of the inclusion compounds with cold other organic solvent and thorough drying.

c) Instrumental analysis to establish that inclusion compound formation has taken place.

d) Release of the guest compounds by decomposition of the inclusion compounds with aqueous NaOH, followed by extraction with

a nonpolar solvent, or purification by TLC. The host compounds can be recycled by recovering them and then purifying them.

e) Measurement of the enantiomeric excess of recovered guest compounds by ^1H NMR through their Mosher ester formation.

Table 17 reports obtained results of duplicate experiments using the modified procedure. Nine racemic alcohols were tested. The residues were solid (four cases) or oils (five cases). The inclusion compounds which formed also had quite different melting points from those of either TB or TB methosulfate (five were oils). The residues contained alcohol in every case and, significantly, anisochrony was observed for all nine racemic alcohols tested (Sec. 3. 1. 5). Eight gave good results, that is, eight racemic alcohols were resolved by inclusion compound formation with **107a**. The e.e. of these alcohols reached 10-60% based on ^1H NMR analysis of these inclusion compound. Inclusion compound formation was evidenced by the integral stoichiometry of components of quaternized TB, $CH_3SO_4^-$ and alcohol mole ratio of 1 : 1 : 2, in four cases, as confirmed by ^1H NMR spectra (in DMSO-d_6); the other cases examined have apparent stoichiometries of 1 : 1 : 4 and 1 : 1 : 6. The errors are all less than ±0.2. The various alcohols were found in the residues in

Table 17. Inclusion Compounds of Alcohols in Tröger's Base Methosulfate 107a[a]

Structure	Compound Number	R'	R''	M.P. (°C)	Yield[b] (%)	^{1}H NMR Analysis of the Alcohol e.e. of Inclusion Compound[c]	e.e. of Mosher Ester[d]
$C_6H_5CR'(OH)R''$	**83**	H	CH_3	36-8	81 (1:1:2)	10	7
$C_6H_5CR'(OH)R''$	**84**	H	C_2H_3	45-6	77 (1:1:2)	18	12
$C_6H_5CR'(OH)R''$	**88**	CH_3	C_2H_3	30-1	77 (1:1:2)	47	e
$C_6H_5CR'CH_2(OH)R''$	**89**	H	CH_3	oil	42 (1:1:6)	60	80
$C_6H_5CH_2CR'(OH)R''$	**90**	H	CH_3	oil	42 (1:1:6)	52	43
$C_6H_5CH_2CR'(OH)R''$	**91**	H	C_3H_7	oil	37 (1:1:6)	54	-
$CH_3CR'(OH)R''$	**92**	H	C_2H_5	27-8	65 (1:1:4)	18	13
$CH_3(CH_2)_3CR'(OH)R''$	**93**	H	$(CH_2)_2CH_2$	oil	72 (1:1:2)	42	-
$CH_3CR'(OH)R''$	**94**	H	$CH(OH)CH_3$	oil	48 (1:1:4)	3	3

a. *In situ* formation with heating [(+)-TB : dimethyl sulfate in ratio 1 : 2 or 1 : 1.5] (see Table 18)
b The yield calculation is based on TB : dimethyl sulfate : alcohol ratio shown, which is that found in the residue (putative inclusion compound).
c. From integration of anisochronous nuclei in DMSO-d_6
d. From ^{1}H NMR analysis of Mosher ester prepared from recovered alcohols (measured in $CDCl_3$)
e. ^{1}H NMR peak overlap.

enantiomerically enriched form (Table 17): we infer that the chiral alcohols were resolved by inclusion in the onium TB salt **107a** formed *in situ*. Very satisfactory anisochronies were observed in eight cases. The enantiomeric compositions were directly calculated by integration of selected nuclei in ^{1}NMR spectra of the inclusion compounds, i. e., the residues, dissolved in $CDCl_3$ or DMSO-d_6.

In order to independently confirm the enantiomer compositions, the included alcohols were converted to the Mosher's esters.[176, 186] The results matched well. The highest efficiency observed in this process, 80% ee, was obtained with alcohol **89**. The alcohols **83**, **84**, **90** and **92** all were obtained with ees of 7-43% by the Mosher's ester procedure. These numbers are close to the ees of 10-52% measured directly from ^{1}NMR spectra of the inclusion compounds.

That the two aliphatic alcohols were resolved is also significant. For the most part, chiral compounds listed in the literature as being resolved by inclusion compound formation are compounds with aromatic rings.

The enantiomeric excesses of alcohols **88** and **91** could not be measured by ^{1}H NMR analysis of Mosher's esters prepared from recovered alcohols, for their ^{1}H NMR peaks overlapped. This situation was not observed in ee measurements in which **107a** served as CSA.

The lowest ee observed, (3% by ^1H NMR analysis) was obtained in the resolution of alcohol **94** with **107a** serving as host. The same ee value was given by Mosher's ester analysis.

All of these alcohols could be recovered by decomposition of the inclusion compound with aqueous NaOH. The method is simple, the yield of recovered alcohols is high, and the TB also can be recovered very easily. The results of inclusion experiments, which were carried out with mole ratio of (+)-TB to dimethyl sulfate of 1 to 1, were worse in that yields and ee's were lower than with mole ratio of 1 to 2 or 1 to 1.5 (Table 18). In all the same nine alcohols, anisochrony was observed for every racemic alcohol tested. However, no resolution was observed for alcohols **83**, **84**, **94**.

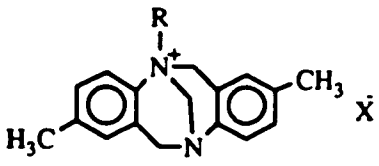
Further, comparison of the results obtained with a 1 : 2 mole ratio (TB to dimethylsulfate) with those using a 1 : 1.5 ratio showed no difference in resolution results. In contrast to resolution trials with a 1 : 1 mole ratio, alcohols **83** and **84** are seen to be resolved by inclusion compound formation using a mole ratio of (+)-TB to dimethyl sulfate equal 1 to 1.5. These results are shown in Table 18.

Table 18. Yield and Enantiomeric Compositions Observed in Resolution of Alcohols by Inclusion Compound Formation. Effect of TB to Me_2SO_4 Ratio

Mole Ratio[a]	1 : 2	1 : 1.5	1 : 1	1 : 2	1 : 1.5	1 : 1
Compound	Yield(%)			ee(%)[b]		
83	79	81	52	9	10	-
84	76	77	48	15	18	-
88	77	77	37	47	47	34
89	42	40	31	60	61	48
90	42	41	34	52	50	27
91	37	37	31	54	51	42
92	65	63	52	18	17	12
93	72	71	41	42	40	36
94	48	42	26	3	3	-

a. Mole ratio of (+)-TB to dimethyl sulfate
b. All ee's measured from inclusion compound by ^1H NMR interaction of anisochronous nuclei in DMSO.

3.1.4. Attempted Resolution of Racemic Alcohols by Inclusion Compound Formation with Enantiopure TB Onium Salts 114, 115, 116



114 R = H_3CO-C$_6$H$_4$-CH_2 X = Cl mp 127-8 °C

115 R = H_3C-C$_6$H$_4$-CH_2 X = Br mp 174-5 °C

116 R = C$_6$H$_5$-CH_2CH_2 X = Cl mp 136-8 °C

The results (Tables 19 and 20) of a study of inclusion compound formation with preformed onium salt **114** in the presence of the racemic alcohols and a solvent, with heating or with sonication

conditions, were essentially the same as those reported in Tables 12 and 13.

In Table 19 and 20, many inclusion compounds were found. The majority were solvent inclusion compound. Racemic alcohol inclusion compounds were observed almost the same in "thermal conditions" and sonication. The inclusion ability observed with **114** (Table 19, 20) and **107a** (Table 12, 13) was also the same and was very satisfactory.

When attempted resolution of racemic alcohols was carried out by inclusion compound formation with *in situ* formed **114**, as with **107a**, much better results were found. From Table 21 [(+)-TB : *p*-Methoxybenzyl chloride = 1 : 1] and Table 22 [(+)-TB : *p*-Methoxybenzyl chloride = 1 : 2]. Tested alcohols were found in many crystals. It is possible that **114** may act as a very good host in resolution by inclusion compound formation.

In contrast to salt **114** [formed from (+)-TB and *p*-$CH_3OC_6H_4CH_2Cl$], salt **115** (Table 23) formed *in situ* [from (+)-TB and *p*-$CH_3C_6H_4CH_2Br$] appears to have quite different inclusion behavior. Compound **115** exhibited a strong ability to crystallize by itself. No included guest was observed by ^1H NMR analysis, just pure **115** itself was found as confirmed by the mp of a crystallized sample of **115**.

Table 19. Attempted Resolution of Alcohols by Inclusion Compound Formation with 114 (Heating)[a], Salt of TB with p-Methoxybenzyl chloride (preformed)

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b,c]
83	-	-	-	+	-	-
84	-	+	-	+	-	-
89	+	+/n[d]	-	+/n	-	-
92	-	-	-	-	+/n	-
94	-	-	-	-	+	-

a. Resolution solutions were heated for 30', cooled to 0 °C, and were kept one month at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.19.1).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **114** and solvent.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

Table 20. Attempted Resolution of Alcohols by Inclusion Compound Formation with 114 (Sonication[a]), Salt of TB with p-Methoxybenzyl chloride (preformed)

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b,c]
83	+/n[d]	-	-	-	-	+
84	+/n	+	+	+	+	-
89	+	-	+/n	+	-	-
92	-	-	-	-	-	+
94	-	-	+/n	-	-	+

a. Resolution solutions were sonicated for 20', cooled to 0 °C, and were kept one month at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.19.2).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **114** and solvent.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

Table 21. Attempted Resolution of Alcohols by Inclusion Compound Formation. *In Situ* Formation of TB p-Methoxybenzyl chloride Salt with Heating[a] [(+)TB : p-Methoxybenzyl chloride = 1 : 1]

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b,c]
83	+/n[d]	+	-	-	+	-
94	+	+	-	-	-	-
89	+	-	-	+	-	-
92	+	+/n	+	-	+	-
94	-	-	+/n	+	-	-

a. Resolution solutions were heated for 30', cooled to 0 °C, and were kept one month at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.19.3).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **114** and solvent.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

Table 22. Attempted Resolution of Alcohols by Inclusion Compound Formation. *In Situ* Formation of TB-p-Methoxylbenzyl chloride Salt with Heating[a] [(+)-TB : p-Methoxybenzyl chloride = 1 : 2]

Solvent Alcohol[e]	MeOH crystals[b,c]	EtOH crystals[b,c]	n-BuOH crystals[b,c]	Me_2CO crystals[b,c]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b,c]
83	+/n[d]	+/n	+/n	-	+	+
84	+/n	+/n	-	+/n	+	+
89	-	+/n	-	+	-	+
92	+	+/n	+	-	-	+
94	-	-	+/n	-	-	+

a. Resolution solutions were heated for 30', cooled to 0 °C, and were kept one month at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2.3.19.4).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **114** and solvent.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Tested alcohol was observed by ^1H NMR (300 MHz). Symbol "n" means that no anisochrony was observed.
e. Structural formulas are given in Sec. 1.10.

However, in contrast to other hosts in our inclusion study, it was observed that crystals of **115** formed very rapidly and nicely in the majority of experiments. The speed of crystallization is much faster than with **114**, **107a** or **82a**. The minimum time of crystal formation was 5 min and the maximum time was two days in our experiments. Table 23 shows that crystals formed in majority case.

In contrast to **115**, **116** [(+)-TB · $C_6H_5CH_2CH_2Cl$] never formed crystals on standing for a whole month at 0 °C. The same solvents, the same resolution conditions, and the same racemic alcohols were used, but no crystals formed.

The idea of selecting **114**, **115** and **116** as hosts in inclusion compound formation was to study the effect 1) of R (see below) with a benzene ring on inclusion compound formation; 2) of the substituent groups on the benzene ring in resolution; 3) of R size in molecular recognition; 4) of the X^- group on inclusion compound formation. The idea was to try to find some useful information about good structures in the onium salt forming reagent (R) leading to inclusion compound formation. Our experiments do not show that R with a benzene ring specially facilitates inclusion formation. These experiments also could not tell us what is the function of X^- in inclusion compound formation. Obviously, our limited study cannot answer all these questions. However, it is clear that **115** with a strong ability to crystallize does not correspond to a strong ability to form inclusion compounds.

Table 23. Attempted Resolution of Alcohols by Inclusion Compound Formation with 115 (Heating)[a]

Solvent Alcohol[d]	MeOH crystals[b]	EtOH crystals[b]	n-BuOH crystals[b]	Me_2CO crystals[b]	$CHCl_3$ crystals[b,c]	Cyclohexane crystals[b]
83	+	+	+	+	+	+
84	+	+	+	+	+	+
89	+	+	+	+	-	+
92	+	+	+	+	-	+
94	+	+	+	+	-	+

a. Resolution solutions were heated for 30', cooled to 0 °C, and were kept one month at 0 °C. The detailed procedure is given in the Experimental Section (Sec. 2. 3. 20. 1).
b. Result labelled "+" implies that more than 2.0 mg of crystals deposited; they were characterized as **115**.
c. Result labelled "-" implies that no crystals, or less than 2.0 mg of crystals deposited.
d. Structural formulas are given in Sec. 1.10.

Why is **116** so different from **115** and **114** as a potential host? Why is **115** different from **114** in its ability to crystallize and form inclusion compounds; the differences are the anions (Cl^-, Br^-) and **115** has one oxygen atom less than **114**? These questions may not be answered just from the structural formulas alone.

3.1.5 Enantiopure TB and its Onium Salts as Chiral Solvating Agents (CSA)

3.1.5.1 Enantiopure TB as Chiral Solvating Agent (CSA)

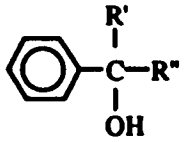
Comparison of ^1H NMR spectra of racemic alcohols **83-87**, run alone in $CDCl_3$, with spectra of these alcohols run in the presence of (+)-TB, led to the observation of anisochrony at room temperature. All these five alcohols are relatively acidic to other tested alcohols, they have at least one phenyl group in their structure. The results obtained and the experimental conditions are summarized in Table 24.

In all cases examined, except alcohol **83**, the signal separations obtained are large enough to allow enantiomeric excess (ee) determinations. This is illustrated in the case of alcohols **85** and **87** (Figs. **12** and **13**). In these figures are reported the expanded regions of the ^1H NMR spectra of **85** and **87** highlighting the resonances of the protons of the ≡CH and CH groups (Fig. **12c** and **13c** respectively). Compounds containing triple bonds or more hydroxyl groups and aromatic rings are particularly sensitive to these measurements, because these groups serve as sensitive probes for magnetic

nonequivalence and thus for ee determination. The signals stemming from these externally enantiotopic groups (R' or R" in Table 24) are appreciably separated in the presence of enantiopure TB. Compound **83** may have too little magnetic nonequivalence, and the anisochrony of the CH group may exhibit a little overlap. Since temperature reduction generally provides a several fold enhancement of the magnitude of nonequivalence,[187-189] the spectrum of alcohol **83** in presence of (+)-TB was measured at - 30 °C, and a nice separation of signals appeared. The composition of a sample **83** with 85.8% ee [based on specific rotation (Sec. 2.3.9.3)] was further confirmed by this method: 87.6% ee was found at - 30 °C. (Fig. **14**). Moreover, a value of 86.4% ee was found in an easier way. ^{1}H NMR decoupling at room temperature (Fig **14**).

Nuclei which are diastereotopic will, in principle, differ in chemical shift, i.e. they will be " anisochronous". Two simultaneous nonbonded interactions, such as hydrogen bonding, π–π interaction, occur between racemic alcohols and enantiopure TB that populate chelate like conformations (Sec. 3.2.1.3) in the diastereomeric solvates. The third interaction between enantiopure TB and the two enantiomers of the alcohol should be so different that the diastereomeric solvates formed will show intrinsically nonidentical chemical shifts in some of the sensor nuclei, i.e., those atoms or groups that show anisochrony (detailed discussion in Sec. 3.2).[190]

Table 24. Chemical Shifts of Anisochronic Group Signals of Diastereomeric Complexes (A and B) Formed by Racemic Alcohols 83-87 in Presence of Tröger's Base (+)-TB[a]

Alcohol[f]	R'	R''	Observed Group	δ_A[b]	δ_B[b]	Multiplicity
83 	CH_3	H	CH	4.89	4.91	q
				4.87	4.88	
				4.85	4.86	
				4.82	4.84	
84	H	CH_2CH_3	CH_3	0.91[c]	0.92	t
				0.89	0.90	
				0.86	0.87	
85	CH_3	C≡CH	≡CH	2.63	2.66	s
86	H	CH_2CH	CH	4.78[d]	4.80[d]	q
				4.76	4.77	
				4.73	4.74	
87	H	$CH(OH)C_6H_5$[e]	CH	4.63	4.66	s

a. (±)-Alcohol (0.1 mmol) and (+)-1(0.1mmol) in $CDCl_3$ (0.2 M) at 25 °C (1 : 1 ratio).
b. ^1H NMR chemical shifts referred to TMS as internal standard (300 MHz).
c. Ratio = 2 : 1 (Tröger's base : alcohol).
d. Two overlapping quartets with the center peaks having 2X the intensity of the outer doublets.
e. (±)-Hydrobenzoin.
f. Structural formulas are given in Sec. 1.10.

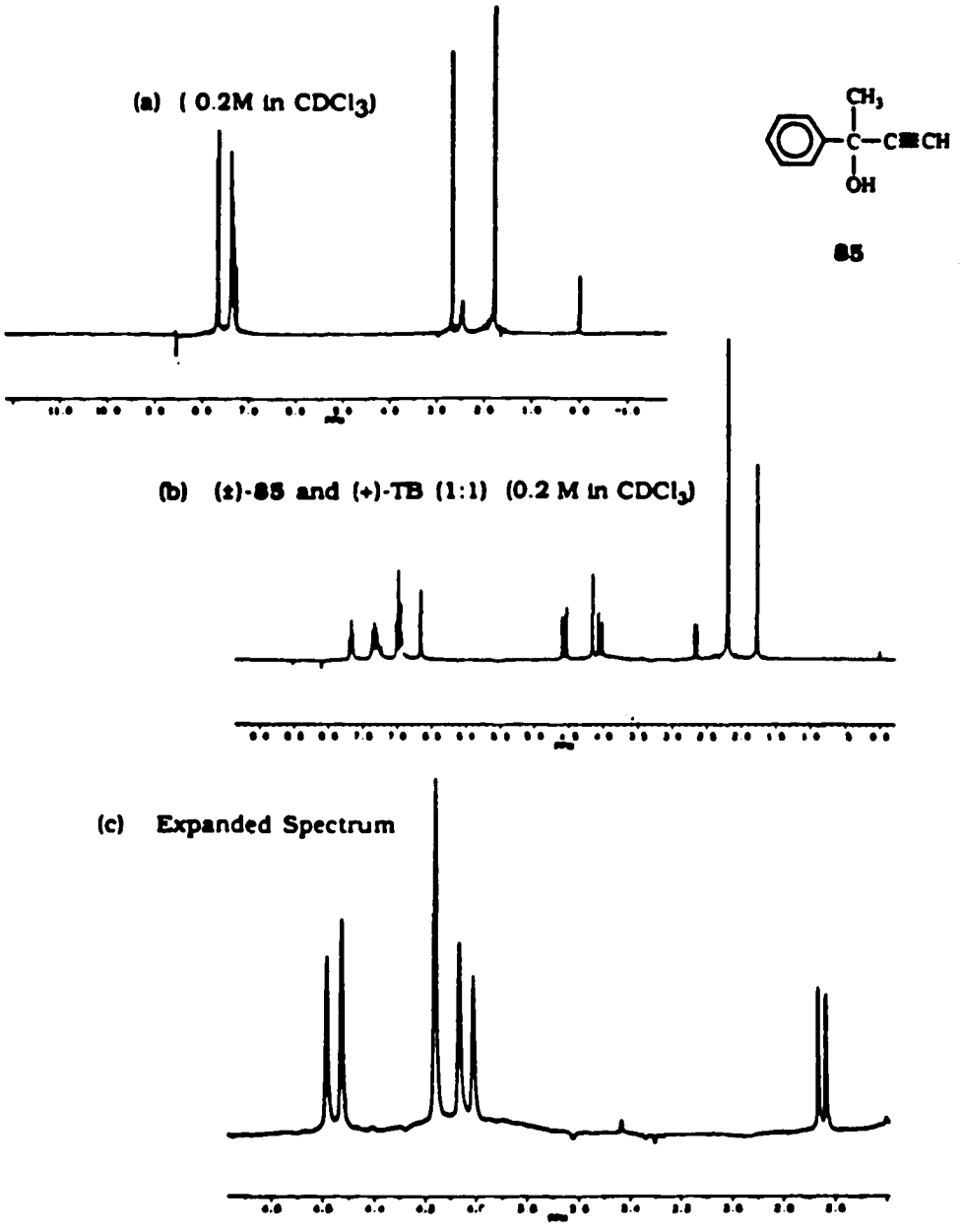


Fig. 12 Comparison of ^1H NMR spectra of alcohol (±)-85 in the absence (a) and in presence (b) of (+)-TB in $CDCl_3$ (mole ratio 1 : 1) (300MHz)

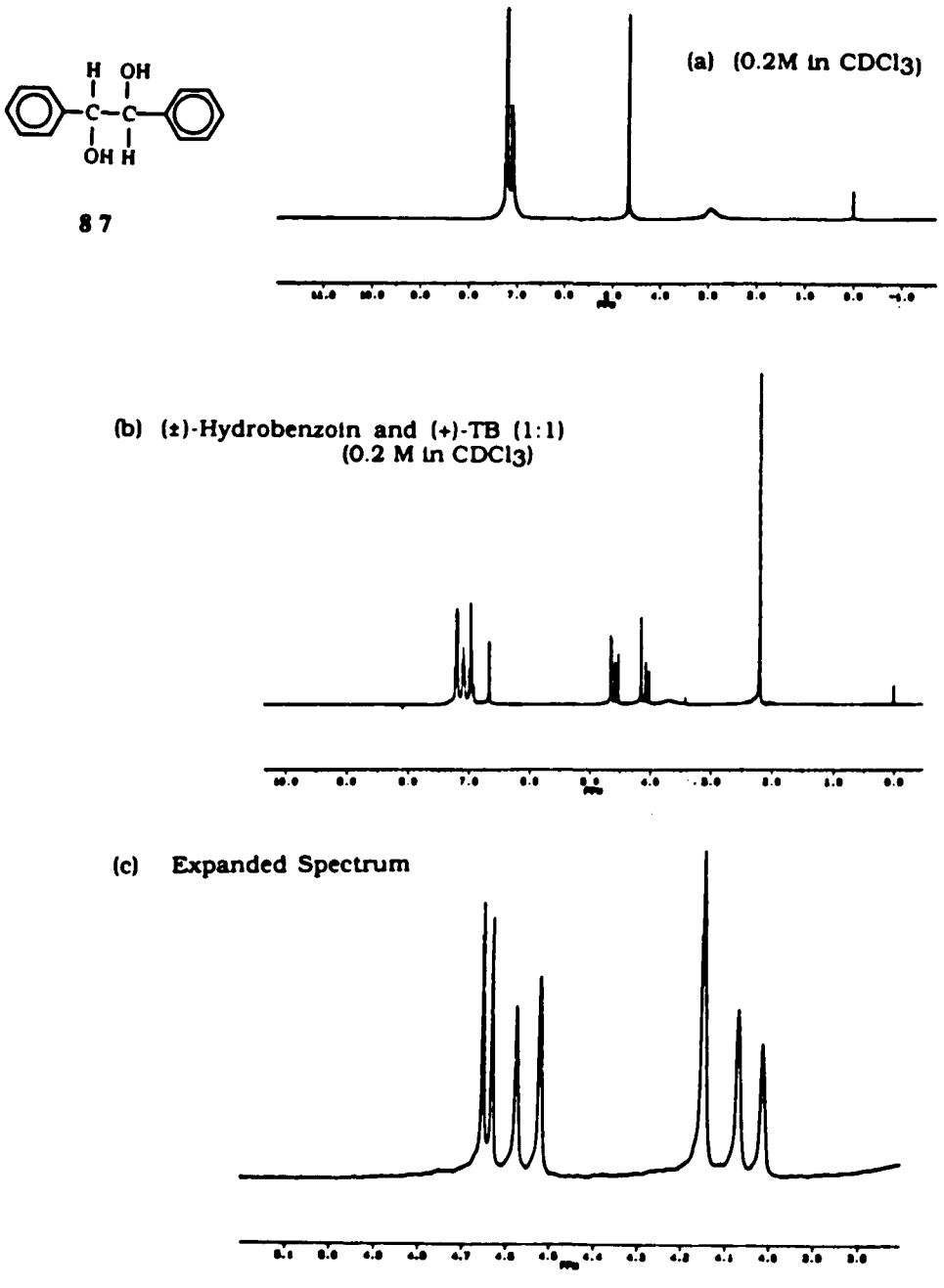


Fig. 13 Comparison of ^{1}H NMR spectra of alcohol (±)-**87** in the absence (a) and presence (b) of (+)-TB in $CDCl_3$ (mole ratio 1 : 1) (300MHz)

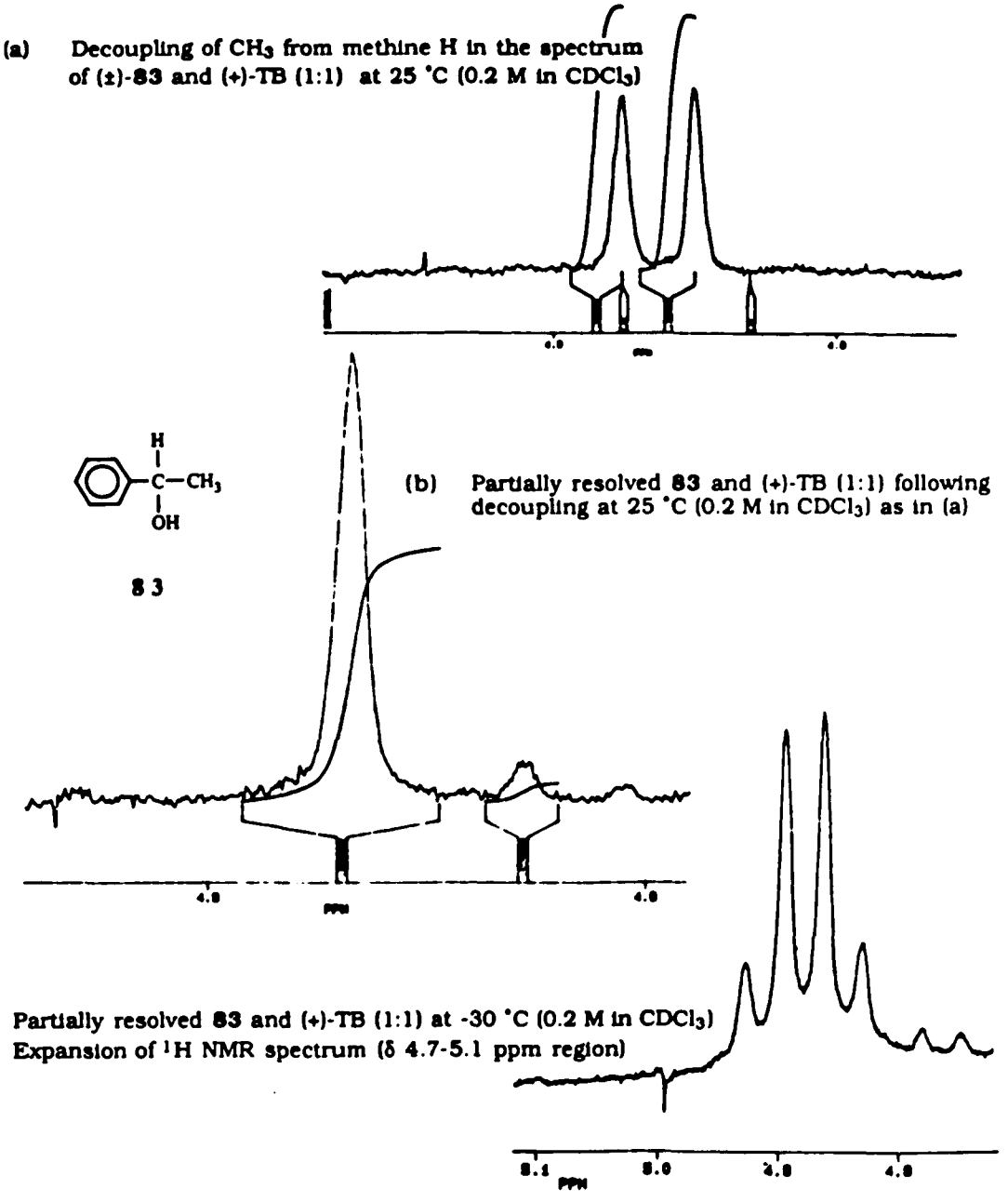


Fig. 14 Comparison of ^1H NMR spectra of racemic alcohol (a) and partially resolved alcohol (b) **83** with (+)-TB at 25 °C. The methine proton is decoupled from methyl (0.2 M in $CDCl_3$ (300 MHz); (c) is a spectrum of partially resolved **83** with (+)-TB at -30 °C (0.2 M in $CDCl_3$ 200 MHz).

The equilibrium constants for formation of the diastereomeric solvates may also be unequal (Sec. 3.2.1.1).[161, 191] We believe that the more alcohols we explore, the more examples of anisochrony will be observed using enantiopure TB, and under appropriate conditions, enantiopure TB may serve in the determination of the enantiomeric purity of such alcohols. The experimental section shows that the method is simple, and it is suggested that enantiopure TB is readily obtainable.

In summary, we have observed that enantiopure Tröger's base may serve as a chiral solvating agent (CSA) (Reviews on chiral solvating agents) [161, 192] toward chiral alcohols. Our results are comparable to and complementary with those observed when quinine is used as CSA.[193] Rosini, et al., have observed that the enantiomers of alkylarylcarbinols exhibit different chemical shifts (by ^{1}H NMR) when mixed with quinine. The $\Delta\delta$ of the observed group is 0.01 ppm in the majority of cases. When TB is used as CSA with similar alcohols, in the majority of cases the $\Delta\delta$ is 0.02 ppm.

3.1.5.2. Enantiopure TB Onium Salts as Chiral Solvating Agents

A larger proportion of the alcohols studied exhibited ^{1}H NMR anisochrony in presence of onium salt **107a**. This is illustrated with compound **90** (Fig. **15**) which did not exhibit anisochrony in presence of (+)-TB. Spectrum (c) was measured on the inclusion compound recovered from a resolution trial (Sec. 2.3.13.9). From Tables 23 and 24, we observe the following:

1) In comparing the effects of the CSA (onium salt **107a** vs. TB), we see that for the same alcohol, such as **83**, $\Delta\delta$ of the observed CH group in the ^{1}H NMR spectrum is obviously larger with the onium salt ($\Delta\delta$ with **107a**, 0.51 ppm) than with (+)-TB ($\Delta\delta$ with (+)-TB, 0.01 ppm). This is certainly convenient for measurement of the enantiomeric excess. For some alcohols, measurement of the ee by this method may not require low temperatures or decoupling.

2) In the experiment of **107a** as CSA, there was no anisochrony phenomenon observed by using preformed **107a** as CSA at the same concentration, and with the same ratio of TB to **107a**, and same ^{1}H NMR test solvent as in Table 25. Even when the ^{1}H NMR test solution was heated 1 h, the result was still negative. These facts raise very interesting question which should be further studied.

3) Using TB onium salt (TB methosulfate formed *in situ*) as CSA, two chiral *aliphatic* alcohols, **92** (Fig. **16**) and **93**, neither of which exhibited anisochrony in the presence of (+)-TB, were observed to exhibit anisochrony very clearly. Obviously, the enantiopure quaternary TB onium salt acts as a more powerful CSA toward alcohols than does Tröger's base itself.

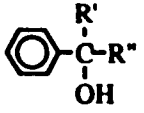
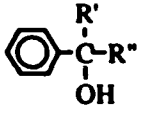
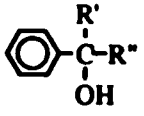
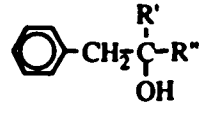
3.1.6 Differential Scanning Calorimetric (DSC) Analysis of Tröger's Base

3.1.6.1 Determination of the Phase Diagrams for Fusion of Tröger's Base

DSC analysis can provide accurate heats of fusion (ΔH^f) and melting points which in turn permit the construction of phase diagrams. DSC analysis of our resolved TB and of racemic TB was carried out and the results were compared with those obtained on a commercial sample of (+)-TB (Fluka). ΔH's and mp's for racemic and enantiopure TB are listed in Table 2. These not only permitted us to construct experimental binary phase diagrams for TB (Fig. **17**), but also permitted us finally to construct theoretical binary phase diagrams for TB (Fig. **18**).

An experimental phase diagram demonstrates that Tröger's base is a racemic compound (Sec. 3.1.6.1). As a further check on our experimental phase diagram, we applied the equation of Schröder-Van Laar (Eq. **8**) to calculate the enantiomer branch, and the equation of Prigogine and Defay (Eq. **9**) to calculate the racemate branch of the heoretical phase diagram. The equation of Prigogine and Defay (Eq. **9**), which does not incorporate the specific heats of the constituent solids and liquids, is formally comparable to the simplified Schröder-Van Laar equation **8**.

Table 25. Chemical Shifts of Anisochronous Signals of Inclusion Compounds Formed from Racemi Alcohols (83, 84, 88-93) with Tröger's Base Methosulfate[a]

Structure	Compound Number	R'	R''	Observed Group	A (ppm)	B (ppm)	mutiplicity
	83	H	CH_3	CH[b]	5.21	4.70	q
					5.19	4.68	
					5.17	4.66	
	84	H	C_2H_5	CH_3	0.88	0.80	t
					0.86	0.78	
					0.84	0.76	
	88	CH_3	C_2H_5	CH_3	1.04	0.67	t
					1.02	0.65	
					1.00	0.63	
$C_6H_5CR'CH_2(OH)R''$	89*	H	CH_3	CH_3	3.06	2.94[c]	m
$C_6H_5CH_2CR'(OH)R''$	90*	H	CH_3	CH_3	1.26	1.20	d
					1.24	1.18	
	91	H	C_3H_7	CH_3	0.83	0.77	t
					0.81	0.75	
					0.79	0.73	
$CH_3CR'(OH)R''$	92*	H	C_2H_5	CH_3	1.30	1.21	d
					1.28	1.19	
$CH_3(CH_2)_3CR'(OH)R''$	93*	H	$(CH_2)_2CH_3$	$(CH_2)_3/(CH_2)_2$	1.41	1.25[c]	m

a. ^1H NMR spectra were run in $CDCl_3$ (*)or DMSO-d_6 (about 0.05-0.1M) at room temperature (300 MHz)
b. Fourth peak obscured by overlap with peak due to onium salt.
c. Center of multiplet.

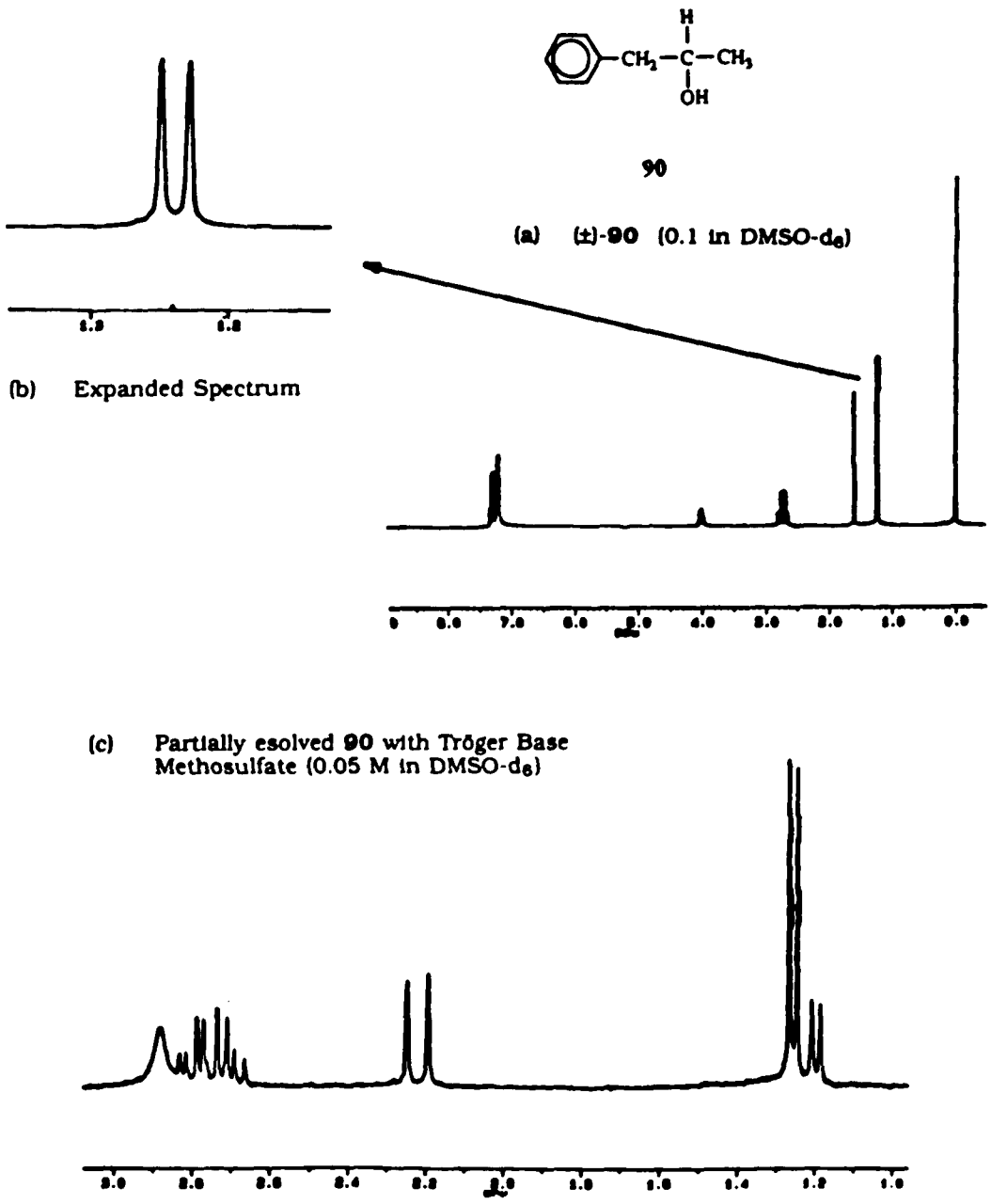


Fig. 15 Comparison of ^{1}H NMR spectra of (±)-**90** in the absence (a) and presence (c) of Tröger's Base methosulfate (**107a**). The third spectrum exhibits anisochrony. [Partial spectrum (b) is an expanded view of the CH_3 group in (a)]

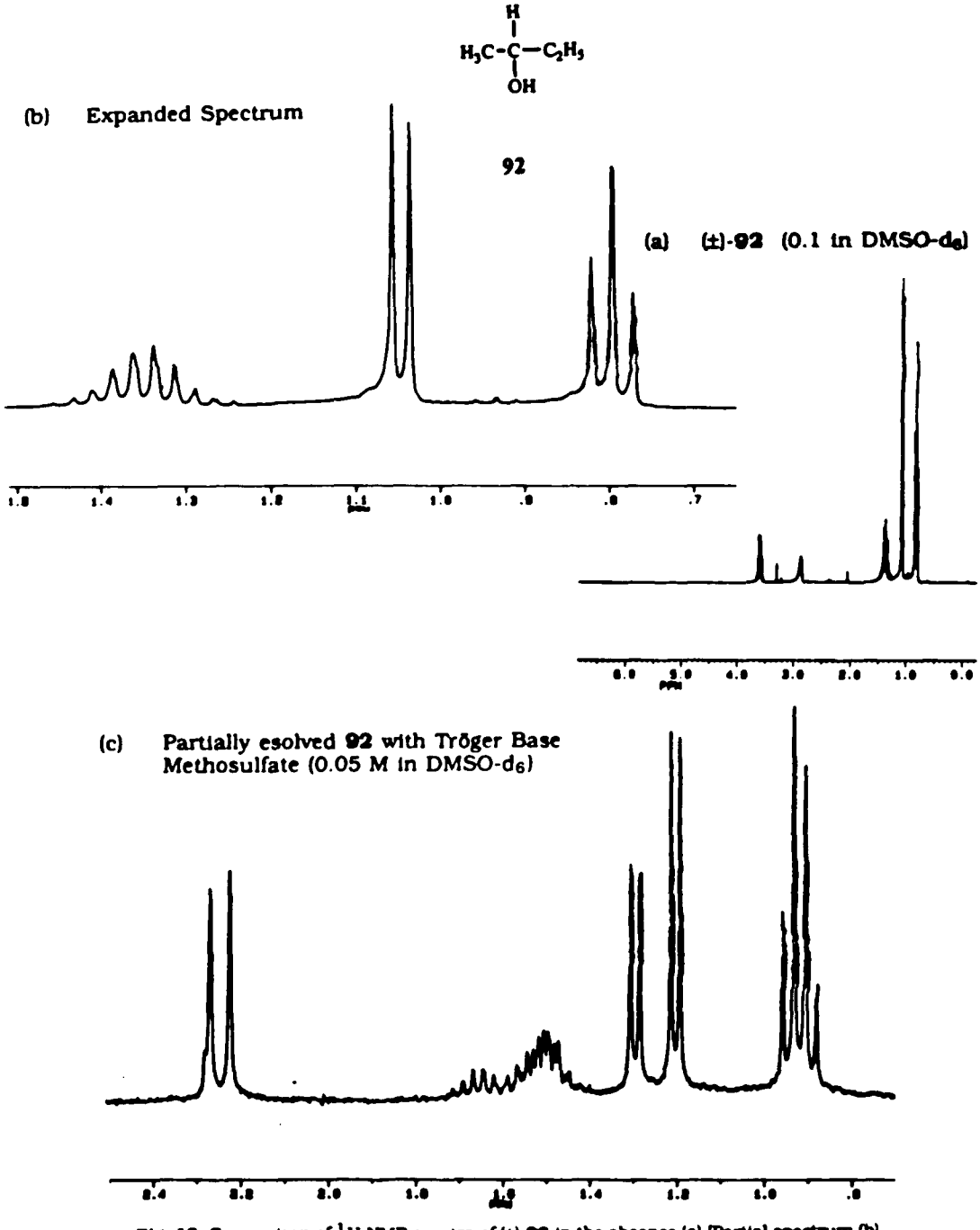


Fig. 16 Comparison of ^{1}H NMR spectra of (±)-**92** in the absence (a) [Partial spectrum (b) is an expanded spectrum of (a)] and presence (c) of Tröger's Base methosulfate. The third spectrum exhibits anisochrony.

Experimental Plot of TB Melting Point against Composition

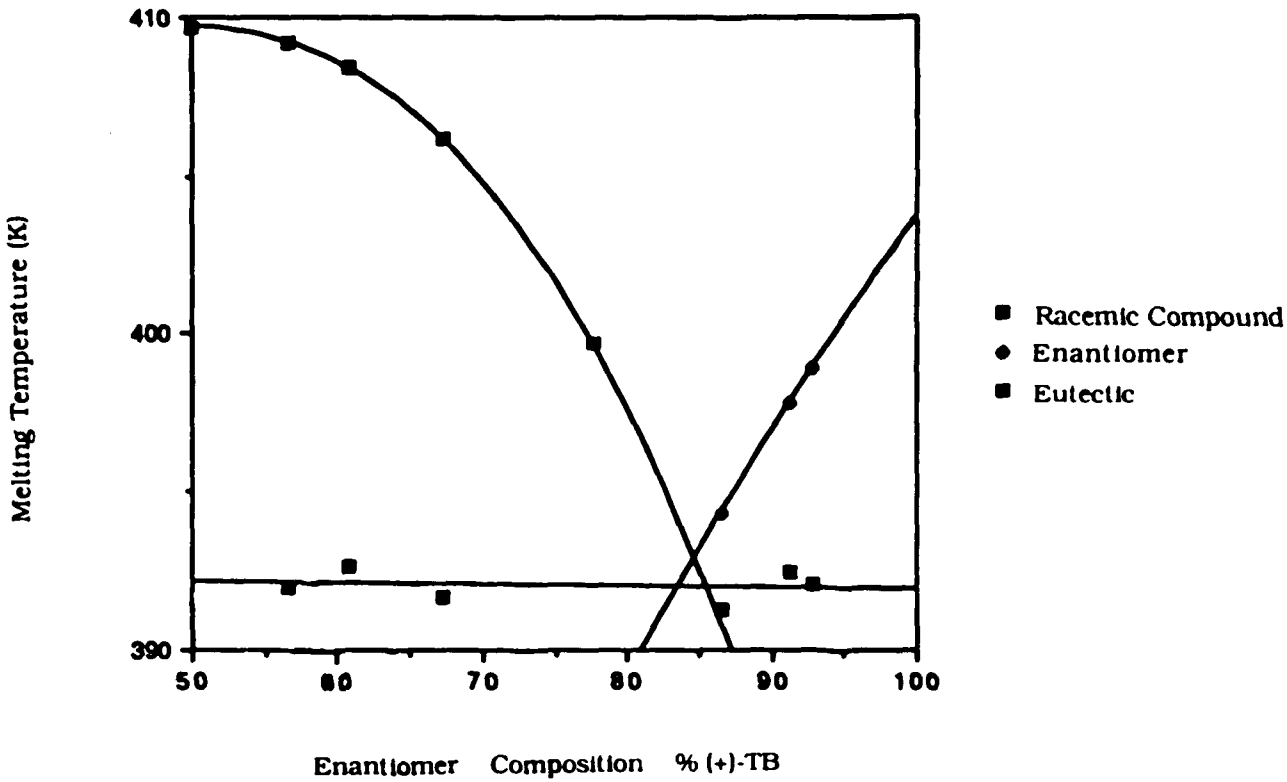


Fig. 17 Experimental binary phase diagram

Using equations (**8**) and (**9**) (Sec. 1.7.1.2), we calculated the melting points (K) for different enantiomer compositions (Table 26). A plotting program (Cricket Graph; Cricket Software, Inc.) was used to generate the best fit phase diagrams (Fig. **17**, **18**) from the experimental and theoretical points (Tables 3 and 26), which match each other quite nicely (Fig. **19**).

The whole binary phase diagram of TB (Fig. **20**) was calculated by means of a program written in Turbo Pascal and run on the VAX computer (11/780) with the Q-plot program. A listing of the program is given in Appendix I and II.

The melting point phase diagrams describe solid-liquid equilibria, in which the behavior of systems that consists of two components, enantiomers D and L, is described a function of variables such as temperature, pressure, concentration and so on. In a case of a given mixture of D and L, the composition of the mixture can immediately be obtained from the phase diagram if the melting point (termination of melting) of this mixture is known. It can be used to independently confirm and prove the ee measured by NMR or polarimetry.

Thus the binary phase diagram can in turn be used to determine the enantiomer composition of samples of resolved TB. In our study there were a lot of resolved TB samples in hand, therefore determination of the ee was very easy and fast by measuring their melting points. Table 27 showed that the difference in ee as measured

from the binary phase diagram and from the ee of sample (+)-TB by weighing is small. The average difference is 2.4%. However, the error in e.e.s determined from binary phase diagrams and from the measured specific rotations was 1.7%.

3.1.6.2 Sensitivity of DSC in the Determination of Enantiomer Purity of TB

A DSC analysis requires only a very small sample ranging from 0.1-10 mg for analysis. The aluminum sample pan containing the sample (S) and reference (R) are heated simultaneously and their temperatures are monitored. The interval between an isothermal baseline and the heating baseline gives the difference in specific heats of S and R. The peak areas in DSC spectra give the enthalpies of the transitions. Specific heats, heats of transformation and heats of fusion of organic compound are of interest in the determination of the purity of a crystal.

For virtually all mixtures of enantiomers, DSC scans exhibit both eutectic and enantiomer peaks, or eutectic and racemate peaks. The area ratio of these two peaks changes with the enantiomer composition of the substance, as in the case of TB (Fig. **21**). Fig. **21** is a DSC scan of the fusion of a 1.80 mg sample of (+)-TB having 64.9% e.e. Two peaks corresponding to melting of eutectic (A) and racemate (B)

Table 26 Calculation of Melting Points of TB as a Function of Enantiomer Composition

Enantiomer Composition of TB (%)	Calculated Melting Point (K)
60	408.5
70	404.9
80	397.5
84	393.0
85	393.2
90	396.8
95	400.5
100	403.9

Table 27 Comparison of ees Determined from the Binary Phase Diagram with Optical Purities Determined from Specific Rotations.

(+)-TB (ee of sample)[a]	mp (°C)[b]	ee (%) determined by specific rotation[c]	ee (%) determined by bin. phase diagram[d]
56.3	136.5	57.2	54.1
60.2	136.0	61.3	61.8
66.0	133.5	67.5	66.5
85.1	123.5	86.3	88.9
91.4	127.0	93.0	94.4

a. Enantiomer excess of (+)-TB. (by weighing).
b. Melting points were measured on Fisher-Johns melting point apparatus.
c. $[\alpha]^{25}_{D}$ (c 0.30, hexane). $[\alpha]^{25}_{D}$ + 309.0 (c 0.30, hexane)was taken as reference for pure (+)-TB.
d. All values were given by computer reading from binary phase diagram.

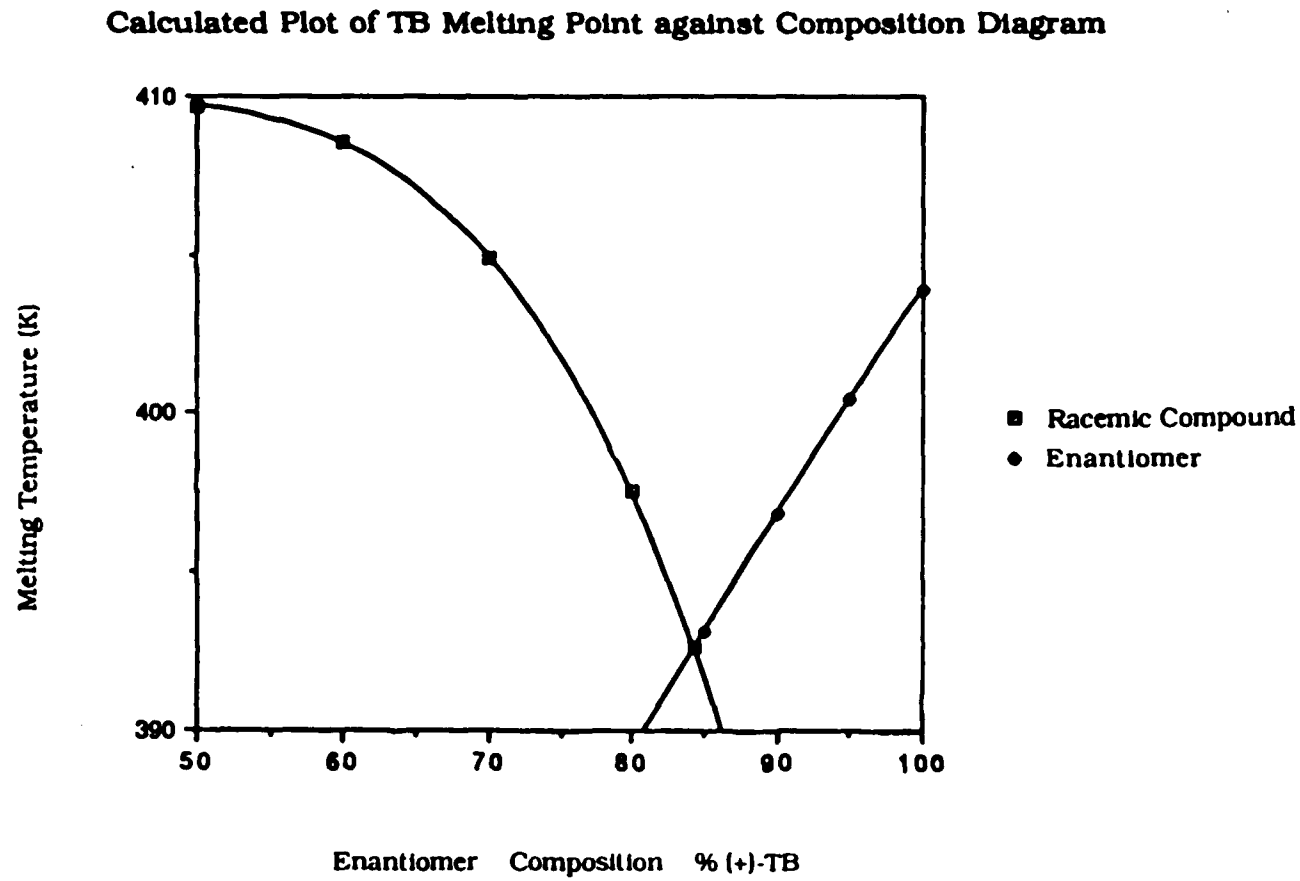


Fig. 18 Theoretical binary phase diagram

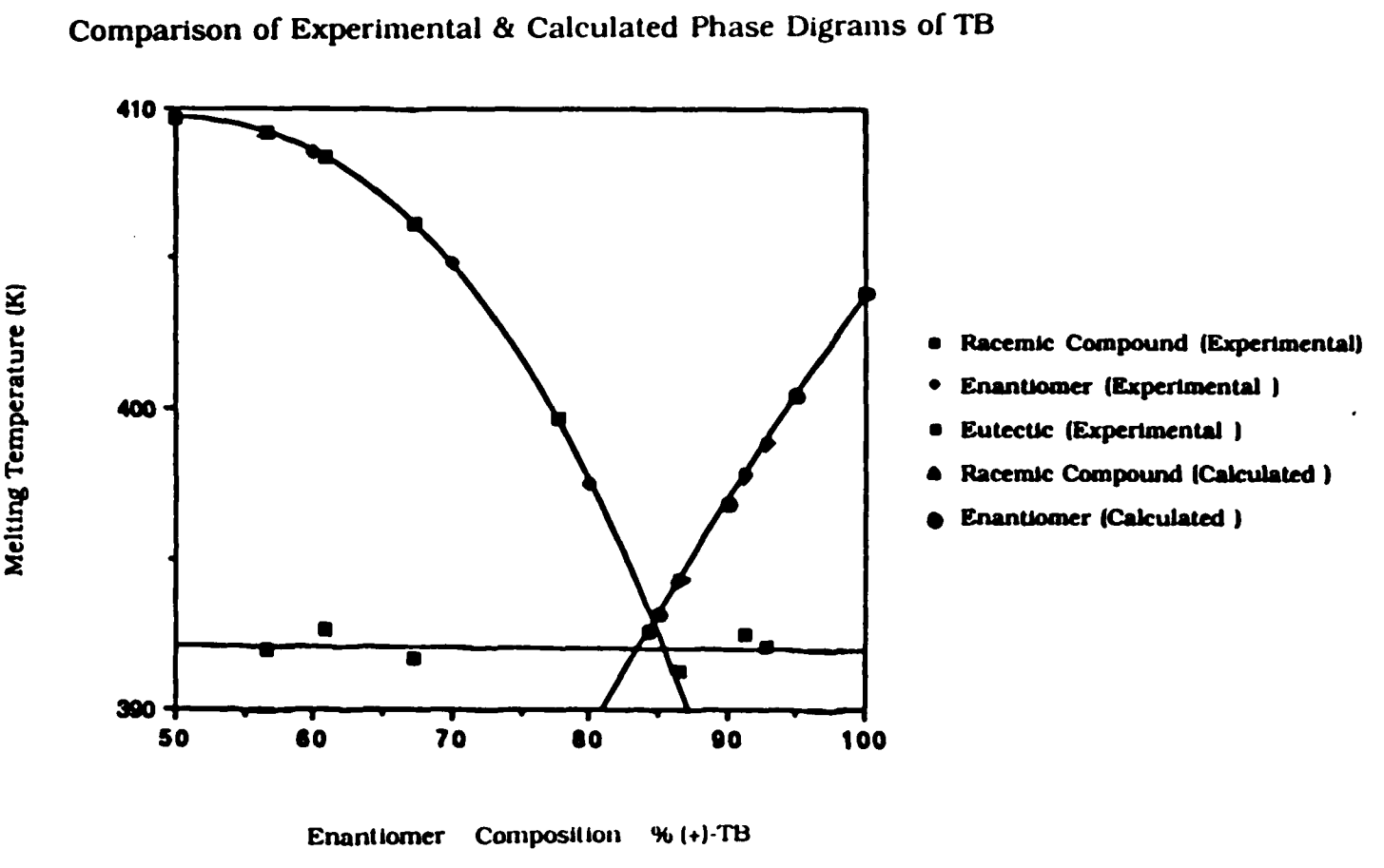


Fig. 19 Comparison of theoretical and experimental binary phase diagrams of TB

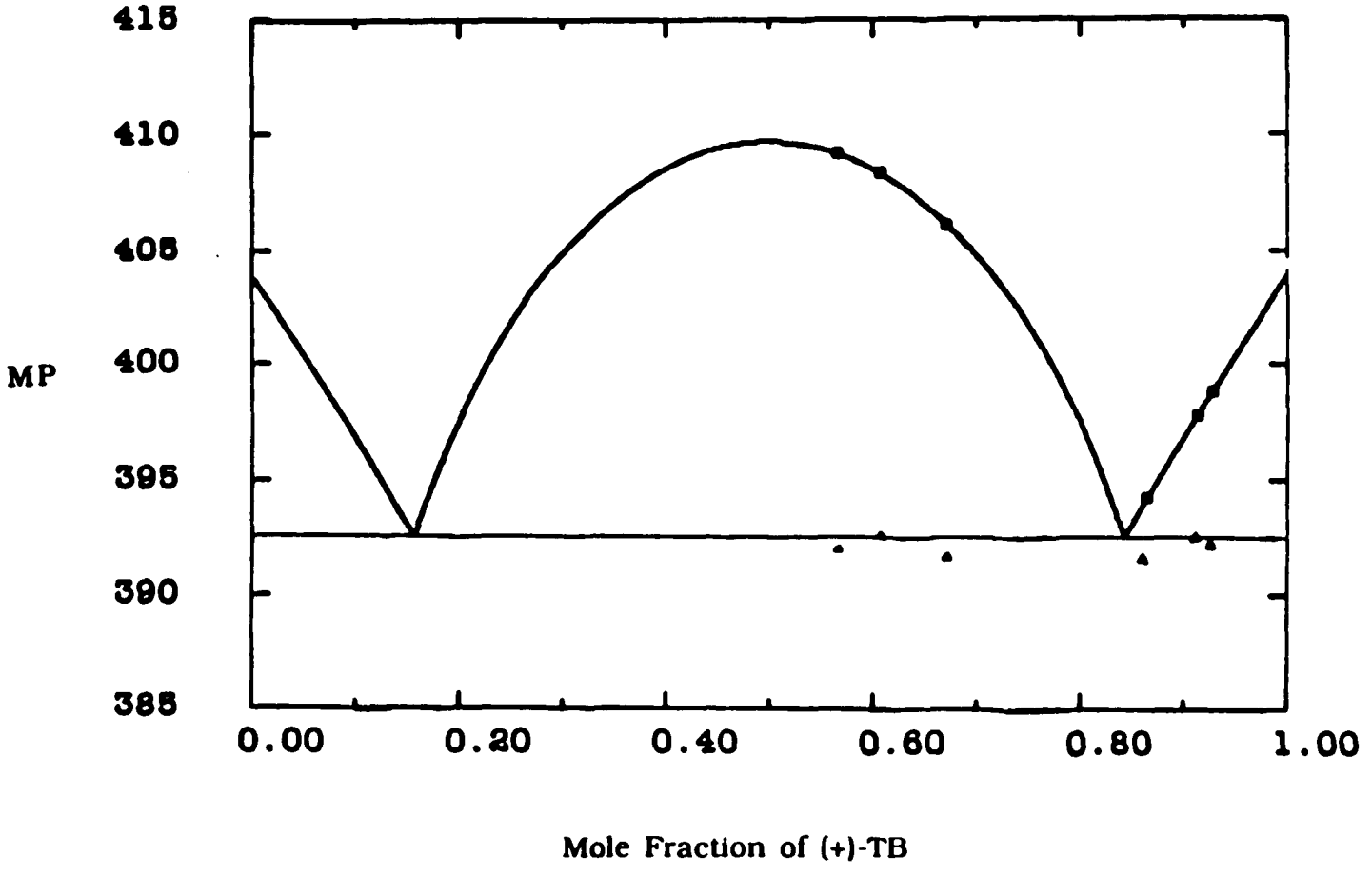


Fig. 20 The whole calculated binary phase diagram of TB slowing experimental DSC melting points

were observed. As the enantiomer purity increases from the racemate, peak A first increases in area as peak B decreases and, after the composition exceeds the eutectic composition (ca. 16%), the eutectic peak decreases in area. For a sample with 99.2% ee, the eutectic peak is already very small (Fig. **22**, in this scan, peak B' is due to the enantiomer) though it is still evident. For a sample with 99.5% ee, only a single peak (due to the enantiomer) could be observed. We concluded that the minimum % of one enantiomer of TB which could be detected by DSC is of the order of 0.5% (Sec. 2. 3.8.3 Table 5).

DSC is an another tool for determining the enantiomer composition. The applications of DSC include qualitative observations as well as quantitative measurements. It is an excellent tool to determine the sample e.e. after resolution.

3.1.7 The Result of Circular Dichroism (CD) and UV Analysis for Tröger's Base

The circular dichroic (CD) and UV absorption spectra of enantiopure TB were measured to confirm the configurations of our samples, to get more accurate CD and UV data than are reported in the literature as well as to check the sample's purity.

In Fig. **23**, is shown the summation curve of two Cotton effects of opposite sign. Therefore in the UV spectrum, the summation of the two components leads to a single maximum in the range of 240-280

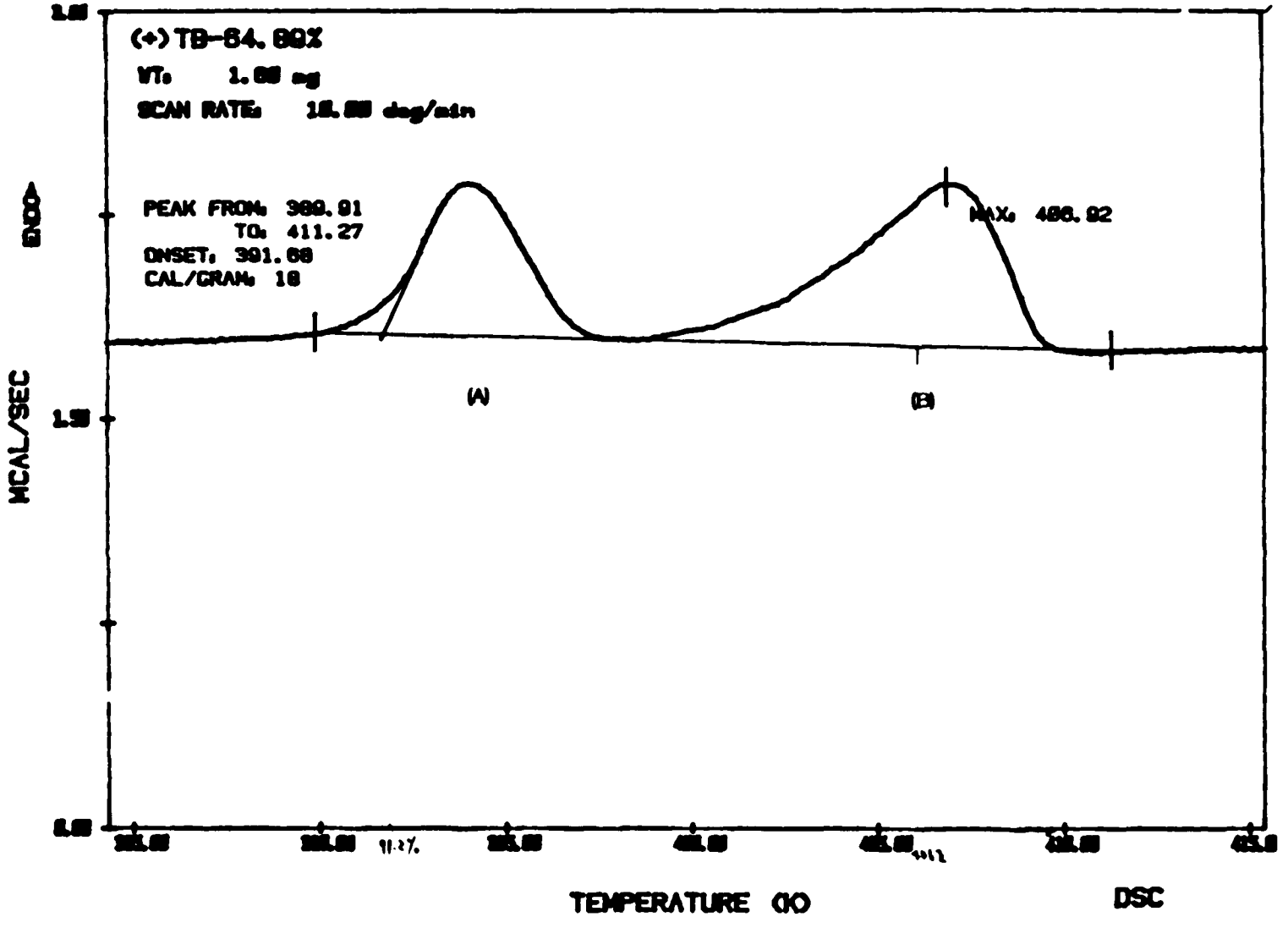


Fig. 21 DSC scan of a sample containing 64.89% (30% ee.) of (+)-TB.

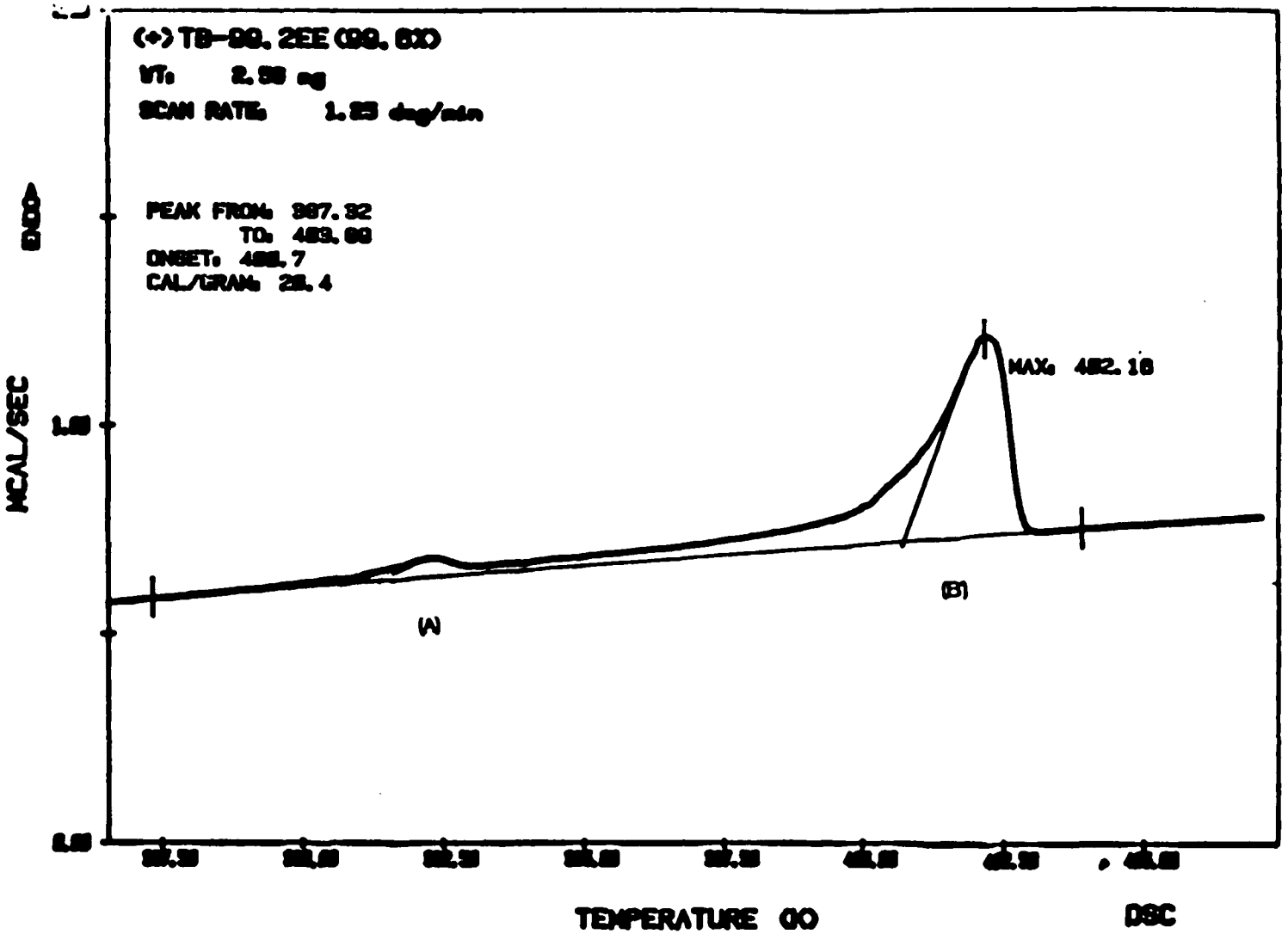


Fig. 22 DSC scan of (+)-TB (99.2% ee). Two peaks corresponding to melting of eutectic and enantiomer were observed

Circular Dichroism Spectra of (+)-TB, (-)-TB and (±)-TB in Ethanol at 295 K

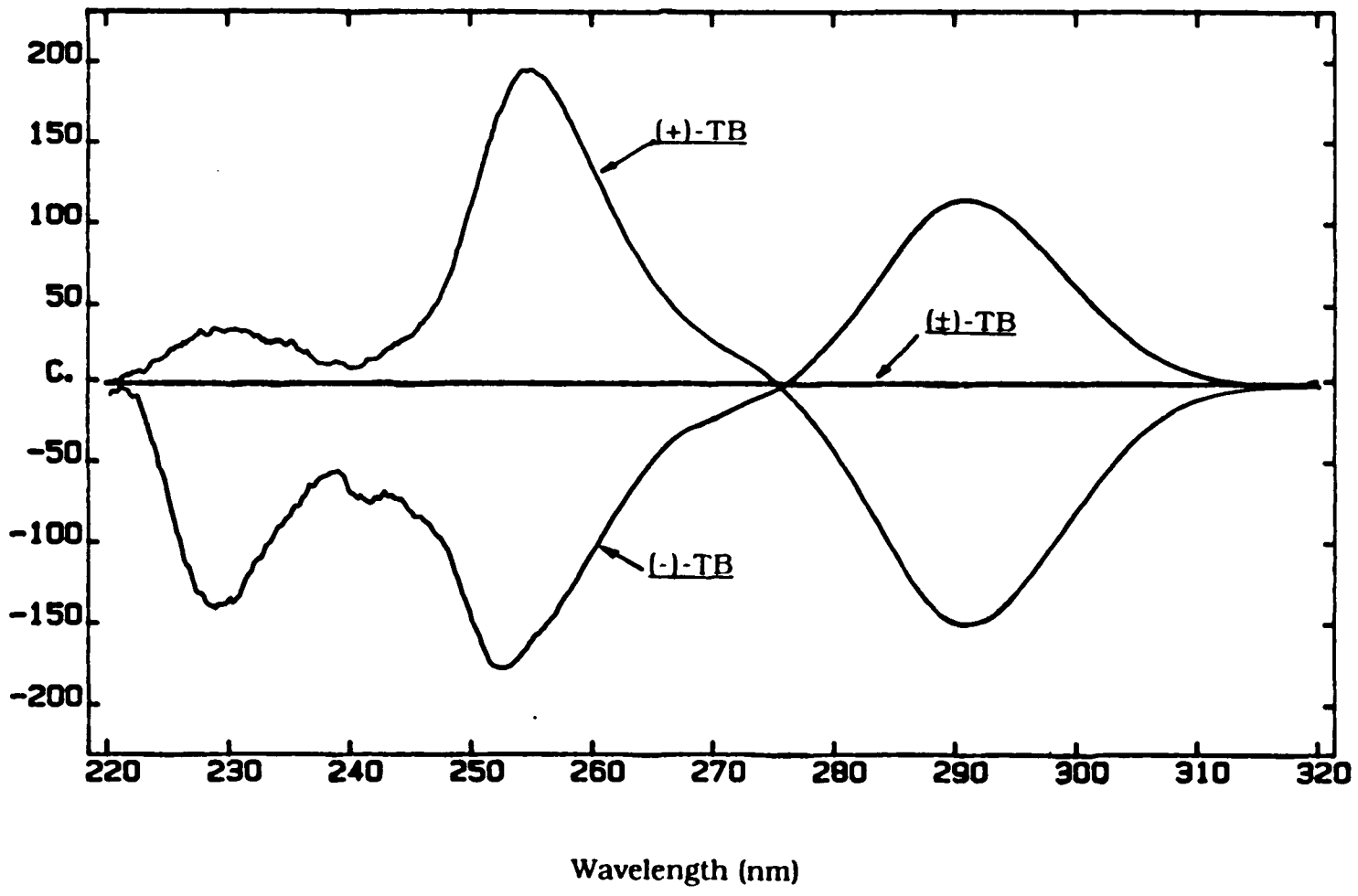


Fig. 23 Superposed CD spectrum of (+)-TB, (-)-TB and (±)-TB

The Absorption spectrum of (+)-TB in Ethanol at 295 K

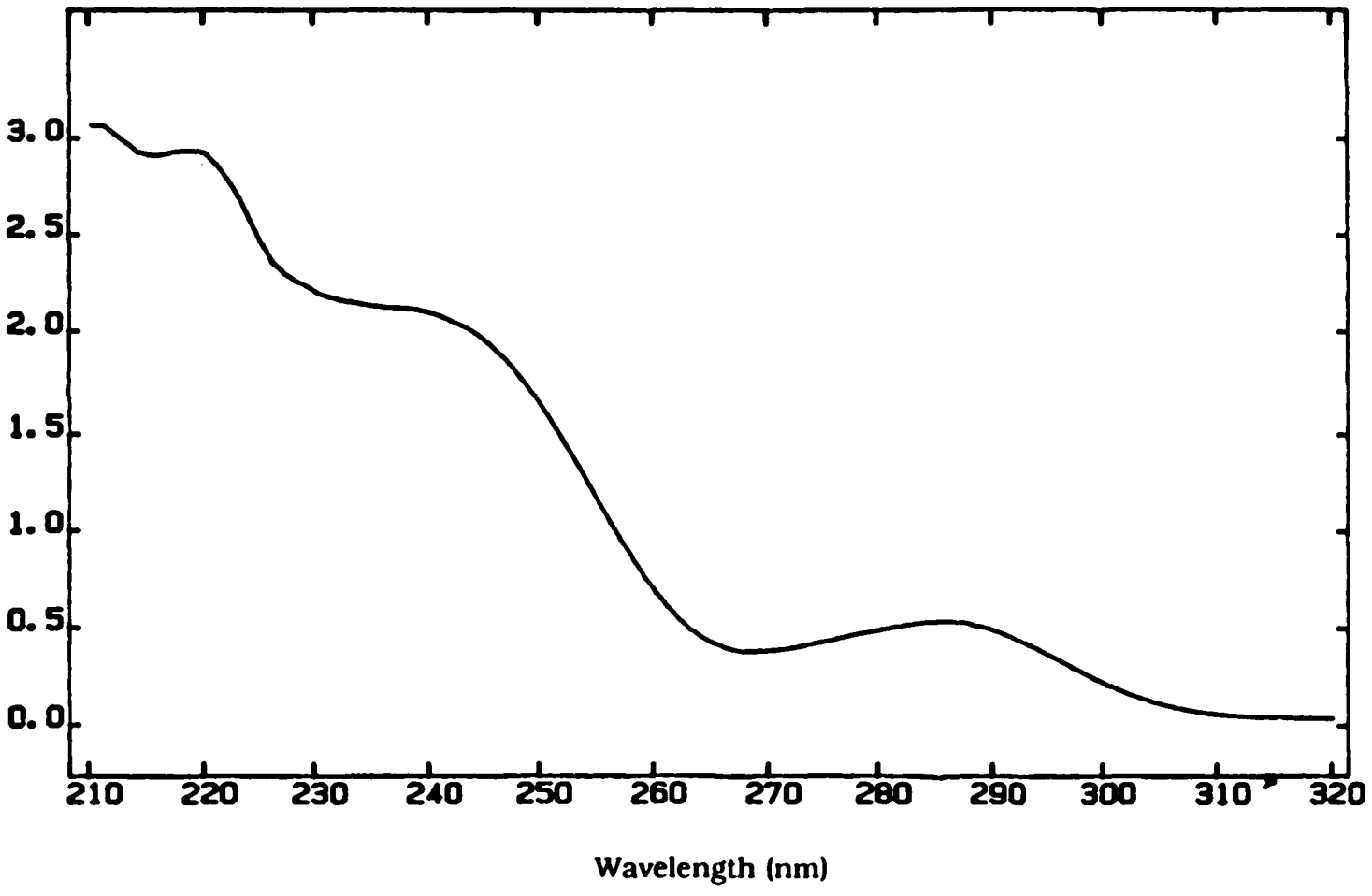


Fig. 24 The UV absorption spectrum of (+)-TB (ethanol, c 0.14mg/ml) at 295 K

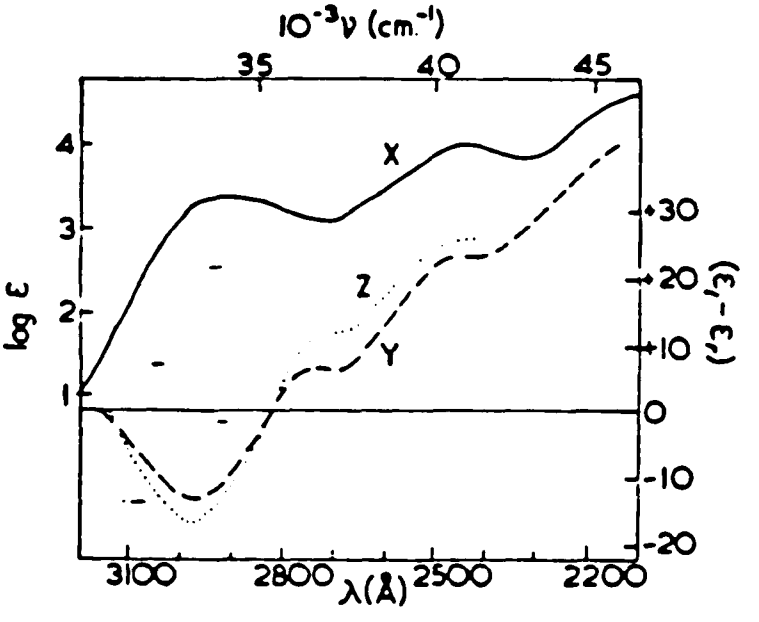


Fig. 25 CD and UV spectra of (+)-TB as reported by Mason, et al.[159] The absorption spectrum (X), and the circular dichroism at 295 K (Y) and at 80 K (Z) of (+)-TB

nanometers (Fig. **24**). This matches Mason's CD and UV spectra (Fig. **25**). In Fig. **23**, it is observed that the circular dichroism spectra at 295 K of (+)-TB and (-)TB are almost symmetric with the CD spectrum of (±)TB as a symmetric axis. Some impurity in the (-)-TB sample may be responsible for the slight departure from true mirror symmetry of the two CD spectra.

3.1.8 The Configuration of Tröger's Base

The CD exciton chirality method (See Sec. 1.7.1.3)[160] and X-ray crystallography[194-198] are key methods for determining the absolute configuration of chemical compounds. Although the two methods are independent of each other, the conclusion obtained by both methods should be consistent.

Mason, et al., early in 1967 determined that (+)-TB has the (5*R*, 11*R*) configuration. This determination stems from the calculated relative frequencies and signs of the rotational strengths of the aniline chromophores in relation to the positions and the signs of the bands observed in the CD spectrum. In the CD spectrum, the aniline chromophores (λ_{max} of aniline at 285 nm) is split giving rise to a negative band at longer wavelength (ca. 295 nm) and a positive one at shorter wavelength (ca. 275 nm) for one enantiomer, (+)-TB, and the reverse for the other, these wavelengths being solvent dependent.

To study the crystal lattice of TB and its salt, X-ray experiments for TB salt **82a**, was carried out. The X-ray crystallographic analysis of

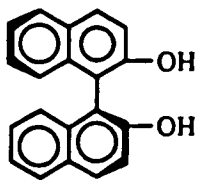
compound **82a** was carried out by Prof. Paul.Williard (Brown University) and the results are shown in Fig. **26**. As reported by Prof. Williard, compound **82a** [(+)-**79**·(-)-**81**] (Sec. 2.3.5.1) crystallized in the noncentrosymmetric, orthorhombic, space group $P2_12_12_1$.

The unit cell parameters were determined to be a=10.432 (3) Å, B=16.164 (3) Å, and c=19.879 (4) Å based upon least-squares fitting of 25 reflections in the range 24° < 2q < 26°. The unit cell contains four asymmetric units of molecular formula $[(C_{17}H_{18}N_2)\cdot(C_{20}H_{13}O_4P)\cdot(C_2H_5OH)]$ in a volume of 3351.9 (1.2) $Å^3$ which produces a calculated density of 1.28 g/cm^3. A total of 2857 reflections were recorded in the range 3.5° < 2q < 47° with a Nicolet $R3_m/E$ crystallographic system using the q-2q scan routine and graphite monochromated Mo Ka radiation (l=0.71069 Å). After Lorentz and polarization corrections and an absorption correction based upon a crystal measurement (0.3 mm x 0.3mm x 0.6mm), the structure was solved by the SHELXTL 5.1 programs. All non-hydrogen were refined anisotropically except the terminal carbon of the somewhat disordered ethanol molecule. The approximate location of all hydrogen atoms was determined by Fourier difference synthesis. In the final stages of refinement the hydrogen atoms were placed in calculated positions and allowed to ride

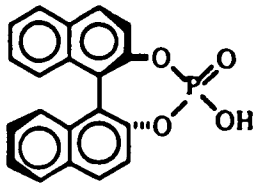
with the atom to which they are attached. The final agreement factors are R=0.056 and R_w=0.058 for 2407 unique, observed reflections [$F_o > 3s(F_o)$] and 421 independent variables.] Fig. **27** is a thermal ellipsoid plot of the molecular structure of **82a**.

In Figure **26**, the configuration of TB (**79**) in the crystal is seen to be 5*S*, 11*S* relative to that of **81** taken as R. However, the X-ray results cannot differentiate between (R)-**81**·(5*S*, 11*S*) **79** and (S)-**81**·(5*R*, 11*R*)-**79** (mirror image configurations). In our experiment, we used (-)-BNP (**81**) as resolving agent and confirmed, by isolation of TB from **82a**, that salt **82a** contained (+)-TB (**79**).

BNP (**81**) is a derivative of binaphthol. Jacques, et al., prepared the corresponding methyl ester of (+)-**81**, which was reduced and cleaved with $LiAlH_4$ to give (-)-binaphthol.[199] The absolute configuration of this (-)-binaphthol is known to be S (by X-ray diffraction)[200, 201] Obviously, BNP (+)-**81** has the same configuration as (S)-(-)-binaphthol and (-)-**81** has the configuration R.



S-(-)-binaphthol



R-(-)-BNP (**81**)

Since the (-)-**81** is known to be R, it follows that salt **82a** consists of (R)-**81**·(5S, 11S)-**79**, and therefore the configuration of (+)-**79** is 5S, 11S. This experimental finding is inconsistent with the configurational assignment by Mason, et al, based on an exciton chirality calculation.[159]

In our case, the incontrovertible assignment based on crystallography requires that the configuration of Tröger's base that has been cited in the literature since 1967 must be reversed.

From Fig. **26**, hydrogen bond formation is observed between the nitrogen on TB and the hydroxyl group on BNP. One molecule of ethanol is observed to be included in the unit lattice. It could be inferred that there is, or may be, a channel or cavity in the crystal lattice of salt **82a**. This experimentally suggests that an onium salt of TB can act as host in inclusion compound formation. It also shows that the original hypothesis concerning the cleft in TB as a site for inclusion was incorrect.

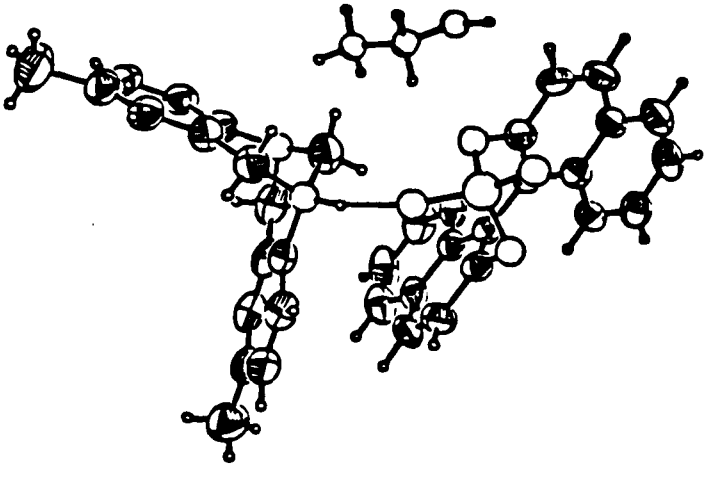


Fig. 26 X-Ray crystallographic structure plot of (+)-TB·(-)-BNP, salt **82a** [163]

3.2. Discussion

3.2.1 Nonequivalence in ^1H NMR Spectra: Induction by Enantiopure TB and Its Onium Salt

3.2.1.1 Origins and Intrinsic Features

Before discussion, some definitions are necessary:

1) Solute (d, l): This refers to the alcohols whose NMR spectra are being discussed; the solute may be racemic, enantiomerically enriched, or a single enantiomer.

2) CSA: The chiral solvating agent (CSA) is a nonracemic substance (preferably enantiopure) whose chirality influences solute spectral behavior, e.g., TB or the TB onium salt and which interacts with enantiomeric solutes d and l to form diastereomeric solvates. In turn, different physicochemical behavior between diastereomeric solvates leads to identifiable differences in the NMR spectrum.

$$d + CSA \overset{K}{\rightleftharpoons} dCSA \qquad (10)$$

$$l + CSA \overset{K'}{\rightleftharpoons} lCSA \qquad (11)$$

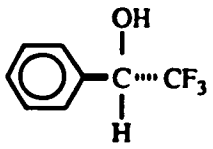
The nonequivalence in the NMR spectra of d and l may be induced by CSA through a combination of two factors. First, the diastereomeric solvates may have intrinsically nonidentical spectra for

they have different properties. Second, since the CSA is nonracemic (ideally a single enantiomer), solvation may occur to a different extent leading to a difference in K and K' (Equations 10 and 11). This difference in equilibrium constants can also result in spectral nonequivalence between the rapidly averaging species. In a solvating solution system, the four species bearing, e.g., a methine H in $PhCH(OH)CH_3$ (Eqs. 10 and 11), rapidly equilibrate giving two averaged signals (for CH) one for each solute chirality sense provided that the NMR experiment takes place more slowly than that of the equilibrium. In the second case, no intrinsic spectral difference between dCSA and lCSA need be invoked, although it may be present.[161]

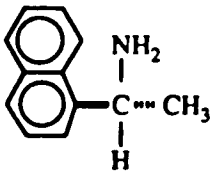
3.2.1.2 Solvent, Temperature, and Concentration Effects

The first observation of spectral nonequivalence due to a CSA was that of Pirkle and Burlingame[203] who described fluorine nonequivalence for racemic TFPE in optically active NEA (see below) in the ^{19}F NMR spectrum. The earliest studies of diastereomeric solvates verified the importance of hydrogen bonding to the CSA-solute interaction. Thus, no nonequivalence is observed for TFPE methyl ether in NEA under the same conditions as those under which TFPE exhibited anisochronous NMR signals. Obviously, when hydrogen on the hydroxy group was substituted by a methyl group, TFPE lost the strong ability to hydrogen bond to NEA. Similarly, the magnitude of fluorine nonequivalence observed for a series of trifluoromethylaryl carbinols [$ArCH(OH)CF_3$] in PEA was smallest for the α-pyridyl analog,

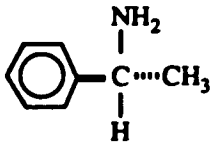
in which a considerable amount of intramolecular hydrogen bonding occurs.[202]



TFPE



NEA



PEA

Solvent effects are generally dramatic. In nonpolar solvents, such as $CDCl_3$, association is strong, and large nonequivalence was accordingly obtained with enantiopure TB as the CSA in $CDCl_3$. In this case, addition of a couple of drops of a relatively polar solvent, e.g. acetone, did severely reduce the extent of nonequivalence. On addition of a couple of drops of methanol, a more polar solvent, the anisochrony was totally eliminated. It may be that the polar solvent competes with the solute for the CSA, or the polar solvent may alter the conformations of the solvates that give rise to nonequivalence.[203-205] When acetone-d_6 was used instead of $CDCl_3$, loss of nonequivalence was also observed, e.g., in **85**-**87**. (Sec. 2.3.9.1)

Using TB onium salts as the CSA, the interaction between the chiral solvating agent and solute may be stronger than with enantiopure TB alone. Solvent effects are not as severe as above. In Table 25, ^1H NMR spectra of compounds **83**, **84**, **88**, and **91** which did not dissolve in $CDCl_3$, were all run in DMSO-d_6. Here $\Delta\delta$ are still large (from 0.06 to 0.51 ppm). However, ^1H NMR spectra of compounds **89**,

90, **92**, and **93**, which did dissolve in $CDCl_3$, were run in $CDCl_3$; $\Delta\delta$ observed were 0.06-0.16ppm. When the solvent was changed to DMSO-d_6, (for **89**, **90**, **92** and **93**) $\Delta\delta$ were still 0.03-0.07 ppm.

If the interaction between solute molecules is not so strong, the greater the concentration of CSA, the more completely solvated is the solute. So, usually, the concentration of the CSA substantially influences the magnitude of nonequivalence: nonequivalence increases with an increase in the CSA concentration until the solute is completely solvated by the CSA[206] (Sec. 2.3.9, Table 5). However, in the case of TB as CSA, racemic alcohol **83** [$C_6H_5CH(OH)CH_3$] gave no observed anisochrony in the ^1H NMR when the concentration of (+)-TB and (±)-**83** was 0.25 M - 0.30 M ($CDCl_3$ as solvent). When the concentration of TB was reduced to 0.20 M, nonequivalence was observed. This may be caused by a smaller interaction strength for the CSA-solute pair than for the solute-solute pair. More concentrated solutions may promote hydrogen bond formation among the polar solute molecules.

According to Pirkle, et al. and others, a sufficient temperature reduction can provide a severalfold enhancement of the magnitude of nonequivalence.[187-189] A solution of **83** in (+)-TB (0.20 M) yielded a small nonequivalence at room temperature. The quartet peaks of the CH group overlapped in the ^1H NMR spectrum such that the enantiomeric excess could not be measured at room temperature. When the temperature was cooled to -30 °C, the magnitude of nonequivalence was increased significantly (see Sec. 2.3.9.3).

The enhancement in the magnitude of nonequivalence as the temperature is reduced may be explained as follows:

1) If one of the two equilibria [(**10**) and (**11**)] is more exothermic than the other, an increase in the equilibrium constant for CSA-solute association can result from a reduction of temperature and this increase can contribute to the increase in nonequivalence.

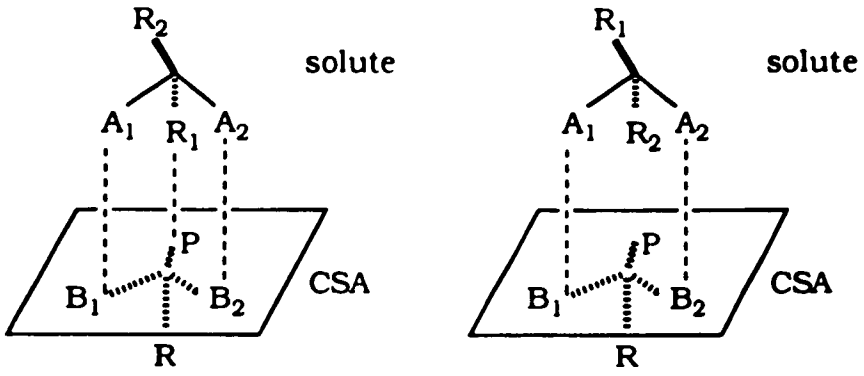
2) A lower temperature may increase the intrinsic spectral difference of the diastereomeric solvates, by increasing the populations of specific conformations that are responsible for nonequivalence.[207]

3.2.1.3 Effect of Solute Structure

The utility of TB as chiral solvating agent was tested on numerous alcohols. Five alcohols (**83**-**87**) (Table 24) gave satisfactory i.e. palpable, anisochrony. From an analysis of the structures of these alcohols, it may be inferred that the stronger acidity of these five alcohols[179] relative to the others may lead to more efficient hydrogen bond formation with TB. That is, hydrogen bonding may make these compounds more efficient in forming diastereomeric solvates with TB leading to observable anisochrony. Similar examples could be found in the literature, e.g., substituting heptafluoropropyl for the trifluoromethyl group of TFPE increases the maximum nonequivalence

attainable for a given solute. It leads to a great difference in chemical shift for this given solute in these cases.[208]

In very general terms, solute enantiomers having appropriately situated acidic sites, A_1 and A_2, e.g., hydroxyl and carbinyl hydrogens, or something like hydroxyl and acetylene hydrogens, will simultaneously interact with the basic sites of TB (see below). The acidic alcohol function interacts strongly with a hydrogen bond receptor in TB. The carbinyl hydrogen or acetylene hydrogen seeks interaction with a secondary basic site in Tröger's Base. This secondary site may be the π electrons of the aromatic rings or unshared electron pairs of nitrogen. Increased acidity enhances the population of specific nonequivalence-engendering conformations. Increased acidity may be a very important cause of the observed anisochrony in these five alcohols.[207]



Ogston pointed out as early as in 1948 that the two simultaneous interactions occurring between the solute and the CSA, constitute two

of three necessary reference points (three points of interaction between solute and CSA).[209, 210] Previously enantiotopic solute nuclei e.g. R_1, in (I) and R_1 in (II) are now in different positions relative to a chemical shift-perturbing group P of the CSA, whose effect on the magnetic environment of R_1 constitutes a third reference point.

The aryl group has a substantial effect on the magnitude of nonequivalence in each of the above mentioned five alcohols. The importance of having such a group in the solute is demonstrated by the fact that no aliphatic alcohol is among the five alcohols that exhibit anisochrony in presence of TB. In aromatic alcohols, the aryl group may function by interacting either attractively or repulsively with the pertuber P in the CSA. One enantiomer of the solute might thus simultaneously experience three bonding interactions with the CSA while the other may only experience two. The former would then be the more stable. Stereochemically dependent third interactions (Ogston model) allow enantiomer recognition in NMR spectra.

3.2.2 Binding Forces Contributing to the Formation of Inclusion Compounds by TB or TB Onium Salts

Interaction between host and guest depends upon the binding forces contributing also to inclusion compound formation. Usually several attractive forces act simultaneously but to different extents depending on the nature of host and guest.

Obviously, the following discussion mainly focuses on **107a** (Tröger's base methosulfate) as host since other potential hosts (such as **114**, **115** and **116**) were poor or ineffective.

3.2.2.1 Hydrogen Bonding

The hydrogen bond was first introduced as an important principle in structural chemistry by Pauling's: "It was recognized that under certain conditions an atom of hydrogen is attracted by rather strong forces to two atoms, instead of only one, so that it may be considered to be acting as a bond between them."[211] Molecular aggregations are controlled by hydrogen bonding is obvious.[212]

Hydrogen bonds were recognized as stronger than van der Waals forces and more directional leading to compounds with high melting points and generally harder crystals.[213] Summing up the function of hydrogen bonds in inclusion compound formation, two aspects merit comment:

1) Construction of host crystal structure: Dianin's compound is a typical example of a host in which hydrogen bonds are involved in constructing the host with cavity or channel structure. This host structure forms crystalline inclusion compounds with a great variety of substances.[84] This situation is a host-host interaction by hydrogen bonds to form coordination-assisted clathrate host lattice (Fig. **27a**). In some host compounds, such as hydroquinone, phenol,[84, 93] urea[40, 41] and Dianin's compounds,[92] hydrogen bonds are often an essential part

of the lattice forces of the inclusion compound. Host molecules designed via considerations of lattice formed by hydrogen bond is one of the most important design strategies.[214]

2) Formation of the inclusion compound: In many inclusion compounds, hydrogen bonding connects host and guest to form a clathrate in two ways: a) coordinative host-guest interaction, only to form a coordinatoclathrate, e.g., crystal inclusion of methyl sulfoxide (**9a**) in (R)-(+)-**5**-binaphthol (Fig. **5**). This is shown in Figure **27b**; and b) both coordinative host-host and host-guest interaction, to form a coordinatoclathrate in a coordination-assisted host lattice, e.g., inclusion compound of ethanol in 9,10-dihydroxy-9,10-diphenyl-9,10-dihydroanthracene (**65**),[108, 109] this is shown in Figure **27c**.

In sections (1) and (2), hydrogen bond donors and acceptors are arranged in particular geometries with specific, additive and often cooperative strengths for interactions. In inclusion compound formation and enantiomer discrimination, it is obvious that the hydrogen bond plays an important role[215] as an intra- and intermolecular cohesive force, in determining geometry and mode of recognition and in the association of host-guest molecules.[212]

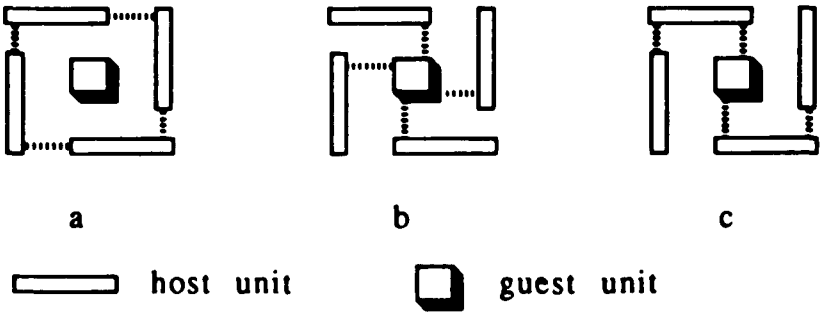


Fig. 27. Diagrammatic representation of lattice inclusions. **a**. host-host interaction of hydrogen bonds; **b** and **c**: host-guest interaction of hydrogen bonds (hydrogen bonds are indicated by broken lines)[32]

The role of hydrogen bond is diversified; it not only plays a fundamental function in host-guest interaction but also plays an important role in host lattice formation.

Hydrogen bond formation in a quaternary TB salt acting as host takes place more readily than in TB as host. In Tröger's Base monomethosulfate, one nitrogen lone pair is substituted by a methyl group to form the onium salt. The aromatic ring directly connected to this onium nitrogen is relatively electron deficient, and may interact with a π-electron rich aromatic unit, for example the benzene ring of α-methylbenzyl alcohol, to increase the acidity of the hydroxyl group on the α-methylbenzyl alcohol. This acidity enhancement of a hydroxyl group will lead to the formation of stronger hydrogen bonds with the trivalent nitrogen of the TB onium salt through a favorable geometric arrangement of functional groups. In this case, the inclusion ability of the host compound is increased. The other enantiomer of the racemic alcohol, due to a different spatial arrangement of the bonding groups, cannot form hydrogen bonds well, or may totally lose the ability to hydrogen bond to the host and enantiomer recognition is achieved.

NMR methods are very sensitive to differences in the electronic environment of the atom in the proximity of a hydrogen bond through the measurement of chemicals shifts.[216] The downfield chemical shift of the proton resonance in ^1H NMR spectroscopy, is a diagnostic tool for hydrogen bonding formation.[217] Compared to protons not hydrogen bonded, in the ^1H NMR spectrum (Table 28), protons which are hydrogen bonded are shifted downfield since hydrogen bonding decreases the electron density around the proton.[218] It is the large asymmetry of hydrogen electron density with respect to the nucleus on bonding[217] that causes the chemical shift to be more downfield as the strength of the hydrogen bond is enhanced, i.e., the stronger the hydrogen bond, the larger the δ value.[218]

6/8 alcohols significantly resolved show appreciable $\Delta\delta$ (>1.7 ppm). In our attempted resolution with **107a** as host, the NMR analysis of the formed inclusion compounds with alcohols showed a qualitative correlation between hydrogen bond formation and resolution. Alcohols **83-93**, which exhibit strong hybonding (Table 28), were all partially resolved on inclusion in **107a**. Compound**94** was poorly resolved that exhibits weak hydrogen bond formation (Table 28): the e.e. of **94** was only 3% (Table 25).

Inclusion compounds of **107a** with **83**, **84** and **88-93** (Table 25) all have relatively large $\Delta\delta$ attributed to hydrogen bond formation of the OH group or CH group[219] with **107a**. We believe that when resolution by inclusion compound formation takes place, guest

molecules are oriented in the binding site with geometries that maximize hydrogen bonding to the host.[220] Examples are given by Still's work on enantioselective complexation of simple amides by a cyclophane linkages host molecule.[220] Enantiomeric guests, e.g., PhCHMeNHCOR and RNHCOMe, have different binding energies by molecular modeling calculation. The difference of two enantiomers' binding energies reaches maximun when guests maximize hydrogen bonding with a proper orientation proved by X-ray crystallography to host, which leads to different stabilities in inclusion compounds formed. In our case, those compounds, which could not be resolved by inclusion compound formation e.g., **94** (Table 25), showed no hydrogen bond formation, or have weakly formed hydrogen bonds, or show hydrogen bond formation but lack some other essential interaction between host and guest. In other words, there is no significantly different association energy between bound enantiomeric guests in the host. Alcohol **94**, with two hydroxyl groups, was expected to be resolved by **107a**; however, even after repeated experiments, the resolution of **94** failed. Weak hydrogen bond formation (0.25 ppm downfield shift) between **94** and **107a** may be one of the important reasons why alcohol **94** formed no inclusion compound. The strong intermolecular and intramolecular hydrogen bonding interaction between molecules of **94** may much weaken the interaction between the host and guest.

Weak hydrogen bond formation between **88** and **107a**, and between **91** and **107a**, was shown (0.26 ppm and 0.03 ppm downfield shift of the OH signal respectively) (Table 28). Compounds **88** and **91**

Table 28. The Chemical Shift Change[a] Between Racemic Alcohols and Alcohols Hydrogen Bonded to 107a.

Alcohol Number	Chemical Shift of OH Group		Chemical Shift Change ($\Delta\ \delta_1$)	Chemical Shift of CH Group		Chemical Shift Change $\Delta\ \delta_2$ (ppm): AC[c]
	Alcohol δ (ppm)	Alcohol in **107a** HB[b] δ (ppm)		Alcohol δ (ppm)	Alcohol in **107a** δ (ppm): AC[c]	
83	2.41	4.29	1.88	4.91	5.19/4.51	0.28/0.40
84	2.10	3.90	1.80	4.55	4.37/3.96	0.18/0.59
88	1.70	1.96	0.26	1.55	1.74/1.13	0.19/0.42
89	1.47	3.61	2.14	2.95	3.11/2.97	0.16/0.02
90	1.61	3.81	2.20	4.01	4.03	0.02
91	3.81	3.84	0.03	1.49	1.41/1.27	0.08/0.22
92	1.41	3.83	2.42	3.74	e	
93	4.22	6.01	1.79	3.36	3.99	0.63
94	3.16	3.41	0.25	3.52	3.57	0.05

a. All ^{1}H NMR spectra were run in DMSO-d_6 (0.05-0.1M) at room temperature (300 MHz). Every δ value shown in Table is the center of the peak.
b. Hydrogen bond.
c. Anisochrony (AC) reveals two set of peaks, the former is downfield, the latter is upfield.
e. The alcohol peak overlapped with **107a**.

were nevertheless resolved by inclusion compound formation with **107a**, while **94** was not resolved. A fundamental reason for **88** and **91** being resolved successfully may be reduced or no hydrogen bonding interaction between guest molecules.

Alcohols **83**, **89** and **92** formed crystals with (+)-TB under the same conditions as these compounds were resolved by **107a**. However, alcohol **92** was not observed in the (+)-TB residue by ^{1}H NMR analysis, whereas **83** and **89** were. For the latter two alcohols, no chemical shift change was observed and no anisochrony was obtained with (+)-TB as host, in contrast to **107a** used as host. These crystals were not further studied.

In Table 28 we see that the difference due to hydrogen bond formation by an OH group between an alcohol in **107a** and alcohol alone is **83** > **84** > **88** ($\Delta\delta$ = 1.88>1.80>0.26). This difference might be thought to be due to the OH groups of compounds **84** and **88** that are likely less acidic than that of **83**. However, the enantiomeric excesses of the resolved alcohols are in the order **88>84>83**. This further shows that the greater extent of hydrogen bonding observed is not necessarily reflected in improved enantioselectivity of inclusion. The ee not only depends on hydrogen bonding but also depends on other interaction forces.

The same problem could be observed with compound **91**. The latter exhibits a very small $\Delta\delta$ value (0.03 ppm) for the chemical shift difference of the OH group. The C-H···O hydrogen bond is becoming

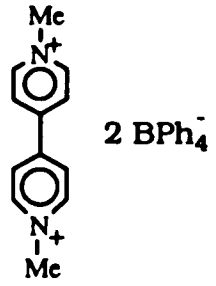
increasingly important for our understanding of how molecules align themselves in crystals. The more acidic the C-H bond, the more likely hydrogen bond is to have a shorter interaction.[219] If the CH bond is acidic in our tested alcohols, we believe that there are hydrogen bond between CH group and hydrogen acceptor. NMR will give evidence that the chemical shift of CH will be downfield.The Δδ value of the CH group is relatively high, **91** gave a higher ee in inclusion with **107a** than that of all alcohols except **89** in Table 17. Furthermore, the OH group of **92** has almost the same Δδ value as that of **90**. The % ee of **92** is much smaller than that of **90**. Why? Whether the Δδ value of the CH group of **92** has the same situation as **91**? Unfortunately the CH peak of **92** overlaps with peaks due to **107a**, we can not measure the Δδ value of CH group of **92** here. If the Δδ value of the CH group of **92** is as high as **91**, a higher % ee of **92** is possible, but still is not obviously. The ee can not be just linked to the Δδ value should be realized.

Hydrogen bonding was inferred in eight (out of nine) of the residues isolated (Table 28). We believe that, in many cases, hydrogen bonds play a leading role in resolution, where the hydrogen bond is responsible for holding the guest within lattice channels and/or cavities and for assisting the host in discriminating between the two enantiomers. However in some cases, enantiomers were efficiently selected by host without hydrogen bonding, with the results being confirmed crystallographically.[221-223] Actually there is a whole set of interactions between host and guest. Other effects, such as molecular shape, size, and van der Waals forces, also play roles in the inclusion phenomenon. A balance of all kinds of effects probably controls a

successful resolution, or one dominant function may be offset by some other interaction. When possible, X-ray crystallographic analysis is desirable, as it may reveal the existence of hydrogen bonding directly.

3.2.2.2 Aryl-Aryl Interaction

π–π interaction as a main bonding force in molecular recognition is not seldom observed.[224] In inclusion compound formation, aryl-aryl contact, mainly as a π–π interaction, is another important driving force. This contact, corresponding to interaction between a π-electron rich aromatic ring and a π-electron deficient aromatic ring, is frequently observed. When the aromatic rings of host and guest reach a proper position, face-to-face or face-to-edge, (Fig. **28**.)[225] interaction takes place and develops to a maximum,[226] for example, π-π interactions between tetraphenylborate anions and paraquat dications.[227] Both face-to-face and face-to-edge (T-shaped arrangement of the π-electron deficient pyridinium and π-electron rich phenyl rings) interactions are characteristic of the geometry associated with the global potential energy minimum for two interacting aromatic rings.



paraquat bis(tetraphenylborate)

Fig. 28 Space-filling representation of the structure of paraquat bis(tetraphenylborate) highlighting both face-to-face and edge-to-face interactions between the pyridinium rings of the dication and the orthogonally disposed phenyl rings of the anions[227]

Reddington, et al.,[225] observed a charge-transfer absorption band in the visible spectrum of UV for aryl-aryl interaction. Quantitative analysis of the dependence of the absorption intensity upon the concentration of the complex provided evidence for the stoichiometry of an "inclusion complex",[225] and also afforded an association constant (K_a) for the "inclusion complex" formation. We can assume that there are hypothetical interactions between enantiopure TB and racemic alcohols as showing in Fig. **29**.

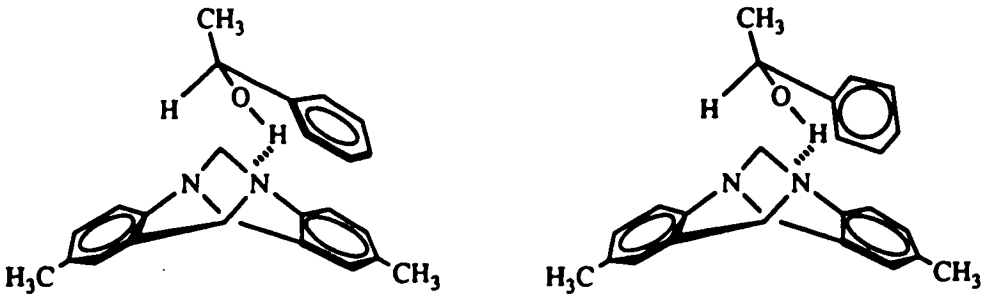


Fig. 29 Hypothetical interaction between (+)-TB and alcohol **83**: face-to-face (left) and edge-to-face (right)

Significant chemical shifts of host and guest signals can be observed by ^1H and ^{13}C NMR spectroscopic investigations of inclusion

compounds.[228] On account of the relative simplicity and speed of the procedure, the ^1H NMR method has become an important and reliable method for gaining insight into molecular encapsulation.[229, 230]

In contrast to the unincluded guest, ^1H NMR signals of the included guest, and often of the host too (in presence of guest), are frequently significantly shifted upfield (in contrast to dowfield shifts due to hydrogen bonding). This is due, in most cases, to the especially short distance between the host and guest in solution. The guest is affected by anisotropic effects of the aromatic units or by field effects of the ionic center of the host.[231, 232] As these effects decrease quickly with increasing distance, the protons dependence on their orientation show different chemical shift sensitivity.

In our results, as well, the aryl-aryl group interaction between host and guest in inclusion compound formation was revealed by these ^1H NMR results.

Diamagnetic anisotropy, or the "ring-current effect", accounts for the large deshielding of aromatic ring protons which appear downfield, with large δ values. Protons located above or below the ring should be shielded, and should have smaller δ values.[217]

If the guest aromatic ring interacts with the host benzene ring, a guest proton located above or below the ring should move upfield due to the ring current effect, and the chemical shift of the proton will become smaller. From Table 29, most of the values of these chemical

shift differences between a racemic alcohol and an alcohol in inclusion compound are clearly very small. The maximum value of these chemical shift differences between a racemic alcohol and an alcohol in inclusion compound (**107a**), in the case of **91**, is 0.15 ppm in the aryl-H region. This suggests that the benzene ring of alcohol **91** has a interaction with the aromatic ring of **107a**. The ring protons undergo a strong mutual shielding and they move upfield. In Table 29, the $\Delta\delta$ values in the majority of cases are less than 0.1 ppm. Perhaps most alcohols have too weak aryl-aryl interactions in solution to leading to changes in chemical shift.

Table 29. Chemical Shift Change[a] Due to Interaction of Alcohols and Host 107a

	Aryl-Aryl and Aryl-methyl Interaction		
Alcohol[e]	Alcohol Alone[b]	Alcohol in **107a**	$\Delta\delta$ (ppm)
83	7.39	7.38	0.01
84	7.38	7.36	0.02
88	7.45	7.44	0.01
89	7.34	7.36	-0.02
90	7.34	7.34	0.00
91	7.45	7.30	0.15
92	0.94[c]	0.83	0.11
93	0.84[c]	0.82	0.02
94	1.17[d]	1.18	-0.01

a. All NMR spectra were run in DMSO-d_6 (0.05-0.10M) at room temperature (300 MHz).
b. Every value here is the largest δ value one in the one set of peaks.
c. The methyl group of -C_2H_5 (aryl-methyl interaction).
d. The methyl group (aryl-methyl interaction).
e. Structural formulas are given in Sec. 1.10.

The data in Table 30 further suggest that the interaction between aryl and methyl groups is significant in connection with inclusion. Table 30 permits us to check the aryl-methyl interaction from another direction, namely that of host **107a**. Here, a shift from δ 7.26 to 7.31 ppm in the chemical shift of host **107a** aryl protons is observed on interaction with **93**. Compound **93** has two long chains; the long aliphatic group may interact with the protons on the aromatic ring by Van der Waals forces, and electron repulsion between the aliphatic group and aromatic protons will lead to a decrease in electron density, causing the chemical shift of the aromatic protons to move downfield. Compounds **92** and **94** may have insufficiently long chains, so no Van der Waals effect was observed in these cases. This hypothetical interaction could be supported by Dalcanale's work[233] and Berscheid's work.[234] Based on X-ray crystal structure, they both proved respectively that CH_3-Aryl interaction is one of the driving forces responsible for inclusion compound formation.

Table 30. Chemical Shift Change of the Protons on Aromatic Rings of 107a in Presence of Aliphatic Alcohols[a]

Alcohol	**107a**	**107a** with Alcohol	Δ δ (ppm)
92	7.26	7.27	0.01
93	7.26	7.31	0.05
94	7.26	7.26	0.00

a. Same experimental conditions as in Table 28.

Two points should be further elucidated. First, the Δδ values in Tables 29 and 30 are very small, which means that both kinds of interaction, aryl-aryl and aryl-methyl, are very weak. Moreover, the interaction between aliphatic groups and the aromatic protons of **107a** may be weaker than the interaction between the aromatic ring of the aryl alcohol and aromatic ring of **107a**. The small Δδ might be increased by increasing sample concentration and changing solvent. Yet another probe would be solid state ^{1}H NMR spectroscopy; this may give us more accurate information about aryl-aryl interaction in inclusion formation.

Second by, X-ray crystallography reveals the interior structure of an inclusion compound.[235] Various aspects of inclusion of the guest in the host lattice could be more accurately studied by this technique. It would have been very desirable to use X-ray crystallography to prove the above conclusions. However, up to now we have been unsuccessful in obtaining good crystals of these clathrates. Numerous crystallization trials of formed inclusion compounds provided no samples suitable for X-ray analysis.

3.2.2.3 Other Interactions

The onium nitrogen atom of **107a** is positively charged. When TB was modified to **107a**, the electron potential of the aromatic ring which is directly connected to the onium nitrogen was changed, causing an effect that originates with the bond dipole present between groups of differing electronegativity. The onium nitrogen atom places a

net partial positive charge on the adjacent aromatic carbon atom. The resultant dipole can perturb the electronic distribution in the ring in two ways; by inductive and by field effects. Both effects establish a dipole in the aromatic ring.

This dipolar aromatic ring may have a dipole-dipole interaction with the alcohol aromatic ring. The dipole of the alcohol aromatic ring may be induced through its carbon connections, or be induced by the dipole of the aromatic ring of **107a**, or by both. Thus, the above mentioned aryl-aryl interaction will be promoted by a dipole-dipole or dipole-induced dipole interaction. The ^{1}H NMR data should be the sum result of these two interactions; π-π interaction and dipole-dipole/dipole-induced dipole interaction. Despite this, the sum of these two interactions is still very small as evidenced in the ^{1}H NMR spectra.

Finally, in quaternary TB salts, the attraction between the oppositely charged ions in the lattice may be stronger than the interaction between neutral TB molecules in TB crystals. This ionic interaction among hosts components may be helpful for clathrate formation. The interaction model illustrated in Fig. **27 a**, **b** and **c** can also be used to understand this ionic interaction.

3.2.3 Inclusion Compound Formation and Host Ionization

Numerous efforts to obtain inclusion compounds of racemic alcohols in TB itself have not been satisfactory to date. On the other

hand, *in situ* formation of TB onium salt **107a** as host gave eight useful results with nine alcohols fairly rapidly. Limited experiments (Table 21 and 22) show **114** [(+)-TB · *p*-$MeOC_6H_4CH_2Cl$] is a potential candidate for inclusion compound formation. Although **115** and **116** showed negative results in resolution (Sec. 3.1.3 and Table 23) by clathrate formation, they were tested many fewer times than was **114.** Further, quaternary TB salt **82a** [(+)-TB · (-)-BNP] revealed inclusion ability in few cases (Tables 10 and 11).

What is the most significant difference between TB and TB onium salts with respect to inclusion compound formation? Why does ionizing the molecule, in our case, cause so big a difference?

As mentioned in Section 3.2.2.3, ionization of the host molecule may increase the interaction forces in the clathrate lattice. The crystal lattice will be made more stable by the attraction between positive and negative charges. In other words the lattice promotes formation of a chiral microenvironment, channel or cavity, better than does the lattice of neutral TB.

In the recent literature[107, 236] quaternized nitrogen-containing host compounds have been found to contain three-dimensionally extended hydrophobic cavities, in which various hydrophobic guest molecules were recognized. It is possible that the lattice of the onium salt crystal may have more empty space than that of TB. If the size of the host cavity is larger, a larger variety of guest molecules should be

able to enter the host, affording more possibilities for inclusion compound formation.

Knobler, et al., pointed out[237] that the source of chiral recognition in corapalexes with phenylglycine as guest is mainly pole-dipole attractions between $^{+}$NH···O and $^{+}$N···O in host and guest. Schneider, et al., also found[138] that large binding constant difference between aromatic and aliphatic substrates in positively charged cavities is due to naphthalene derivative guests in the cavity of host in a pseudoequatorial manner suitable for such a $^{+}$N···π interaction. In our case, it is also possible that the onium nitrogen of **107a** interacts with the electron rich part of the guest, if the geometry and the space orientation of the guest fits the host. The maximum interactions will lead to the greater enantiomeric recognition.

The ionization of the host molecule introduces one aromatic ring dipole as described above. Moreover, it also leads the two aromatic rings to lose their equality of electronic density, as well as increasing the dissymmetry of the whole host molecule, for the ionization of the host molecule destroys the C_2 symmetry of the original molecule. A symmetry change may also be a force affecting inclusion compound formation.[238] We will discuss this next.

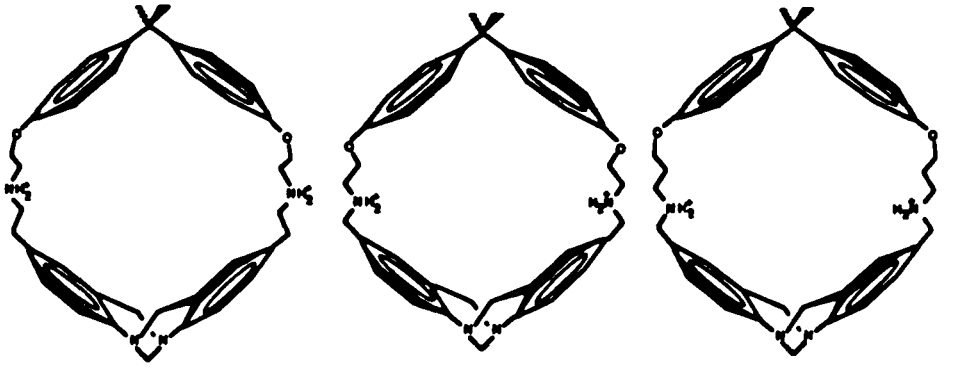
3.2.4 Symmetry and Crystallization

Six months of trial and error gave no satisfactory results in the resolution of alcohols with enantiopure TB as host. In the experiments

using solvents, about 65% gave no crystals at all. The other 35% gave crystals, yet no included alcohol was observed by ^1H NMR, or by ^1H NMR together with GC analysis in some cases. The same negative result was obtained by heating and dissolving TB in excess alcohol, followed by analysis of the crystals obtained by pumping.

This situation was completely changed using **107a** as host as described in Sec. 3.1.2 and 3.1.2.3. On the other hand **114, 115, 116** and **82a** as hosts gave crystals with included alcohol only infrequently. Some of the reasons for the success of onium salts as inclusion hosts have already been given above. Yet there are possibly additional reasons.

Wilcox et al., recently reported[238] that many potential macrocyclic hosts which are designed to have a C_2 axis of symmetry passing across the bonding site have never been observed to form an inclusion compound in the solid state. This is a really interesting aspect. For some time now, Wilcox has studied molecular recognition involving cyclophanes as hosts. His cyclophanes are actually derivatives of TB, and there are many structural similarities between our TB and Wilcox's cyclophanes. Tröger's base (**79**) has a C_2 axis of symmetry. A host molecule like the cyclophane **118** indeed has a connectivity graph which is symmetric. Moreover, it may have a conformation which is symmetric. From crystallographic studies, Wilcox realized that a cyclophane host cannot bind to a guest to afford a complex with a C_2 symmetry axis which traverses the cavity.



118 **119** **120**

However, **118**,**119**, **120** were observed to form inclusion compounds with many aromatic compounds. Wilcox thinks that symmetrical conformations of these hosts are relatively unstable. If their C_2 symmetry axis is lost in solution then nothing has been gained by requiring C_2 symmetry in the host. On the basis of these considerations and available X-ray structural data, Wilcox concluded that **118**,**119**, **120** do not have a C_2 symmetry axis transverse to the cavity, and there are no conformers with a C_2 axis transverse to the cavity that are of low enough conformational energy to be considered as likely contributors to the observed properties of the host.

Very clearly, Wilcox's conclusion is helpful to us in understanding some phenomena in our inclusion study. In our study of TB and quaternized TB, much effort led to unsatisfactory inclusion compound formation by TB, but satisfactory results were given by a TB onium salt as host. TB has C_2 symmetry, and is a rigid molecule that is different from the compounds Wilcox mentioned, TB is stable and the

conformational energy for TB should be low. So even though TB interacts with a guest upon heating or sonication, numerous efforts still resulted in no inclusion phenomena observed (Sec. 2.3.5; Table 8, 9).

When TB was modified by conversion to a quaternary salt, TB lost its C_2 symmetry. Wilcox calculated his results based on the MM2 or the AMBER force field and combined the calculatins with his crystallographic studies. He concluded (see above) that the best binding shapes are not symmetrical, and that unsymmetrical shapes are of high energy.[238] Maybe this is also true in TB compound. Unsymmetrical shapes of onium TB molecule could be of higher conformational energy than symmetrical TB shape. Then this tendency of unsymmetrical shapes will increase by raising the temperature. Obviously, the increasing tendency is favorable for binding in inclusion compound formation. Furthermore, by heating, the conformations of quaternary TB salts may change to conformations more suitable for binding with guest.

Now in Tables 10-15, 17, 19-21, TB onium salt **82a**, **107a** and **114** all showed that, in resolution by inclusion compound formation, they are not only able to bind guest molecule but this binding is also promoted by change from normal heating to sonication. Both factors, unsymmetrical shapes of quaternary TB and heating promoting suitable conformation for binding, may contribute to inclusion compound formation. Table 18 shows that when the mole ratio of Me_2SO_4 to TB is more than 1 to 1, the yield of formed inclusion

compound is greater. This demonstrates that a higher concentration of TB onium salt promotes inclusion compound formation.

Our conclusion is that for some C_2 symmetric hosts, disturbing or destroying the symmetry may be very helpful in inclusion compound formation.

3.2.5 A View of Host Molecular Shape and Size in Inclusion Compound Formation

The size of host cavities/channels (host lattice voids) should be larger than the guest molecules. Otherwise, it is obvious that, in the majority of cases, guest molecules could not enter the cavities/channels of the host molecule. In other words, the size of the host cavities/channels determines whether guest molecule can be included. If there is no inclusion compound formation in a given resolution trial, then the cavities/channels size of the host molecule should first be basically considered. In our resolution experiments with TB as host, no inclusion compound was observed. Perhaps TB has a lattice void with insufficient space to let a guest molecule enter (Fig. 30).

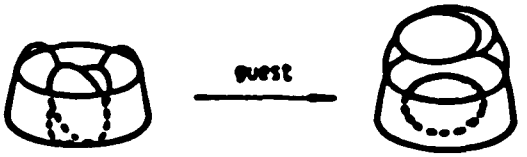
However, in some cases, where the lattice void of host molecule has enough space for one of the racemate enantiomers to enter, there was still no inclusion phenomenon observed. Evidently, in this case whether the molecular size of the guest is appropriate to the host should be considered. Inclusion phenomenon is controlled by the balance of all forces among host, guest and solvent.

According to Wilcox,[238] compounds **118** and **120** have the same cavity size. The difference between **118** and **120** is that the positions of a carbon and a nitrogen atom have been reversed. In **118**, the connecting chain sequence is C-C-N-C-C-O whereas in **120** the sequence is C-N-C-C-C-O. The finding that **120** is a poor host and that **120** binds more weakly than **118** to benzenoid guests is interesting. Wilcox suggested that the observed drop in inclusion compound formation with **120** as host may be due to stronger interaction of solvent to the host or weaker interaction of guests to host **120**, or may be due to a combination of these factors.[238] Although Wilcox's explanation is not satisfied, however, it is true that, for inclusion compound formation, the interactions between guest and guest, guest and solvent affect the molecular recognition. The interaction between host and guest is the most important if the host has a lattice void with enough space.

The cyclodextrins are a more interesting case. They have been generally considered to be rigid hosts with pre-determined cavity sizes, but are converted into flexible hosts by changing the bulkiness of spacer (attached naphthalene) moieties (Equations **12** and **13**). Veno, et al., reported[239] that two naphthalene moieties attached to γ-cyclodextrin have been shown to change their positions from inside to outside the cavity upon binding with a guest (Equation **12**). Another interesting example is that with one naphthalene attached to γ-cyclodextrin, the naphthyl moiety has been shown to enter the cavity together with a guest molecule and to act as a spacer (Equation **13**).[240]

Here it was shown that again, in inclusion compound formation, that the size of the host molecule is of low significance, when the size of the host lattice void (cavities/channels) is larger than the size of the guest.

The molecular size should be considered in inclusion compound formation.[241] However, more important is the structure feature of the host molecule,[131] which drives the binding forces and the strength of interaction among host, guest and solvent. In other words, the structure feature of the host molecule is the key for inclusion compound formation.



(12)

(13)

3.3 Conclusion and Outlook

From the above discussion, we believe that several factors may explain why TB does not form inclusion compounds with a variety of alcohols:

1) TB is a C_2 symmetric rigid molecule whose conformational energy may be low. This permits no or little conformational change to facilitate interaction with a guest molecule leading to inclusion compound formation.

2) The interaction of the TB molecule with a guest molecule may be too weak to form an inclusion compound. The bonding forces, such as hydrogen bonds and aryl-aryl interaction may be insufficiently large.

3) The two aromatic rings and the two nitrogens in the TB molecule are equivalent. However, the two aromatic rings and the two nitrogens in TB onium salt are non-equivalent. This may lead the chiral environment in the host lattice void of TB to have less enantiomeric selectivity than the corresponding chiral environment in the TB onium salt. This may also cause TB to show reduced ability to act as a chiral solvating agent in comparison to quaternary TB: Five alcohols were discriminated by TB as CSA (Table 24). However, nine alcohols were discriminated by TB onium salt **107a** as CSA (Table 25).

4) In our TB X-ray crystallography, no guest molecule was observed in its cavity or channel. However, ethanol was observed in

the cavity or channel of **82a** (Fig. 30). The TB crystal lattice may have too small cavity or channel. If this is true, few guest molecules will be able to enter the host cavity.

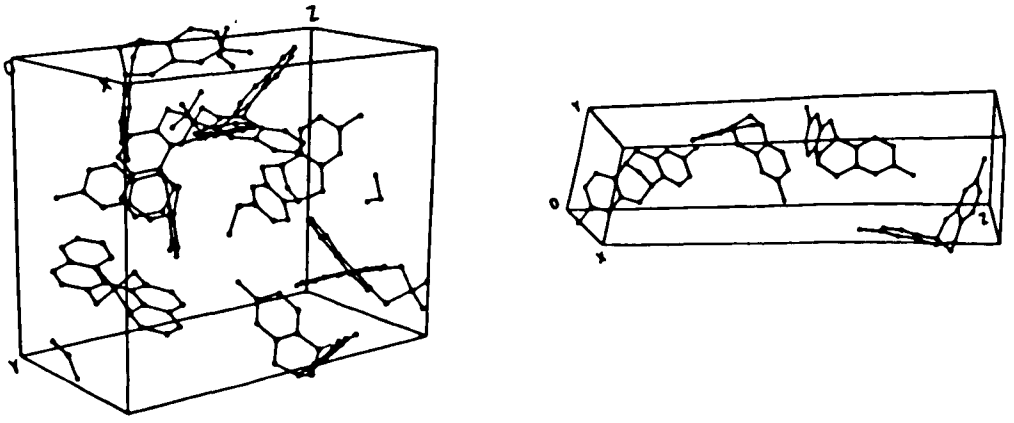


Fig. 30. Stereodrawing of the 1 : 1 ethanol of **82a** (left); and stereodrawing of the (+)-TB recrystallized from EtOH (right).

5) TB is a neutral compound. There is no inductive effect caused by an ionic atom. The dipole effect in TB molecule is relatively small. Weak binding forces among TB molecules may be less favorable for building a host lattice in inclusion compound formation and for interacting with guest molecules than quaternary TB does.

In contrast, quaternization of one of the nitrogens of TB, e.g. in **107a**, leads to the following:

a) The conformational energy of the quaternary TB host may be greater than TB. This leads more readily to changes in the host conformation making the quaternary TB lattice more suitable for interaction with a guest in inclusion compound formation. The host

formed *in situ* may benefit from interaction with racemic alcohols during crystallization of the clathrate on quaternization.

b) Every kind of bonding force may be increased, thus promoting inclusion compound formation. Hydrogen bond and π–π donor-acceptor interactions will be much more significant in stabilizing inclusion compound formation and molecular recognition.

c) Methylation of one nitrogen on TB makes the two nitrogens and the two aromatic rings non-equivalent. A more chiral environment in the host lattice void may promote the ability of the modified TB to differentiate molecular shapes and configurations of guest molecules.

Further, only one trivalent nitrogen is able to act as hydrogen bond when quaternary TB acts as host. This may be an important bonding force in inclusion compound formation and molecular recognition by quaternary TB as host. ^{1}H NMR spectra strongly support hydrogen bond formation. The maximum downfield chemical shift observed in an alcohol in presence of **107a** is Δδ 2.42 ppm (Table 28). This means that hydrogen bonding is vigorous in the interaction between **107a** and an alcohol molecule. Quaternization of a nitrogen induces a strong dipole in the neighboring benzene ring, enhancing the second important interaction between host and guest, aryl-aryl interaction. ^{1}H NMR spectra revealed that the protons of the guest benzene ring were shifted upfield in a few cases. The maximum value of the proton chemical shift change in the guest ring observed was 0.15 ppm.

^1H NMR spectra also revealed that the protons of a guest $-CH_2-CH_3$ group moved upfield. The maximum value of this proton chemical shift change observed was 0.11 ppm, clearly indicating that the host aromatic ring which is directly connected to the onium nitrogen interacts with an aliphatic methyl group as well.

Unfortunately, in both above cases the value of the proton chemical shift change in the benzene ring of **107a** could not be identified due to the peak overlap between host and guest aromatic rings. Otherwise proton chemical shift changes of the benzene rings of **107a** might confirm the interaction of aryl-aryl and aryl-CH_3 in clathrate formation.

Clearly the enhancement of host bonding forces and improvement of the host chiral environment serve as the main driving forces contributing to an increase in host inclusion ability in **107a**.

Under unoptimized conditions, the maximum enantiomeric enrichment achieved by the quaternized TB, **107a**, is 80% (Table 17). It is quite possible that a higher ee might be obtained under optimized condition.

Numerous literature reports and our study on resolution by inclusion compound formation allow us to identify the features of a good host molecule for inclusion compound formation:

First, C-OH, P-OH, -N(H)H, $\rangle N^{+}H$, $\rangle NH$ all are the most common functional groups for donors of hydrogen bonding; O=P, Cl^{-}, S=C<, O=C<, N<, O<C-H all are the most common functional groups for acceptors of hydrogen bonding[178, 242] The creation of hydrogen bonds provides an effective driving force for inclusion compound formation.[140, 243, 244] Hydrogen bonding is a general guiding principle for the molecular recognition of complicated biorelevant molecules such as amino acids,[245] sugars,[246] quinones,[247] nucleobases and related nitrogen heterocycles.[132, 248] Obviously a host compound with more functional groups containing O and N atoms would seem favorable for hydrogen bond formation.[131, 217a,249]

Second, a host compound with more benzene rings would have the advantage of more dipole-dipole, dipole-induced dipole, and $\pi-\pi$ donor-acceptor interactions between host and guest.[250] and even have a hydrogen-bonding interaction between the OH group and the π-electron cloud of a phenyl group.[251] So host compounds which have classical aromatic rings were found to include a wide variety of guest compounds by surrounding these with the aromatic ring in crystal for separation of isomers and optical resolution.[252]

Third, ionization of the host molecule may promote its bonding forces to guest molecules. It may also change the geometric shape of the host molecule, as well as change the size and shape of the host cavity or host channel.[135, 253]

Additionally, host compounds with functional groups, so-called "clathratogenic groups" such as carboxyl groups, may promote clathrate or crystalline inclusion formation.[254] Compound **107a** may just have this kind of functional group, so it exhibits more inclusion compound formation.

Inclusion processes are evidently governed by several types of simultaneous intermolecular interactions. The extent to which these interactions contribute depend on the nature of the host and guest molecule. It is evident that further studies of the mechanism of resolution by inclusion compound formation is warranted.

In conclusion, while resolution is not an art, it is an immature science. The study of resolution by inclusion compound formation is an essential, more advanced and thorough aspect of resolution, and will bring a higher level of understanding of enantiospecificity in such important applications as biology and pharmacology.

Appendix I

```
{*****************************************************************}
{*                                                               *}
{*  Program for the Intersection of Two Theoretical Curves       *}
{*                                                               *}
{*              Qingdong Huang & Jianzhong Qi                     *}
{*   Department of Chemistry, City University of New York        *}
{*                      May 22, 1990                             *}
{*                                                               *}
{*****************************************************************}


var
    i: integer;
    R, ha, hr, tfa, ta, tfr, tr, x: real;
    datafile : text;
    filename : string[11];

begin
    R := 1.987;
    ha := 4.77 * 1000;
    hr := 5.95 * 1000;
    ta := 403.87;
    tr := 409.69;

    filename := 'qidata1.prn';
    assign(datafile, filename);
    rewrite(datafile);

    for i := 1 to 1999 do begin
       x := i/2000;
       tfa := (ta*ha)/(ha-R*ta*ln(x));
       tfr := (2*tr*hr)/(2*hr-R*tr*ln(4*x*(1-x)));
       writeln(datafile, x:6:4,'     ',tfa:6:4,'      ',tfr:6:4);
    end;
    close(datafile);
end.
```

Appendix II

```
{*************************************************************************}
{*                                                                       *}
{*  Program for Equations of Schroder Van Laar and Prigogine-Defay       *}
{*                                                                       *}
{*                    Qingdong Huang & Jianzhong Qi                      *}
{*         Department of Chemistry, City University of New York          *}
{*                             May 22, 1990                              *}
{*                                                                       *}
{*************************************************************************}

var
    i : integer;
    R, ha, hr, tfa, ta, tfr, tr, x : real;
    datafile : text;
    filename : string[11];
    f : array[1..1999] of real;
begin
    R := 1.987;
    ha := 4.77 * 1000;
    hr := 5.95 * 1000;
    ta := 403.87;
    tr := 409.69;

    filename := 'qidata2.prn';
    assign(datafile, filename);
    rewrite(datafile);

    for i := 1000 to 1685 do begin
       x := i/2000;
       f[i] := (2*tr*hr)/(2*hr-R*tr*ln(4*x*(1-x)));
    end;

    for i := 1686 to 1999 do begin
       x := i/2000;
       f[i] := (ta*ha)/(ha-R*ta*ln(x));
    end;

    for i := 315 to 999 do begin
       f[i] := f[(1000-i) + 1000];
    end;

    for i := 1 to 314 do begin
       f[i] := f[(1000-i) + 1000];
    end;

    for i := 1 to 1999 do begin
       x := i/2000;
       writeln(datafile, x:6:4,'     ',f[i]:6:4);
    end;

    close(datafile);
end.
```

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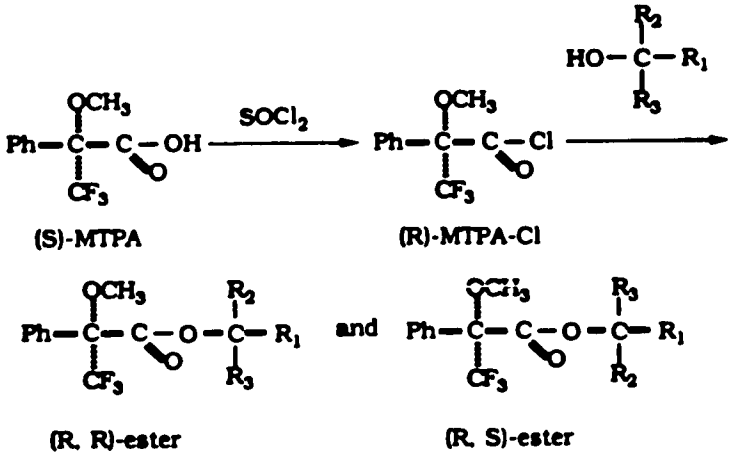

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