Enantiomeric Recognition of Amine Compounds by Chiral Macrocyclic Receptors

Xian Xin Zhang, Jerald S. Bradshaw,* and Reed M. Izatt*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602

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I. Introduction

The study of enantiomeric recognition of amine and protonated amine compounds is of significance since these compounds are basic building blocks of biological molecules. Amino acids are major components of proteins in natural living systems and their versatile abilities to form complexes with a variety of molecules present various types of interaction modes. Enantiomeric recognition is a fundamental property of biological molecules. A characteristic of many enzyme systems, for example, is their ability to distinguish between enantiomers in reaction catalysis. The active sites of the enzymes are asymmetric and members of an enantiomeric pair of the substrate interact with the enzymes at different rates and different free energies.

A better understanding of the interactions operating in chiral recognition is helpful in developing new methods of asymmetric synthesis and chromatographic resolution of enantiomers. The high effectiveness of chiral macrocyclic compounds in enantiomeric separations has been demonstrated by chromatographic methods,[1−13] capillary zone electrophoresis,[13−18] and other approaches.[19−22] Enantiomers resolved include amino acids,[1−4,6,8−12,17,18] various peptides,[5,15,16] tocainides,[7] racemic drugs,[13] various amine derivatives,[6,12−14,17,18,21,22] and other compounds.[6,12,19,20]

Among several types of compounds studied, such as native or derivatized amino acids and cyclodextrins, proteins, and derivatized linear or branched carbohydrates (e.g., cellulose or amylose), chiral crown ethers have been recognized as the most successful selectors used in LC chiral stationary phases for the resolution of primary amine-containing compounds.[12] It has been predicted that chiral macrocyclic compounds will play a major role in future enantiomeric separations.[20]

Several review articles have been published on the synthesis of chiral macrocyclic compounds and their

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Xian Xin Zhang was born in Shandong province, China. He received his B.S. degree at Zhengzhou University in 1982 and his M.S. degree in 1985 with Professor Zhi-Xian Zhou in inorganic chemistry at Zhengzhou University. After five years of teaching and research at Zhengzhou University, he enrolled in a Ph.D. program at Brigham Young University in 1991 and received his Ph.D. degree in 1995 with Professor Reed M. Izatt in physical/analytical chemistry. He was the recipient of the 1993–1994 Jennie R. Swensen Award. He received the H. Tracy Hall Graduate Award (1995) and Spring Research Conference Award from the Central Utah section of the American Chemical Society (1995). Since 1995, he has been working as a postdoctoral research associate with Professors Reed M. Izatt and Jerald S. Bradshaw. He is a member of the American Chemical Society. His research interests include enantiomeric and molecular recognition, macrocycle complexation chemistry, spectroscopy, separation chemistry, amino acid and food chemistry, and the use of calorimetry, potentiometry, NMR, and other methods to determine thermodynamic quantities.

Jerald S. Bradshaw, Reed M. Izatt Professor of Chemistry, was born in Cedar City, UT, and received a B.A. degree in chemistry at the University of Utah in 1955. After four years as an officer in the U.S. Navy, he received his Ph.D. at UCLA in 1963 with Professor Donald J. Cram. He received an NSF postdoctoral fellowship for the 1962–1963 academic year to work with Professor George S. Hammond at the California Institute of Technology. After three years as a research chemist at Chevron Research in Richmond, CA, he joined the faculty at Brigham Young University in 1966. He was named Professor of the Year at BYU in 1975. He was U.S. National Academy of Sciences Exchange Professor for 1972–1973 with Professor Miha Tisler at the University of Ljubljana, Slovenia. He was a visiting Professor with Professor J. F. Stoddart at the University of Sheffield, England, in 1978, and an NSF Cooperative Research Fellow with Professor L. F. Lindoy at James Cook University, Townsville, Australia, in 1988. He is a member of the American Chemical Society. He received the 1989 Utah award from the Salt Lake and Central Utah sections of the American Chemical Society and the American Chemical Society Award in Separations Science and Technology for 1996. He received the State of Utah Governor's Medal in Science in 1991. His research interests include the synthesis and cation complexation properties of macrocyclic multidentate compounds and the preparation of new polysiloxanes for chromatography uses.

ability to recognize enantiomers.[23−39] Cram and his co-workers summarized studies on the chiral recogni-

Reed M. Izatt was born in Logan, UT. He received his B.S. degree at Utah State University in 1951 and his Ph.D. degree in 1954 with Professor W. Conard Fernelius in coordination chemistry at The Pennsylvania State University. After two years of postdoctoral work at Carnegie-Mellon University, he joined the Brigham Young University Chemistry Department in 1956. He is the Charles E. Maw Professor of Chemistry, Emeritus, at BYU. He delivered the Annual Sigma Xi Lecture at BYU in 1966 and the Annual BYU Faculty Lecture in 1970. He was BYU Teacher of the Month in October 1974. He received the BYU Karl G. Maeser Research and Creative Arts Award in 1967 and was the recipient of an NIH Career Development Award (1967–1972), the Utah Award (American Chemical Society) in 1971, the Huffman Award (Calorimetry Conference) in 1983, the Willard Gardner Award of the Utah Academy of Sciences, Arts, and Letters in 1985, the State of Utah Governor's Medal in Science in 1990, and the American Chemical Society Award in Separations Science and Technology for 1996. He is a fellow of the American Association for the Advancement of Science and is Chairman of the Organizing Committee for the annual International Symposium on Macrocyclic Chemistry. His research interests include the design of novel molecular recognition systems for the selective separation of cations, anions, and neutral species; calorimetry applied to metal–ligand and nonelectrolyte interactions, particularly at elevated temperatures and pressures; and the compilation of thermodynamic data.

tion of amino acids by binaphthyl-containing macrocycles.[23−25] Stoddart's reviews focused on synthesis of chiral macrocycles having carbohydrate attachments and their ability to achieve chiral discrimination between enantiomers of amine compounds.[26−28] Bradshaw, Izatt, and their co-workers reviewed syntheses and properties of chiral pyridine-containing macrocycles.[29−32] In Kaneda's review attention was paid to enantioselective-coloration macrocycles.[33] Still and his co-workers summarized enantioselectivity and sequence-selective peptide binding by a series of C_2- and C_3-symmetric macrocycles.[34,35] Five of these and several other macrocyclic compounds were included in the review article by Webb and Wilcox.[36] Synthesis and enantiomeric recognition properties by chiral polymeric macrocycles were summarized by Yokota, Haba, and Satoh.[37] A short review by Naemura, Tobe, and Kaneda focused on chiral crown ethers incorporating cyclohexane-1,2-diol derivatives as a steric barrier.[38] Sawada recently summarized chiral recognition involving host−guest complexation and related systems evaluated by fast atom bombardment mass spectrometry (FAB/MS).[39]

The present review covers all chiral macrocycles reported up to early 1997 for their enantiomeric recognition properties toward amine compounds. Macrocyclic peptides, cyclophanamide-type macrocycles, Zn−porphyrin-based macrocycles, and several other types of macrocycles are included (sections XI-XIV). In this article, we present the general principles of enantiomeric recognition of amine com-

pounds by chiral macrocycles (section II). We also summarize factors influencing enantiomeric recognition by chiral macrocyclic compounds studied in homogeneous solution systems. It was found that the extent of enantiomeric recognition in solutions parallels separation factors demonstrated by chromatographic methods.[4,8,14,21−24,40] It has been shown that enantioselectivities of chromatographic separation are determined by the difference in the Gibbs free energies, $\Delta(\Delta G)$, of the complexation of two enantiomers, or by the difference in stability constants for the formation of diastereomeric complexes.[13−15,17,41] The best resolution was obtained where $\Delta(\Delta G)$ was maximized while ΔG values were minimized.[17,41] Therefore, studies and quantitation of enantiomeric recognition in solutions are particularly important for the design of new and more effective systems for practical enantiomeric resolution. A major purpose of this review is to summarize this information.

II. General Principles of Enantiomeric Recognition

The potential of chiral macrocyclic receptors for use in enantiomeric recognition lies in the ability of the macrorings that can interact with certain enantiomeric substrates to form stable complexes and in the presence in these macrorings of chiral barrier(s) that may lessen the stability of one of the host−guest complexes. Most enantiomeric substrates studied so far are amine compounds since oxygen- and nitrogen-containing macrocycles form stable complexes with ammonium cations.[42−47] A variety of chiral macrocycles have been synthesized and studied for their enantiomeric recognition abilities. Many chiral macrocycles contain a molecular frame of 18-crown-6 (18C6) or similar structures since the D_{3d} symmetry of the 18-crown-6 molecule[42,48−52] matches the molecular symmetry of NH_3 (C_{3v}). X-ray crystal structural studies show that the complex cation of NH_4^+-18C6 has a pseudo D_{3d} symmetry[47,53] and in the complexes of 18C6 and its derivatives with various substituted ammonium ions the macroring portion retains the D_{3d} symmetry.[42,54−58] Any chiral macrocycles (not only those containing 18C6-type structures), on the other hand, have the potential of being enantioselective as long as they form complexes with guest enantiomers. However, the extent of enantiomeric recognition varies greatly, depending on different systems. Several general rules governing effective enantiomeric recognition are summarized below.

A. Essential Requirements for Enantiomeric Recognition

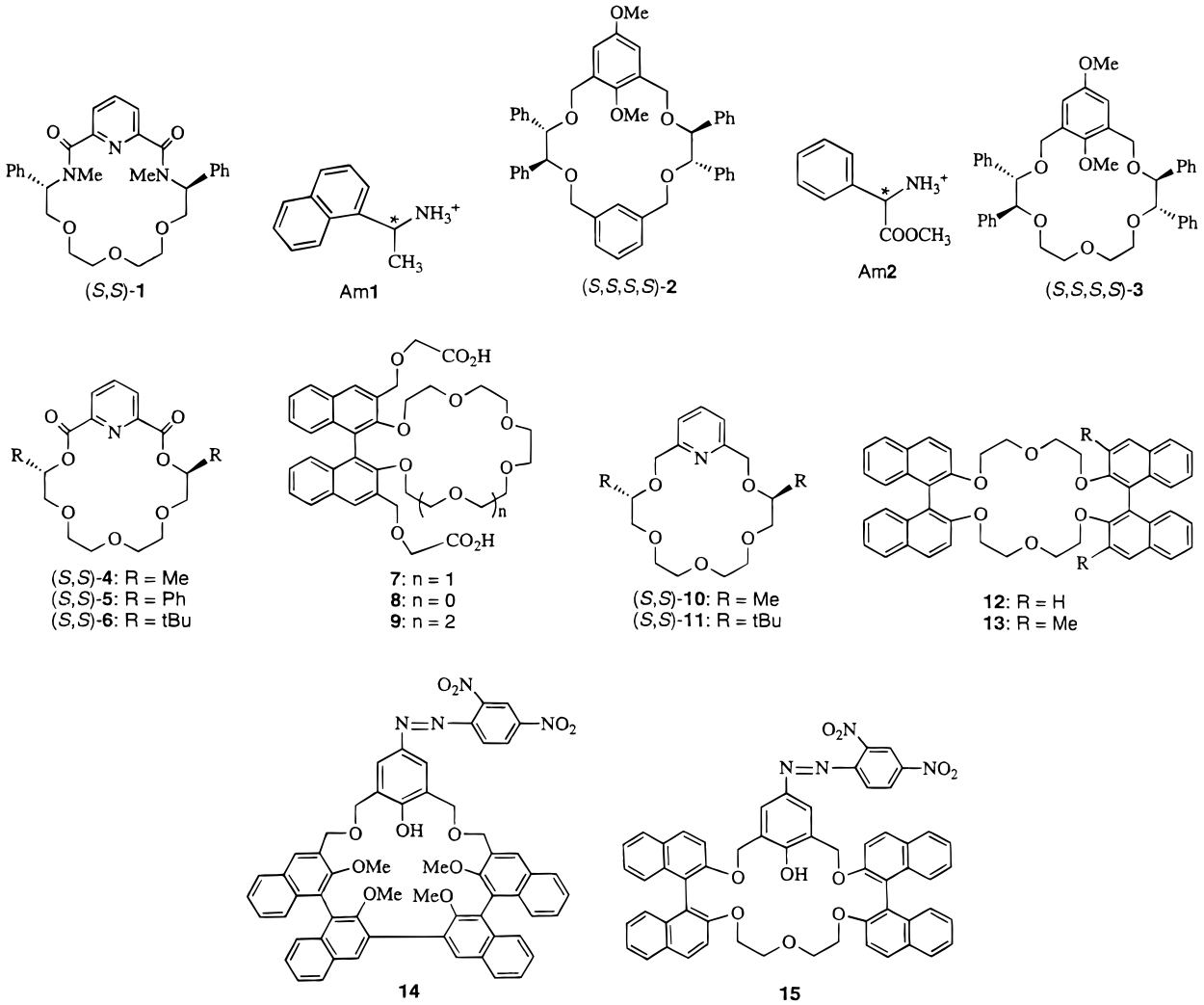
A primary requirement for enantiomeric recognition using chiral macrocyclic compounds as host molecules is that guest enantiomers form reasonably stable complexes with the hosts. No recognition is observed or is present if complexes are not formed. In this case, neither enantiomer appreciably interacts with the macrocyclic ligand, resulting in no difference in "binding energies" between the two enantiomers. In a chromatographic experiment, the two enantiomers pass through the chromatographic column simultaneously due to no significant interaction of either enantiomer with the chiral macrocycle.[4,13,14]

log K values determined by ^{1}H NMR titration indicated that chiral macrocycle (*S*,*S*)-**1** exhibited very weak interaction with α-(1-naphthyl)ethylammonium ion (Am**1**) (Chart 1) in a 5:5 (v/v) $CDCl_3/CD_3$-OD solvent mixture. In this case, no recognition was detected.[59] This result was supported by a measurement of free energies of activation ($\Delta G^{\ddagger}$) in CD_2Cl_2. Ligand (*S*,*S*)-**1** showed almost the same $\Delta G_c^{\ddagger}$ values with (*R*)- and (*S*)-Am**1** (11.3 and 11.2 kcal/mol, respectively).[59] A study of FAB/MS performed by Sawada and co-workers on complexation of (*S*,*S*,*S*,*S*)-**2** with the enantiomer pair of the methyl ester of phenylglycine (Am**2**) showed small complex ion peaks, indicating weak interaction between the host and guest molecules.[60] This lack of the typical strong interaction is a result of a missing $-CH_2OCH_2-$ unit in the macroring, which results in no enantiomeric recognition. On the other hand, chiral macrocycle (*S*,*S*,*S*,*S*)-**3**, an analog of (*S*,*S*,*S*,*S*)-**2**, displayed strong complex ion peaks in the FAB mass spectrum and showed a high degree of (*S*)-enantiomer selectivity.[60]

Interaction between the host and guest species results in a proper conformation of the diastereomeric complexes, creating an appropriate environment for the host macrocycles to conduct enantiomeric recognition toward the guest species. In addition, the formation of stable complexes prevents free rotation and other movement of the enantiomers resulting in increased chiral recognition. The enantiomeric recognition stems principally from the steric repulsion between the substituents at the chiral portions of the host macrocycle and the guest molecules. Greater steric hindrance may occur with one enantiomer of a guest than with the other one, resulting in a different degree of recognition by the host. This difference can then be detected by various measurements of the system.

Thermodynamic quantities determined by calorimetry,[30,59,61−63] ^{1}H NMR,[63,64] and fourier transform ion cyclotron resonance mass spectrometry (FTICR/MS)[65] showed that macrocycles (*S*,*S*)-**4** and (*R*,*R*)-**4** (Chart 1) formed stable complexes with (*R*)- and (*S*)-Am**1** and exhibited high degrees of enantiomeric recognition, as shown by the large $\Delta(\log K)$ values (0.41−0.60) in Table 1. The data in Table 1 indicate that both enthalpy and entropy changes contribute to the recognition of the Am**1** enantiomer by (*S*,*S*)-**4**. Ligand (*S*,*S*)-**4** recognizes (*R*)-Am**1** (larger log K values) over the (*S*)-Am**1** in both methanol (MeOH) and 1:1 MeOH/1,2-dichloroethane (DCE) solvents. For interaction with (*S*,*S*)-**4**, the enthalpy changes for (*R*)-Am**1** are more negative while the entropy changes for (*R*)-Am**1** interaction are less negative than those for (*S*)-Am**1** interaction. Since a more negative ΔH value usually indicates a stronger interaction and one reason for a less negative ΔS value is a smaller conformational change, the thermodynamic data suggest that (*R*)-Am**1** experiences a smaller steric repulsion and smaller conformational change when forming the complex with (*S*,*S*)-**4** than does (*S*)-Am**1**.

Chart 1. Macrocycles 1−15 and Ammonium Cations Am1 and Am2



X-ray crystallographic data support the above conclusions.[61,66,67] Crystal structures of (*S*)- and (*R*)-Am**1** complexes with (*S*,*S*)-**4** (Figure 1) show a larger contact distance between the naphthyl group of (*R*)-Am**1** and the methyl group at a chiral portion of the (*S*,*S*)-ligand than that between the naphthyl group of (*S*)-Am**1** and the methyl group of the ligand. In the (*R*)-Am**1** complex, the distances between the two nearest naphthyl hydrogens and the methyl carbon are 3.33 and >4 Å (this value was estimated from the geometrical positions of the atoms), respectively, while in the (*S*)-Am**1** complex these distances are 3.11 and 3.29 Å. The crystal structure of free (*S*,*S*)-**4** has been determined recently by Böcskei et al.[67] A comparison between the crystalline structure of (*S*,*S*)-**4** and those of the (*S*,*S*)-**4** complexes with (*S*)- and (*R*)-Am**1** reveals that the free (*S*,*S*)-**4** undergoes a much smaller conformational change during the complexation with (*R*)-Am**1** than with (*S*)-Am**1**.

The potential promise of chiral macrocyclic compounds as a practical tool for enantiomeric recognition and separation is closely related to the fact that the macroring of these molecules provides a coordination site to interact with the guest enantiomers while various chiral elements can be introduced to the macroring so that effective recognition and separations can be performed for different enantiomers. Cram and co-workers, for example, designed a binaphthyl-containing macrocycle (**7**, Chart 1) to resolve amino acids.[24,68] The crown-ring portion was capable of binding the ammonium group. Two carboxyl groups on the pendant arms were oriented over the top and bottom, respectively, of the crown ring. One of the carboxyl groups was designed to bind the carboxyl group of the amino acid through hydrogen bonding while the other one provided an anion that could center beneath the ammonium ion of a bound amino acid and form an ion pair. The binaphthyl unit was capable of providing a chiral barrier against which might nestle the hydrogen attached to the asymmetric center of a complexed amino acid of the proper configuration. Both chromatographic and solvent extraction experiments showed that **7** was able to effect a good resolution for valine.[68,69]

Two kinds of interactions with opposite effects on complex formation exist in chiral host−guest systems. These are a bonding interaction between macrocyclic receptors and guest enantiomers and a steric repulsion between the groups at the chiral centers of the guests and the macrocyclic ligand. The first imparts stability to the complex while the second results in a decrease in complex stability. For example, in the interaction of Am**1** enantiomers with macrocyclic (*S*,*S*)-**4**, the fundamental bonding interaction is tripod hydrogen bonding involving a pyridine nitrogen and two alternate oxygen atoms of the

Table 1. log *K*, Δ*H* (kJ/mol), and Δ*S* (J/K·mol) Values for the Interactions of Chiral Pyridine-Containing Macrocycles with Enantiomers of Primary Ammonium Cations at 25 °C

ligand	cation	log *K*	Δ*H*	Δ*S*	Δ(log *K*)[a]	method[b]	solvt[c]	ref
(*S*,*S*)-**4**	(*R*)-Am**1**	2.47	−27.6	−45.2		Cal	M	61
	(*S*)-Am**1**	2.06	−26.4	−49.3	0.41	Cal	M	61
	(*R*)-Am**1**	3.14	−30.7	−42.9		Cal	5M/5DCE	62
	(*S*)-Am**1**	2.54	−27.5	−43.6	0.60	Cal	5M/5DCE	62
	(*R*)-Am**3**	2.33				NMR	M	63
	(*S*)-Am**3**	2.11			0.22	NMR	M	63
	(*R*)-Am**3**	2.80	−32.0	−53.7		Cal	5M/5DCE	62
	(*S*)-Am**3**	2.37	−35.5	−73.8	0.43	Cal	5M/5DCE	62
	(*R*)-Am**4**	2.41	−32.7	−63.4		Cal	5M/5DCE	62
	(*S*)-Am**4**	2.83	−30.7	−48.6	0.42	Cal	5M/5DCE	62
(*R*,*R*)-**4**	(*R*)-Am**1**	2.08				NMR	M	63
	(*S*)-Am**1**	2.50			0.42	NMR	M	63
	(*R*)-Am**1**	2.20				NMR	5M/5C	63
	(*S*)-Am**1**	2.80			0.60	NMR	5M/5C	63
(*S*,*S*)-**5**	(*R*)-Am**1**	2.15				NMR	7M/3C	64
	(*S*)-Am**1**	<1.30			> 0.85	NMR	7M/3C	64
	(*R*)-Am**3**	2.62				NMR	5M/5C	64
	(*S*)-Am**3**	2.06			0.56	NMR	5M/5C	64
	(*R*)-Am**4**	2.24				NMR	5M/5C	64
	(*S*)-Am**4**	2.95			0.71	NMR	5M/5C	64
(*S*,*S*)-**10**	(*R*)-Am**1**	3.00	−29.1	−40.3		Cal	M	63
	(*S*)-Am**1**	2.76	−22.3	−21.8	0.24	Cal	M	63
	(*R*)-Am**3**	3.62				NMR	5M/5C	63
	(*S*)-Am**3**	3.29			0.33	NMR	5M/5C	63
(*S*,*S*)-**11**	(*R*)-Am**1**	1.33				NMR	1M/9C	64
	(*S*)-Am**1**	0.62			0.71	NMR	1M/9C	64
(*S*,*S*)-**18**	(*R*)-Am**1**	2.57	−29.7	−50.6		Cal	5M/5C	63
	(*S*)-Am**1**	2.35	−44.4	−104	0.22	Cal	5M/5C	63
	(*R*)-Am**3**	2.58	−17.3	−8.63		Cal	M	63
	(*S*)-Am**3**	2.44	−17.7	−12.8	0.14	Cal	M	63

[a] The Δ(log *K*) value is the difference between log *K* values for the interactions of enantiomer pairs with a given macrocyclic ligand: $\Delta(\log K) = |\log K_{(R)} - \log K_{(S)}|$. [b] Methods: Cal = calorimetry, NMR = nuclear magnetic resonance spectroscopy. [c] Solvents: M = methanol, C = chloroform. DCE = 1,2-dichloroethane. Solvent mixtures are indicated by volumetric ratios of their components. For example, 5M/5C = 50% methanol/50% chloroform (v/v). For NMR measurements, 100% deuterated solvents were used.

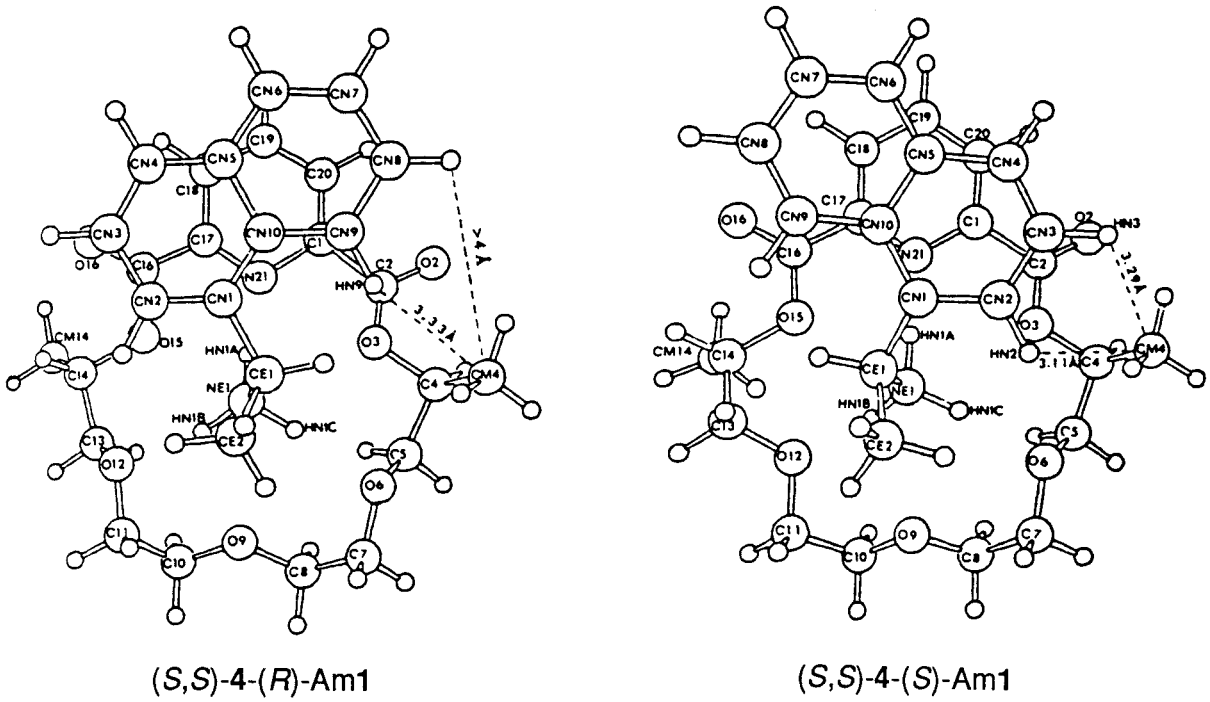


Figure 1. Crystal structures of the (*S*,*S*)-**4**−(*R*)-Am**1** and the (*S*,*S*)-**4**−(*S*)-Am**1** complexes. (Reprinted from ref 66. Copyright 1985 Laser Pages Publishing Ltd.)

macrocycle and three hydrogen atoms of the ammonium cation (see Figure 2).[30,61−66] Different degrees of steric repulsion between the chiral groups result in different extents of decrease in complex stability between the two enantiomers and result in a discrimination between the enantiomers. The bonding interaction is important since it results in stable complexes and also fixes the conformation of the diastereomeric complexes so that the steric interaction can play its role in recognition. Pirkle

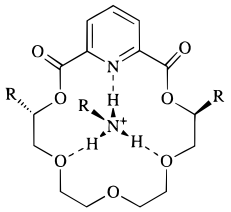


Figure 2. Tripod hydrogen bonding.

and Armstrong and their co-workers have described these two kinds of interactions as "attractive" and "repulsive" interactions.[41,70]

To sum up, *in order to obtain effective enantiomeric recognition, a primary requirement is that chiral macrocyclic receptors form reasonably stable complexes with guest enantiomers so that the repulsive interactions can effectively lessen the stability of the complex of one enantiomer*. An ultimate case is that one enantiomer forms a stable complex with the macrocyclic receptor but the other one does not interact with the receptor at all.

B. Bulkiness of Chiral Substituents

As chiral macrocycles form stable diastereomeric complexes with enantiomeric guests, a reasonably large steric repulsion results in good enantiomeric recognition. An increase in the size of substituents at the chiral center(s) usually increases the extent of enantioselectivity since large chiral barriers on macrocyclic molecules cause large steric repulsions. As the sizes of the substituent groups increase from methyl in **10** to *tert*-butyl in **11** (Chart 1), for example, much improved enantioselectivity is observed for Am**1** (Table 1). Ligand **11** displays a $\Delta(\log K)$ value of 0.71 for the Am**1** enantiomer in a 1:9 $CD_3OD/CDCl_3$ solvent mixture, which is much higher than that by **10** [$\Delta(\log K)$ (MeOH) = 0.24]. Although the $\Delta(\log K)$ value for the **11**-Am**1** system is not directly comparable to that for the **10**-Am**1** system due to the different solvents used, the $\Delta(\log K)$ increase from 0.24 to 0.71 can still be partly attributed to the effect of substituent size increase since the effect of solvent on enantiomeric recognition is not expected to cause such a large $\Delta(\log K)$ increase.[63]

A change in the substituents at the chiral portions from methyl in **4** to phenyl in **5** results in a large increase in the degree of enantiomeric recognition toward Am**1**. Ligand (*S*,*S*)-**5** exhibits a $\Delta(\log K)$ value larger than 0.85 for Am**1** enantiomers in 7:3 $CD_3OD/CDCl_3$, while (*S*,*S*)-**4** favors (*R*)-Am**1** over the (*S*) form by 0.41 log *K* units in MeOH (Table 1).

Not all chiral macrocycles containing bulky groups at chiral portions display high enantioselectivity. If a substituent is sufficiently large that the macrocyclic ligand is prevented from forming a stable complex with the enantiomers, no enantiomeric recognition is detected. Chiral ligand **6**, for example, contains two large *tert*-butyl groups as the chiral substituents. The interaction between **6** and either of the Am**1** enantiomer pairs is too weak to be detected in 1:9 $CD_3OD/CDCl_3$.[63,64] Hence, a limit on the bulkiness of the chiral substituents is that the complexation should not be prevented by repulsive interactions between the chiral groups of host and guest molecules.

Binaphthyl-containing (*R*,*R*)-**12** (Chart 1) exhibits good enantiomeric recognition toward Am**2**, as indicated by the EDC (enantiomer distribution constants) value of 2.5 at 24 °C between $CDCl_3$ and D_2O.[24,71] As the steric barrier of one binaphthyl group is extended by attachment of two methyl groups to form macrocycle (*R*,*R*)-**13**, the EDC value for Am**2** is increased to 12 under the same conditions. Chiral recognition with binaphthyl-containing macrocycles is summarized in section VIII. The second rule of enantiomeric recognition by macrocyclic receptors can be stated: *the larger chiral barrier(s) of a macrocycle usually results in a larger degree of enantiomeric recognition*.

C. Limited Conformational Flexibility

The limited conformational flexibility of diastereomeric complexes is an important factor in obtaining good enantiomeric recognition. Still and co-workers have pointed out that the limited conformational flexibility of the macrocyclic compounds studied by them was one key to enantioselectivity.[34] The fixing of the conformation of the host−guest complexes by an effective bonding interaction allows the chiral host molecules to make full use of their chiral centers to achieve optimum recognition toward the guest enantiomers. On the other hand, if the conformation of the complexes is flexible, both enantiomers can find a proper position to interact with the macrocyclic ligand and avoid the large steric hindrance caused by the chiral centers. The degree of recognition is thus decreased. Therefore, another rule of effective enantiomeric recognition is that *the less flexible the diastereomeric complexes, the better the enantiomeric recognition*.

In general, two factors ensure a fixed conformation of diastereomeric complexes. First, macrocycles should be rather rigid. A rigid macrocycle cannot modify its conformation easily during complexation resulting in a rigid macrocycle complex. Second, a multipoint bonding interaction increases the complex rigidity.

It is seen in Table 1 that (*S*,*S*)-**4** shows a higher degree of chiral recognition toward Am**1** ($\Delta(\log K)$ (MeOH) = 0.41) than does (*S*,*S*)-**10** ($\Delta(\log K)$ (MeOH) = 0.24). Ligand (*S*,*S*)-**10** differs from (*S*,*S*)-**4** by the absence of two carbonyl oxygen atoms. The better recognition of (*S*,*S*)-**4** is due to increased molecular rigidity by the addition of two carbonyl oxygens.[63] The enthalpy and entropy changes upon complexation of enantiomeric guests by less flexible **4** are different from those by more flexible **10**. Both ΔH and ΔS values make contributions to enantiomeric recognition by **4**. In methanol, for example, the ΔH value for (*R*)-Am**1**−(*S*,*S*)-**4** interaction is 1.2 kJ/mol more favorable than that for (*S*)-Am**1**−(*S*,*S*)-**4** interaction, while the ΔS value for (*R*)-Am**1**−(*S*,*S*)-**4** complexation is 4.1 J/mol·K less unfavorable than that for the (*S*)-Am**1**−(*S*,*S*)-**4** one. The more favorable ΔH value indicates that (*R*)-Am**1** interacts more strongly with (*S*,*S*)-**4** and the less unfavorable ΔS value suggests that (*S*,*S*)-**4** experiences a smaller conformational change during complexation with (*R*)-Am**1**. Both the ΔH and ΔS changes suggest that (*R*)-Am**1** fits the (*S*,*S*)-**4** better than does (*S*)-Am**1**. On the other hand, only enthalpy changes contribute to chiral recognition by (*S*,*S*)-**10**. The entropy change of (*R*)-Am**1**−(*S*,*S*)-

Chart 2. Ammonium Compounds: Am3−Am18

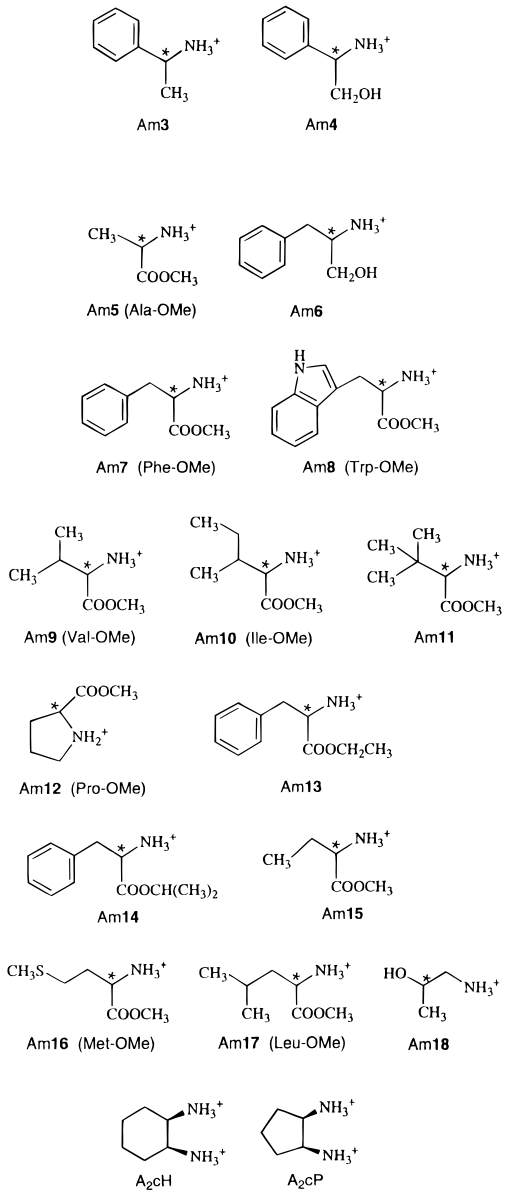
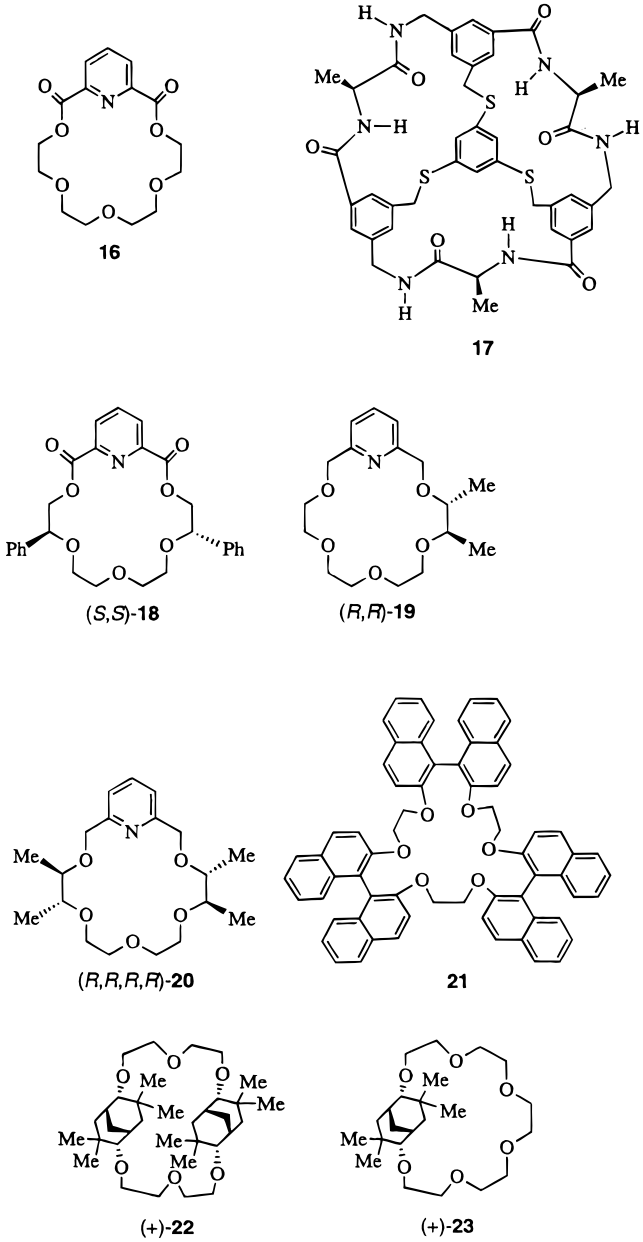


Chart 3. Macrocycles 16−23



10 interaction is 18.5 J/mol·K more negative than that of (*S*)-Am**1**−(*S*,*S*)-**10** interaction (Table 1). The stronger interaction of (*R*)-Am**1** with flexible (*S*,*S*)-**10**, as compared with (*S*)-Am**1**, results in a larger conformational entropy loss due to the flexibility of the macrocyclic ligand, decreasing the extent of enantioselectivity.

Chiral azophenol-containing macrocycle **14** differs from **15** in that **14** has a large and rigid tetranaphthyl sequence which makes up a part of the macroring but **15** has two separate binaphthyl groups (Chart 1). Therefore, **14** is more rigid than **15**.[72] Visible spectral results showed that **14** exhibited a higher degree of enantioselective coloration with three organic primary amines than does the less rigid **15**.[72] Enantiomeric amine-selective coloration by chiral azophenolic macrocycles is summarized in section VI.

Pirkle and Pochapsky described a "three-point rule" for chiral recognition.[41] This rule points out that the chiral recognition requires a minimum of three simultaneous interactions with at least one of these interactions being stereochemically dependent. The stereochemical interaction, or the steric hindrance, results in chiral recognition. The remaining two interactions (if both are attractive) ensure a fixed conformation of the complexes so that recognition can be achieved. In many cases involving macrocyclic receptors, two attractive interactions are not enough to effectively decrease the conformational flexibility of the complexes. Therefore, more than three simultaneous interactions are usually necessary to decrease the conformational flexibility of the complexes and, consequently, to result in a high degree of enantiomeric recognition.

In most cases, as shown in Table 1, recognition of the enantiomers of Am**1** by chiral diester pyridino-18-crown-6 type macrocycles is better than that of enantiomers of α-phenylethylammonium (Am**3**, Chart 2) and of the hydrogen perchlorate salt of 2-amino-2-phenylethanol (Am**4**, Chart 2). This difference is caused by a difference in the numbers of multipoint interactions possible in Am**1**, Am**3**, and Am**4**. NMR

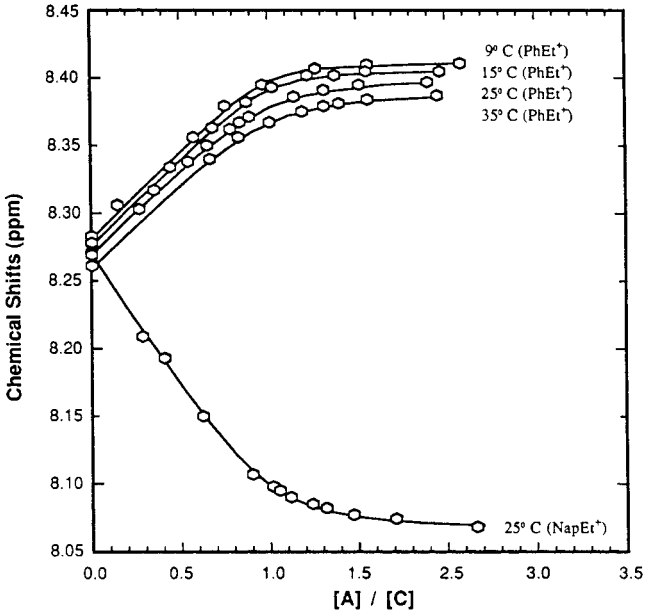


Figure 3. Observed ^{1}H NMR chemical shifts of the 3,5-protons on the pyridine moiety of diketopyridino-18-crown-6 (**16**) in 1:1 $CD_3OD/CDCl_3$ as a function of the molar ratio, [A]/[C], of $NapEt^+$ (Am**1**) or $PhEt^+$ (Am**3**) to **16**, where [A] and [C] represent the concentrations of Am**1** (or Am**3**) and **16**, respectively. (Reprinted from ref 74. Copyright 1992 Kluwer.)

studies showed that the higher degree of enantiomeric recognition toward Am**1** was due to $\pi-\pi$ interaction between the naphthyl group of Am**1** and the pyridine ring of the macrocycles and the lower degree of enantiomeric recognition toward Am**3** was due to the absence of such an interaction. Upon complexation with Am**1** enantiomers in solution, upfield shifts of the pyridine proton signals can be observed,[73−75] indicating that the naphthyl group of Am**1** overlaps the pyridine ring of the macrocyclic ligands. This overlapping causes a magnetic shielding effect,[76] resulting in upfield shifts of ^{1}H NMR signals. On the other hand, complexation of Am**3** and Am**4** with diester-type macrocycles induces downfield shifts of the pyridine proton signals,[73,74] indicating that the phenyl groups of the Am**3** and Am**4** are away from and do not overlap the pyridine ring. In this case, the pyridine group is at the deshielding zone of the phenyl ring, resulting in the downfield shifts of the pyridine protons. The differences in the directions of the chemical shift change and in the conformation of the diastereomeric complexes between Am**1** and Am**3** with a diketopyridino-18-crown-6 (**16**, Chart 3) are illustrated in Figures 3 and 4.

Crystal structures of (*S*)- and (*R*)-Am**1** complexes with (*S*,*S*)-**4** clearly indicate a $\pi-\pi$ interaction between the naphthyl ring of Am**1** and the pyridine ring of **4** in both complexes (see Figure 1).[61,66] The distances between the geometric centers of the naphthyl and pyridine groups are 3.64 and 3.52 Å in (*R*)- and (*S*)-Am**1** complexes, respectively, and the dihedral angles between the two aromatic rings are 11.9° and 6.9° in (*R*)- and (*S*)-Am**1** complexes, respectively. These parameters indicate that the naphthyl ring overlaps the pyridine ring of **4** through $\pi-\pi$ interaction. Therefore, the multipoint interaction including tripod hydrogen bonding and $\pi-\pi$ overlapping anchors the Am**1** cation on the macrocycle and the complex conformation is fixed. Under this condition, the chiral barriers are expected to be fully effective in enantiomeric recognition.

CPK models for (*S*,*S*)-**11**-Am**1** complexes (Figure 5) show that the (*S*,*S*)−(*S*) and (*S*,*S*)−(*R*) complexes each have two possible conformations. In the two conformations of the (*S*,*S*)−(*S*) complex (Figure 5a,b), either the naphthyl or the methyl group of the Am**1** cation must be located very close to one of the chiral *tert*-butyl barriers protruding above the same side of the macrocyclic plane where the ammonium cation is seated, resulting in strong van der Waals repulsion. Such steric repulsion is avoided in one of the two possible conformations for the (*S*,*S*)−(*R*) complex (Figure 5c).

McDonald and Still have used a technique of free energy perturbation to calculate differences in free energy values ($\Delta\Delta G$) for enantioselective binding of peptide guest molecules to certain C_3-symmetric macrotricycles like **17** (Chart 3).[77] For the diastereomeric complexes having high enantioselectivity, the calculated $\Delta\Delta G$ values are in excellent agreement with those determined experimentally. The study indicates that the driving forces for binding between the macrocycles and peptide guests in organic solvents appear to be the formation of hydrogen bonds between the host and guest molecules. There is a relationship between the number of such intermolecular hydrogen bonds and the degree of enantioselectivity. Most structures sampled during the calculation had either two or three intermolecular hydrogen bonds, but the diastereomeric complexes showing high enantioselectivities had a considerable population of structures having four hydrogen bonds. It is concluded that the high enantioselectivities observed with the C_3-symmetric macrotricycles are largely a result of their ability to form more hydrogen bonds with the guest molecules.[77]

The third rule of enantiomeric recognition by macrocyclic compounds can be stated as follows: *The low conformational flexibility of diastereomeric complexes results in a high degree of enantiomeric rec-*

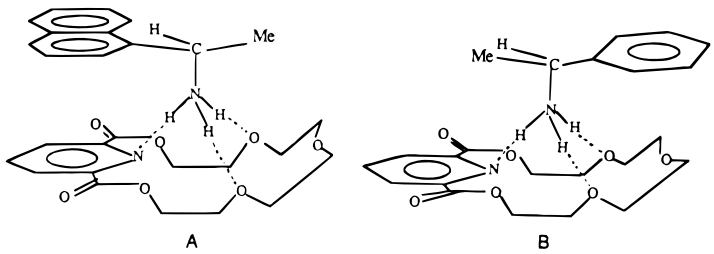


Figure 4. A schematic representation of the molecular structures of the **16**−Am**1** (A) and **16**−Am**3** (B) complexes. (Reprinted from ref 74. Copyright 1992 Kluwer.)

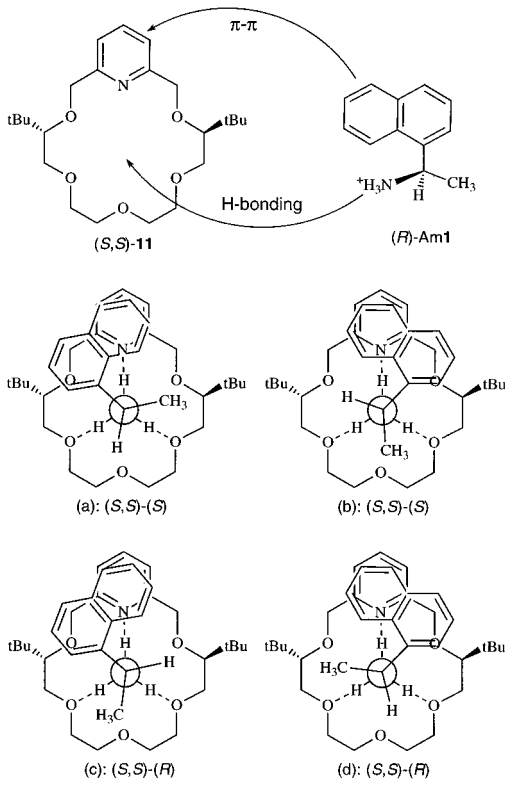


Figure 5. Illustrations of the possible conformations of the (*S*,*S*)-**11**−(*R*)-Am**1** and (*S*,*S*)-**11**−(*S*)-Am**1** complexes.

ognition. Such limited conformational flexibility usually results from the rigidity of the macrocycles and the possibility of multipoint attractive interactions between host and guest molecules.

It should be pointed out that in some cases the highly rigid ligands may reduce the guest-binding energies and result in low or no enantioselectivity. Therefore, the low conformational flexibility is favorable only when the macrocyclic receptor has an appropriately complementary shape and electrostatic surface with the guest molecules, as is discussed below.

D. Structural Complementarity

In order to form reasonably stable complexes and make full use of repulsive interactions between chiral substituents, structural complementarity between host and guest molecules is important. For enantiomeric recognition, structural complementarity requires that steric contacts between the chiral groups of the host and guest molecules result in diastereomeric complexes having different complexation energies when attractive interactions occur between the host and guest molecules. On the contrary, the diastereomeric complexes are not structurally complementary if either of the following cases occurs. (1) The host and guest chiral groups cannot interact with each other or their repulsive interactions are too weak to result in any difference in binding energy between the host and the two guest enantiomers. (2) The presence on the macrocyclic host of too many substituents or of substituents at chiral center(s) that are too large results in macrocycles that cannot interact with guest enantiomers to form stable complexes. One example of a chiral substituent that is too large is seen for receptor **6**. The large *tert*-butyl groups cause a very weak interaction of (*S*,*S*)-**6** with Am**1** enantiomers, resulting in no recognition.[63,64] Therefore, structurally non-complementary interactions cause no enantiomeric recognition. A chiral macrocyclic receptor having a stereochemically complementary structure with the guest enantiomers can form a stable complex with one enantiomer and a significantly less stable complex with the other one.

As has been mentioned, (*S*,*S*)-**5** shows excellent recognition toward (*R*) forms of Am**1** and Am**3** over the (*S*) forms (Δ(log *K*) values are >0.85 and 0.56, respectively, see Table 1). However, its isomer, (*S*,*S*)-**18** (Chart 3), displays a much smaller degree of enantioselectivity toward both of the Am**1** and Am**3** enantiomer pairs (Δ(log *K*) values, 0.22 and 0.14, respectively, see Table 1) than does (*S*,*S*)-**5**. The two chiral centers in **18** are one carbon position farther away from the pyridine ring than those in **5**. Because of this change in macrocycle structure, (*S*,*S*)-**18** is less sterically complementary with the ammonium enantiomers, resulting in a lower degree of chiral recognition. Macrocycle **19** has two chiral centers located on the same side of the pyridine ring and shows no enantiomeric recognition toward Am**1** [log *K* (MeOH) values for (*R*,*R*)-**19** interaction with (*R*)-Am**1** and (*S*)-Am**1** are 3.00 and 2.94, respectively[64]]. The bulky group of each Am**1** enantiomer can find open space on the other side of the pyridine ring where no methyl substituents are present, thus, avoiding steric contact with the ligand.

Binaphthyl-containing **7**, as mentioned above, displays a high degree of chiral recognition toward valine.[68] However, when the crown ring is modified to have one more or one less ethyleneoxy unit, the resulting macrocycles **8** and **9** show no enantiomeric recognition toward valine.[24,68] Molecular models suggest that the crown ring of **8** is too small to accommodate an ammonium group and that in **9** the three alternate oxygen atoms which are capable of forming hydrogen bonds with the ammonium cation are too remote from the chiral barrier.

In many cases, too many chiral centers result in no or decreased enantiomeric recognition due to a decrease in structural complementarity. Compared with (*S*,*S*)-**10**, (*R*,*R*,*R*,*R*)-**20** (Chart 3) with two more chiral methyl groups exhibited no recognition toward Am**1** enantiomers [log *K* (5:5 $CD_3OD/CDCl_3$) values for (*R*,*R*,*R*,*R*)-**20** interaction with (*R*)-Am**1** and (*S*)-Am**1** were 3.00 and 3.05, respectively[63]]. Cram and co-workers observed that macrocycles containing one or two binaphthyl unit(s) (such as **7**, **12**, and **13**) displayed good chiral recognition but those containing three such units (such as **21**) lost the chiral discrimination ability.[24] Naemura and co-workers found that a six-oxygen-containing macrocycle incorporating two 3,3,7,7-tetramethylbicyclo[3.3.1]nonane-2,6-diol units as chiral barriers (**22**, Chart 3) showed no enantiomeric recognition toward Am**2**, as evidenced by a lack of transport ability through a bulk liquid membrane. Over a 10-day period, no significant transport of Am**2** molecule by (+)-**22** was observed.[78] Incorporation of one of these units into a similar macrocycle (+)-**23**, however, resulted in both transport and chiral recognition for Am**2**.[78] Therefore, the fourth rule of enantiomeric recognition can be stated as follows: *in*

order to have a high degree of enantiomeric recognition, the chiral macrocyclic compound should be stereochemically complementary with the guest enantiomers.

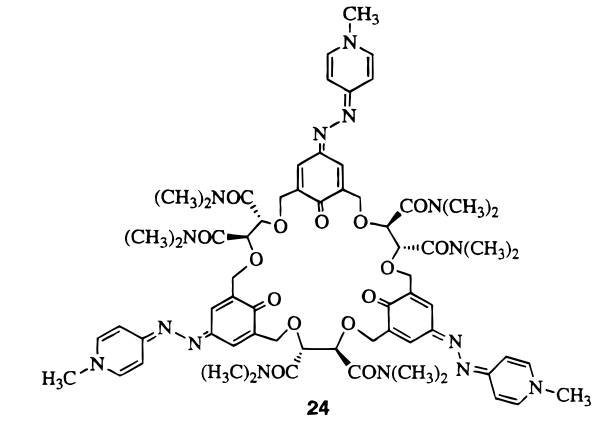
E. Symmetry of Macrocyclic Receptors

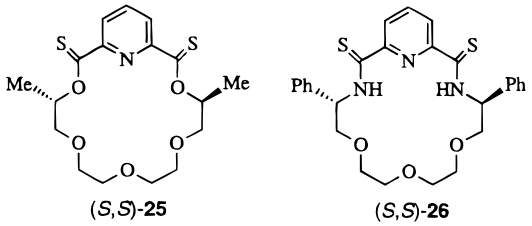
The effect of the symmetry of macrocyclic receptors on chiral recognition was first noted by Löhr and Vögtle.[79] A chiral azamerocyanine-containing macrocycle **24** (Chart 4) was synthesized[80] and its ability of differentiation between enantiomers was examined. No appreciable chiral discrimination of guest enantiomers was observed with receptor **24**. It was rationalized that the D_3 symmetry of **24** was responsible for the lack of chiral recognition.[79] On each side of the D_3-symmetric macrocycle, three equal steric barriers are provided. In the arrangement shown in Figure 6 (parts a and b), the medium substituent M and small S can be exchanged without altering the steric repulsion with the D_3 host. Therefore, a D_3-symmetric ligand does not make a sterically different environment to discriminate between *R* and *S* forms of substrates and the interaction of the D_3-symmetric macrocycle with enantiomeric guests results in little difference in binding energies between the *R* and *S* forms of the guest molecules.

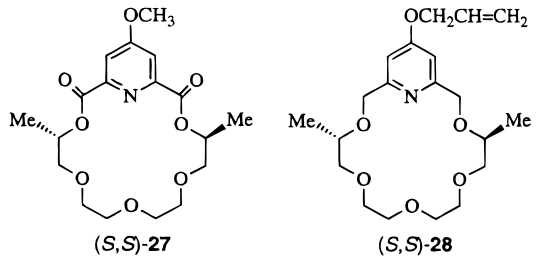
Chiral macrocyclic receptors possessing C_1 symmetry also provide an insufficient steric repulsion for enantiomeric recognition. Naemura and his coworker noted that chiral macrocycles possessing C_1 symmetry showed low enantioselectivity due to "sidedness" problems.[38] A C_1-symmetric ligand **80** (see section VII) exhibits significantly lower enantioselectivity than C_2-symmetric ligands **81** and **82**.[38] Ligand **19**, which is of C_1 symmetry, displays no enantiomeric recognition toward Am**1** (see section II-D). On the other hand, the C_2-symmetric **4**, a structural isomer of **19**, shows enantioselectivity for Am**1**. Figure 6 (parts c and d) illustrates the steric interactions of an enantiomer pair with a C_1-symmetric macrocycle. In order to form stable complexes, as shown in Figure 6 (parts c and d), the substrates interact with the macrocyclic receptor from one side while the chiral barrier protrudes to the other side. A difference in steric repulsion exists between the *R* and *S* substrate interactions with the ligand of C_1 symmetry. However, the interaction of the guest molecules with the host macrocycle on the different macrocyclic plane from that where the chiral barrier protrudes minimizes the role of the chiral barrier, resulting in a low degree of chiral recognition.

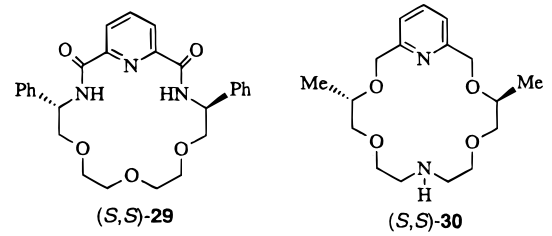
C_2-symmetric macrocyclic receptors usually show good enantioselectivity. As shown in Figure 6, if one guest molecule interacts with a chiral macrocycle of C_2 symmetry with less steric repulsion (Figure 6e, the small substituent S is close to the chiral barrier), its enantiomer must encounter a stronger repulsive interaction with the chiral barrier (Figure 6f, the substituent M is close to the chiral barrier). In Figure 6, it is supposed that the substrates interact with chiral macrocycles in a complementary way so that the chiral barriers play their role. It is believed that chiral macrocycles of D_2 symmetry possess the same effect of steric interactions with enantiomer

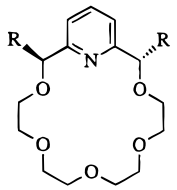
Chart 4. Macrocycles 24−33











substrates as macrocycles of C_2 symmetry.[79] Good chiral recognition demonstrated by D_2-symmetric macrocyclic receptors has been observed by Naemura and Still and their co-workers (see sections VII and XII). Still and co-workers have shown that C_3-symmetric macrocycles also display good enantioselectivity.[34,77] Therefore, according to the enantiomeric recognition data reported so far, the fifth rule of enantiomeric recognition is that *the macrocyclic*

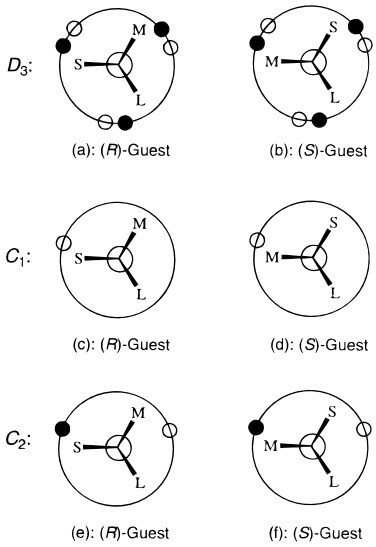


Figure 6. A schematic illustration of chiral recognition of substrates (Newman projection H_3N^+-CSML with S = small, M = medium, and L = large) with C_1-, C_2-, and D_3-symmetric macrocyclic receptors. ●: groups above the macroring plane; ○: groups below the macroring plane.

receptors possessing C_2, C_3, and D_2 symmetry show higher enantioselectivity than those of C_1 and D_3 symmetry.

The following is a summary of the rules for effective enantiomeric recognition with chiral macrocyclic receptors:

1. An essential requirement is that the chiral macrocycles form reasonably stable complexes with the guest enantiomers so that the repulsive interactions can effectively lessen the stability of the complex of one enantiomer.

2. Large chiral barrier(s) result in a high degree of enantiomeric recognition.

3. Low conformational flexibility of diastereomeric complexes plays an important role in good enantiomeric recognition. Two factors, rigid macrocycles and multipoint interactions, ensure a fixed conformation of the complexes.

4. The structural complementarity between chiral macrocycles and enantiomers ensures that the chiral barriers of macrocycles make full use of steric repulsion for enantiomeric recognition.

5. Macrocyclic receptors possessing C_2, C_3, and D_2 symmetry usually show higher enantioselectivity than those of C_1 and D_3 symmetry

On the basis of these rules, an estimate of chiral recognition ability can be made for any given macrocyclic receptors. Therefore, these rules might be used as a basis for the design of new chiral macrocycles.

In the following sections, we summarize enantiomeric recognition of amine compounds according to different types of chiral macrocyclic receptors.

III. Pyridine-Containing Macrocycles

Izatt, Bradshaw, and their co-workers have made an extensive study of enantiomeric recognition using pyridine-containing macrocycles.[30−32,59,61−66,73−75,81−87] Most of these macrocyclic receptors are of C_2 symmetry and show good enantiomeric recognition. The pyridine group has two important roles in chiral recognition. First, tripod hydrogen bonding between the macrocycles and ammonium cations must involve the pyridine nitrogen atom[24,30,88] (see Figure 2). Second, the pyridine ring provides a possibility of a secondary attractive $\pi-\pi$ interaction with aromatic groups of the guests. These two properties of the pyridine ring result in a rather rigid conformation of diastereomeric complexes of the macrocycles with guest enantiomers and thereby increase chiral recognition ability.

Some chiral recognition data involving pyridine-containing macrocycles are listed in Table 1. Other representative data and some new data published since two short reviews appeared in 1992[30,31] are summarized in Table 2. The degree of enantiomeric recognition indicated by $\Delta(\log K)$ values varies noticeably with different types of chiral pyridino-18-crown-6 receptors, ammonium cations, and solvents used.

A. Structural Complementarity

It is seen in Tables 1 and 2 that the degrees of enantiomeric recognition ($\Delta(\log K)$) for five ammonium guests studied by (*S*,*S*)-**5** have the sequence Am**1** > Am**4** > Am**3** > Am**6** > Am**7** (Chart 2). Hence, (*S*,*S*)-**5** shows better chiral recognition toward the ammonium cations having the largest substituent directly attached to the chiral carbons (Am**1**, Am**3**, and Am**4**) than those having the largest substituent attached to chiral carbon through one more $-CH_2-$ unit (Am**6** and Am**7**). Because the large indole substituent of Am**8** connects with chiral carbon through a methylene group, the degree of enantiomeric recognition of Am**8** by (*S*,*S*)-**10** [$\Delta(\log K) = 0.14$, Table 2] is lower than those of Am**1** and Am**3** [$\Delta(\log K)$ values of 0.24 and 0.33, respectively, Table 1]. Therefore, the pyridine-containing macrocycles show better steric complementarity with ammonium guests having the large substituents directly attached to the chiral carbon atom than those having large substituents attached to the chiral carbon atom through other alkyl unit(s). A similar effect has been observed for enantioselectivity of dipeptides using chiral crown ethers in liquid chromatography[6] and capillary zone electrophoresis experiments.[14] If the stereogenic centers of the dipeptides are located too far from the amine groups, baseline resolutions could not be obtained.

Ligand (*S*,*S*)-**4** shows the same degree of chiral recognition toward enantiomer pairs of Am**3** and Am**5** (methyl alaninate hydrochloride) in MeOH [$\Delta(\log K)$ values of 0.22, Table 1, and 0.24, Table 2, respectively]. However, the (*S*,*S*)-**4** exhibits better recognition toward the enantiomer pair of Am**1** that has a large naphthyl group [$\Delta(\log K) = 0.41$ in MeOH, Table 1] than either Am**3** or Am**5**.

A recent study of FTICR/MS by Dearden and coworkers shows the following sequence of extent of enantiomeric recognition for four amines by chiral **4**: *sec*-butylamine < cyclohexylethylamine < phenylethylamine < naphthylethylamine.[89] Essentially no recognition was observed for *sec*-butylamine due to the small ethyl substituent. Change of the ethyl group to the bulkier and less flexible cyclohexyl leads

Table 2. Chiral Recognition Data[a] Determined by Calorimetric and ^{1}H NMR Titrations in Homogeneous Solutions for Enantiomer Pairs of Primary Ammonium Cations with Chiral Pyridine-Containing Macrocycles at 25 °C

ligand	cation	log *K*	Δ*H*	Δ*S*	Δ(log *K*)	method[b]	solvt[c]	ref
(*S*,*S*)-**4**	(*R*)-Am**1**	2.76	−29.0	−44.6		Cal	7M/3DCE	83
	(*S*)-Am**1**	2.26	−26.9	−47.0	0.50	Cal	7M/3DCE	83
	(*R*)-Am**1**	3.35	−28.5	−30.5		Cal	4M/6DCE	83
	(*S*)-Am**1**	2.70	−27.6	−40.9	0.65	Cal	4M/6DCE	83
	(*R*)-Am**1**	3.62	−28.0	−24.5		Cal	3M/7DCE	83
	(*S*)-Am**1**	3.01	−27.1	−33.2	0.61	Cal	3M/7DCE	83
	(*R*)-Am**1**	3.88	−29.3	−24.2		Cal	2M/8DCE	83
	(*S*)-Am**1**	3.38	−26.5	−24.2	0.50	Cal	2M/8DCE	83
	(*R*)-Am**1**	4.47	−31.8	−21.3		Cal	1M/9DCE	83
	(*S*)-Am**1**	4.01	−28.6	−19.1	0.46	Cal	1M/9DCE	83
	(*R*)-Am**1**	3.11	−26.9	−30.9		Cal	5Et/5DCE	84
	(*S*)-Am**1**	2.51	−23.3	−30.2	0.60	Cal	5Et/5DCE	84
	(*R*)-Am**1**	3.43	−26.9	−24.5		Cal	5iPr/5DCE	84
	(*S*)-Am**1**	2.87	−23.0	−22.1	0.56	Cal	5iPr/5DCE	84
	(*R*)-Am**1**	3.42	−35.8	−54.7		Cal	5tBu/5DCE	84
	(*S*)-Am**1**	2.99	−32.2	−50.6	0.43	Cal	5tBu/5DCE	84
	(*R*)-Am**5**	2.02	−14.8	−10.9		Cal	M	61
	(*S*)-Am**5**	1.78	−14.6	−14.9	0.24	Cal	M	61
(*S*,*S*)-**5**	(*R*)-Am**6**	2.18				NMR	5M/5C	64
	(*S*)-Am**6**	1.76			0.42	NMR	5M/5C	64
	(*R*)-Am**7**	1.60				NMR	5M/5C	64
	(*S*)-Am**7**	1.28			0.32	NMR	5M/5C	64
(*S*,*S*)-**10**	(*R*)-Am**1**	3.96				NMR	5M/5C	85
	(*S*)-Am**1**	3.42			0.54	NMR	5M/5C	85
	(*R*)-Am**7**	3.02				NMR	1M/1C	63
	(*S*)-Am**7**	3.11			0.09	NMR	1M/1C	63
	(*R*)-Am**8**	2.43	−14.4	−2.1		Cal	M	61
	(*S*)-Am**8**	2.29	−14.3	−4.5	0.14	Cal	M	61
(*S*,*S*)-**25**	(*R*)-Am**1**	1.72	−13.7	−12.7		Cal	M	62
	(*S*)-Am**1**	1.60			0.12	Cal	M	62
	(*R*)-Am**1**	2.69	−17.95	−8.6		Cal	5M/5DCE	62
	(*S*)-Am**1**	2.10	−12.4	−1.34	0.59	Cal	5M/5DCE	62
	(*R*)-Am**1**	2.87	−20.5	−13.8		Cal	4M/6DCE	83
	(*S*)-Am**1**	2.25	−18.4	−18.4	0.62	Cal	4M/6DCE	83
	(*R*)-Am**1**	3.08	−22.4	−16.1		Cal	3M/7DCE	83
	(*S*)-Am**1**	2.36	−21.1	−25.5	0.72	Cal	3M/7DCE	83
	(*R*)-Am**1**	3.34	−25.3	−20.8		Cal	2M/8DCE	83
	(*S*)-Am**1**	2.74	−21.9	−21.1	0.60	Cal	2M/8DCE	83
	(*R*)-Am**1**	3.86	−28.7	−22.5		Cal	1M/9DCE	83
	(*S*)-Am**1**	3.36	−23.5	−14.4	0.50	Cal	1M/9DCE	83
	(*R*)-Am**1**	2.77	−25.6	−32.9		Cal	5iPr/5DCE	84
	(*S*)-Am**1**	2.41	−22.1	−27.8	0.36	Cal	5iPr/5DCE	84
	(*R*)-Am**1**	3.27	−33.9	−51.0		Cal	3tBu/7DCE	84
	(*S*)-Am**1**	2.73	−32.9	−58.0	0.54	Cal	3tBu/7DCE	84
	(*R*)-Am**3**	2.27	−23.5	−35.2		Cal	5M/5DCE	62
	(*S*)-Am**3**	1.86	−24.2	−45.6	0.41	Cal	5M/5DCE	62
	(*R*)-Am**4**	1.96	−24.3	−44.3		Cal	5M/5DCE	62
	(*S*)-Am**4**	2.34	−23.4	−33.5	0.38	Cal	5M/5DCE	62
(*S*,*S*)-**26**	(*R*)-Am**1**	1.39				NMR	5M/5C	58
	(*S*)-Am**1**	1.02			0.37	NMR	5M/5C	58
(*S*,*S*)-**27**	(*R*)-Am**1**	3.52	−29.3	−30.9		Cal	5M/5DCE	62
	(*S*)-Am**1**	2.96	−24.9	−26.8	0.56	Cal	5M/5DCE	62
	(*R*)-Am**1**	3.59	−26.8	−21.1		Cal	5Et/5DCE	84
	(*S*)-Am**1**	3.01	−22.6	−18.1	0.58	Cal	5Et/5DCE	84
	(*R*)-Am**1**	3.92	−27.0	−15.4		Cal	5iPr/5DCE	84
	(*S*)-Am**1**	3.37	−22.8	−12.1	0.55	Cal	5iPr/5DCE	84
	(*R*)-Am**1**	2.94				NMR	M	83
	(*S*)-Am**1**	2.53			0.41	NMR	M	83
	(*R*)-Am**1**	3.19				NMR	7M/3C	83
	(*S*)-Am**1**	2.73			0.46	NMR	7M/3C	83
	(*R*)-Am**1**	3.35				NMR	5M/5C	83
	(*S*)-Am**1**	2.85			0.50	NMR	5M/5C	83
	(*R*)-Am**1**	3.52				NMR	4M/6C	83
	(*S*)-Am**1**	2.95			0.57	NMR	4M/6C	83
	(*R*)-Am**1**	3.62				NMR	3M/7C	83
	(*S*)-Am**1**	3.11			0.51	NMR	3M/7C	83
	(*R*)-Am**1**	3.82				NMR	1M/9C	83
	(*S*)-Am**1**	3.72			0.10	NMR	1M/9C	83
	(*R*)-Am**3**	2.85	−25.6	−31.3		Cal	M	63
	(*S*)-Am**3**	2.66	−21.6	−21.5	0.19	Cal	M	63
	(*R*)-Am**3**	3.17	−29.7	−38.9		Cal	5M/5DCE	62
	(*S*)-Am**3**	2.76	−32.0	−54.3	0.41	Cal	5M/5DCE	62
(*S*,*S*)-**28**	(*R*)-Am**1**	3.07	−28.3	−36.2		Cal	M	62

Table 2 (Continued)

ligand	cation	log *K*	ΔH	ΔS	Δ(log *K*)	method[b]	solvt[c]	ref
	(*S*)-Am**1**	2.81	−20.8	−16.1	0.26	Cal	M	62
	(*R*)-Am**1**	3.89				NMR	5M/5C	63
	(*S*)-Am**1**	3.54			0.35	NMR	5M/5C	63
	(*R*)-Am**1**	3.96	−32.4	−32.9		Cal	5M/5DCE	62
	(*S*)-Am**1**	3.50	−24.6	−15.4	0.46	Cal	5M/5DCE	62
	(*R*)-Am**1**	4.27	−33.9	−31.9		Cal	5Et/5DCE	84
	(*S*)-Am**1**	3.80	−26.7	−16.8	0.47	Cal	5Et/5DCE	84
	(*R*)-Am**1**	4.45	−39.1	−46.0		Cal	5iPr/5DCE	84
	(*S*)-Am**1**	3.98	−31.2	−28.5	0.47	Cal	5iPr/5DCE	84
	(*R*)-Am**1**	4.98	−48.3	−66.7		Cal	5tBu/5DCE	84
	(*S*)-Am**1**	4.49	−41.3	−52.7	0.49	Cal	5tBu/5DCE	84
(*S*,*S*)-**29**	(*R*)-Am**1**	< 1				NMR	5M/5C	58
	(*S*)-Am**1**	ND				NMR	5M/5C	58
(*S*,*S*)-**30**	(*R*)-Am**1**	1.51				NMR	M	30
	(*S*)-Am**1**	1.49			0.02	NMR	M	30
(−)-**31**	(*R*)-Am**1**	3.92				NMR	5M/5C	87
	(*S*)-Am**1**	3.84			0.08	NMR	5M/5C	87
	(*R*)-Am**3**	3.84				NMR	5M/5C	87
	(*S*)-Am**3**	3.62			0.22	NMR	5M/5C	87
(*S*,*S*)-**32**	(*R*)-Am**3**	3.45				NMR	5M/5C	87
	(*S*)-Am**3**	3.69			0.24	NMR	5M/5C	87
(*S*,*S*)-**33**	(*R*)-Am**3**	1.91				NMR	5M/5C	87
	(*S*)-Am**3**	2.25			0.34	NMR	5M/5C	87

[a] ΔH and ΔS values are in the units of kJ/mol and J/K·mol, respectively. $\Delta(\log K) = |\log K_{(R)} - \log K_{(S)}|$. NR means no observable reaction due to a small log *K* value. [b] See note *b* of Table 1. [c] See note *c* of Table 1. Et = ethanol; iPr = isopropyl alcohol; tBu = *tert*-butyl alcohol.

to a significant enantiomeric preference. The presence of face-to-face $\pi-\pi$ interaction in the phenylethylamine and naphthylethylamine complexes greatly enhances the degree of chiral recognition.

Chiral pyridino-18-crown-6 macrocycles containing five oxygen donor atoms in the crown ring show good recognition toward guest ammonium enantiomers. However, when one or more macroring oxygen atoms are replaced by nitrogen atoms, the resulting macrocycle displays a much lower degree of or no enantiomeric recognition.[30,59] For instance, (*S*,*S*)-**29** and (*S*,*S*)-**30** (Chart 4) differ from (*S*,*S*)-**5** and (*S*,*S*)-**10** in that two (in **29**) and one (in **30**) of the oxygen donor atom(s) in the macrorings are replaced by nitrogen atom(s). These chiral macrocycles are unable to differentiate between Am**1** enantiomers (Table 2). Compared with **25**, (*S*,*S*)-**26** recognizes (*R*)-Am**1** over the (*S*) form to a much lesser extent [$\Delta(\log K) = 0.37$ in 5:5 $CD_3OD/CDCl_3$ for **26** and $\Delta(\log K) = 0.59$ in 5:5 $CH_3OH/ClCH_2CH_2Cl$ for **25**, Table 2] due to two nitrogen atoms in the macroring. These decreases in enantiomeric recognition have been attributed to a distortion in macrocyclic conformation caused by replacement of the oxygen atom(s) by the nitrogen atom(s).[30,59] The conformational distortion results in a decrease in steric complementarity between the macrocyclic hosts and ammonium guests.

Ligands **31**−**33** (Chart 4) differ from **10** and **11** in that the two chiral barriers of **31**−**33** are located next to the pyridine ring. This structural change results in a decreased degree of enantiomeric recognition. Compared with **10** and **11**, compounds **31**−**33** show smaller $\Delta(\log K)$ values for the interactions with enantiomers of Am**1** and Am**3** (Table 2). The observation suggests that the chiral barriers located too close to the pyridine ring (in **31**−**33**) lead to a less complementary structure for enantiomeric recognition toward Am**1** and Am**3**.

B. Diester and Dithiono Macrocycles

Diester macrocycles **4**, **5**, and **27** and dithiono macrocycle **25** exhibit higher degrees of enantiomeric recognition toward ammonium guests than do **10**, **11**, and **28** due to an increase in the molecular rigidity of diester and dithiono macrocycles. Although the rigid ligands increase enantioselectivities, the complex stabilities are decreased. Less flexible (*S*,*S*)-**4**, for example, forms less stable complexes with (*R*)- and (*S*)-Am**1** [log *K* (MeOH) values of 2.47 and 2.06] than does the more flexible (*S*,*S*)-**10** [log *K* (MeOH) values of 3.00 and 2.76, Table 1]. Therefore, the addition of two carbonyl oxygen or sulfur atoms seems to improve the enantiomeric recognition at the cost of complex stability.

Macrocycle **25** differs from **4** in that the two carbonyl oxygen atoms are replaced by sulfur atoms. This substitution retains the molecular rigidity but introduces two large sulfur atoms. Ligand (*S*,*S*)-**25** shows an increased degree of enantioselectivity for (*R*)-Am**1** over (*S*)-Am**1** in 3:7 and 2:8 MeOH/DCE solvent mixtures [$\Delta(\log K) = 0.72$ and 0.60] as compared with carbonyl-oxygen-containing (*S*,*S*)-**4** [$\Delta(\log K) = 0.61$ and 0.50 in the same solvents; see Table 2]. However, in the other solvents (*S*,*S*)-**25** shows lower degrees of enantiomeric recognition than does (*S*,*S*)-**4**.

As can be seen in Tables 1 and 2, in each case the interaction of **25** has a smaller log *K* value and less negative ΔH value than does the interaction of **4** with the same enantiomer pairs in the same solvents, indicating that the bulky sulfur atoms result in less stable complexes. In most cases, ΔS values for the interactions of the ammonium cations with **25** are less negative than those with **4**, suggesting a more extensive desolvation of the complexes of **25** than that of the complexes of **4**. This is due to the large size of the sulfur atom that has a weaker solvation than

does the carbonyl oxygen atom. The high extent of enantiomeric recognition toward Am**1** with (*S*,*S*)-**25** in 3:7 and 2:8 MeOH/DCE solvent mixtures was expected to relate to bulky sulfur atoms. ^{1}H NMR spectra show upfield shifts of the pyridine proton signals of (*S*,*S*)-**25** complexes with (*R*)- and (*S*)-Am**1**.[63,83] Therefore, the naphthyl group of Am**1** overlaps the pyridine group of **25** through $\pi-\pi$ interaction. As the diastereomeric complexes form in this way, the two bulky sulfur atoms act as high-energy barriers which further restrict movement of the naphthyl group of Am**1**. This effect increases the extent of enantioselectivity since the conformation of the complexes is more rigid.

C. 2D NMR and Thermodynamic Evidences of $\pi-\pi$ Interaction

As has been noted, in most cases the recognition of enantiomers of Am**1** by chiral pyridino macrocycles is better than that of enantiomers of either Am**3** or Am**4** due to the presence of $\pi-\pi$ interaction in Am**1** complexes and the absence of such interactions in Am**3** and Am**4** complexes. 2D ^{1}H NMR spectra and thermodynamic data provide evidence for this difference.

The 2D ^{1}H NOESY spectra of the complexes of **16**-Am**3** and (*S*,*S*)-**10**-Am**1** in 5:5 $CD_3OD/CDCl_3$ solvent are shown in Figures 7 and 8, respectively. These spectra are informative concerning the spatial positions of aromatic rings between macrocyclic hosts and ammonium guests.[73,75] In the ^{1}H NOESY spectrum of the **16**-Am**3** complex,[73] off-diagonal signals correlating the chemical shifts of the pyridine protons (ca. 8.1−8.3 ppm) and those of the phenyl protons (ca. 7.2 ppm) are absent. Instead, off-diagonal signals correlating the pyridine chemical shifts of the ligand and methyl chemical shifts (1.5 ppm) of Am**3** are present. These facts indicate that the methyl protons of Am**3** are in close proximity (<5 Å) to the pyridine protons of **16**. On the other hand, a pair of strong off-diagonal signals are seen to correlate the phenyl proton chemical shifts (ca. 7.2 ppm) of Am**3** and the chemical shifts of the ligand's $-OCH_2CH_2O-$ protons (ca. 3.7 ppm), indicating that the phenyl group of the Am**3** is in close proximity to the ethyleneoxy part of the **16** macroring frame. The complex of (*R*,*R*)-**4** with (*R*)-Am**4** in 5:5 $CD_3OD/CDCl_3$ shows similar ^{1}H NOESY spectra.[73] Therefore, the phenyl group of the Am**3** is positioned far away from the pyridine moiety of the ligand indicating conclusively the absence of $\pi-\pi$ interaction.

^{1}H NOESY spectra of the complexes of (*R*)- and (*S*)-Am**1** with (*S*,*S*)-**10** support the presence of $\pi-\pi$ interaction between the naphthyl group of the guest and the pyridine group of the host. Off-diagonal signals of 7.1−8.2 ppm that correlate the pyridine and naphthyl chemical shifts are observed (Figure 8), indicating that the pyridine ring of (*S*,*S*)-**10** is spatially close to the naphthyl group of Am**1**.[75]

A striking difference in ΔS values between chiral interactions involving Am**1** and those involving Am**3** and Am**4** in 5:5 MeOH/DCE is seen in Table 1 for (*S*,*S*)-**4** and in Table 2 for (*S*,*S*)-**25** and (*S*,*S*)-**27**. In each case, the entropy change for Am**3** and Am**4** interactions is more negative (unfavorable) than that for Am**1** complexation, while the enthalpy change for Am**3** and Am**4** interactions is also more negative (favorable) than that for Am**1** interactions. The extensive desolvation resulting from the $\pi-\pi$ interaction between the naphthyl group of Am**1** and the pyridine and carbonyl groups of the ligands (**4**, **25**, and **27**) results in less negative entropy changes.[62] This same process consumes heat produced by the complexation so that smaller $-\Delta H$ values are observed.

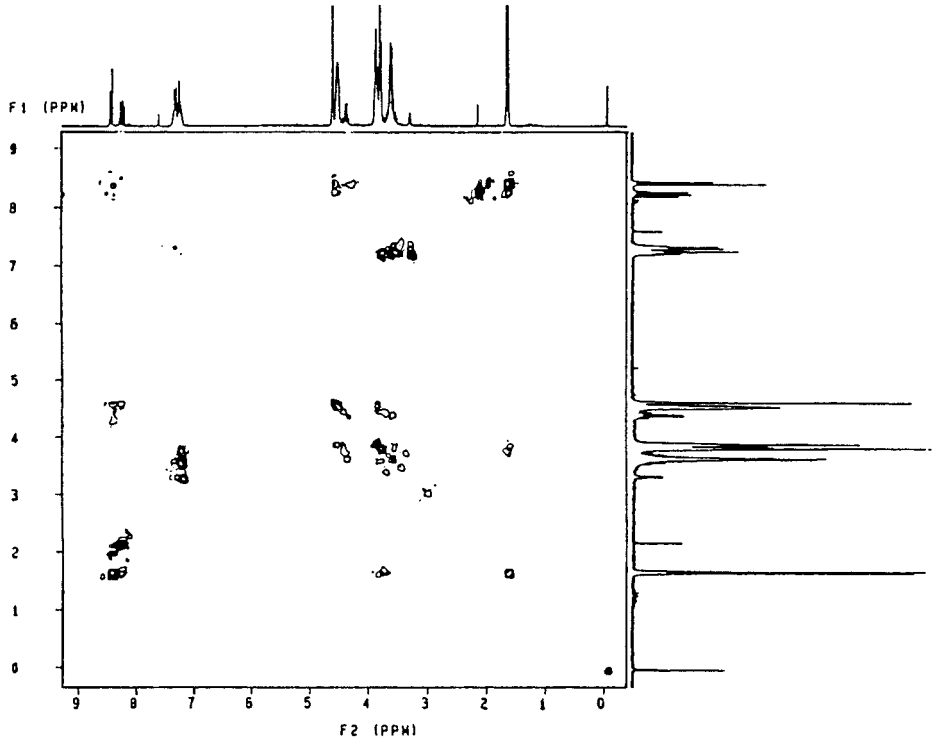


Figure 7. ^{1}H NMR NOESY spectra of **16**−Am**3** complex in 1:1 $CD_3OD/CDCl_3$. (Reprinted from ref 73. Copyright 1992 John Wiley and Sons.)

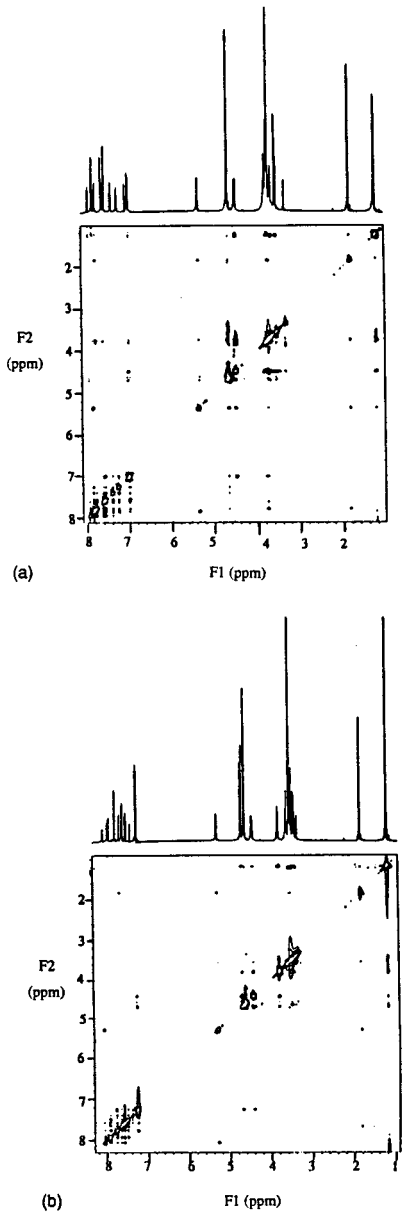


Figure 8. ^{1}H NMR NOESY spectra of (*S*,*S*)-**10**−(*R*)-Am**1** (a) and (*S*,*S*)-**10**−(*S*)-Am**1** (b) complexes in 1:1 CD_3OD/$CDCl_3$. (Reprinted from ref 75. Copyright 1993 Kluwer.)

The π electrons of the phenyl group apparently are not energetic enough to allow the phenyl group to replace the solvent molecules from the keto oxygens of the ligand.[73] This has been considered to be the main reason for the absence of $\pi-\pi$ interaction where phenyl groups are involved. The large negative ΔS values for Am**3** and Am**4** interactions with macrocyclic ligands **4**, **25**, and **27** support this idea. Because of the lack of $\pi-\pi$ interaction, solvent molecules cannot be effectively replaced during complexation. Thus, the formation of complexes and the conformational changes of the host and guest molecules result in large negative ΔS values. Therefore, a multipoint interaction including $\pi-\pi$ stacking in Am**1** complexes with **4**, **25**, and **27** results in a high degree of enantiomeric recognition in each case.

D. Substitution on the Pyridine Ring

No significant change in the extent of enantiomeric recognition has been observed by the addition of a substituent on the pyridine ring. Macrocycles (*S*,*S*)-**27** and (*S*,*S*)-**28** each have a substituent in the *para* position of the pyridine ring. Comparison of (*S*,*S*)-**27** with (*S*,*S*)-**4** and of (*S*,*S*)-**28** with (*S*,*S*)-**10**, (*S*,*S*)-**27**, and (*S*,*S*)-**28** shows the same extent of enantiomeric recognition, within experimental error, toward Am**1** in the same solvents as (*S*,*S*)-**4** and (*S*,*S*)-**10**, respectively (Tables 1 and 2). However, the complex stabilities are increased by addition of the electron-donating groups (OCH_3 and -$OCH_2CH{=}CH_2$). Ligand **27** forms more stable complexes with Am**1**, Am**2**, and Am**3** than does **4**, while **28** forms more stable complexes with Am**1** than does **10**.

E. Solvent Effect

Solvent has a significant effect on enantiomeric recognition. A recent FAB mass spectrometry study indicates that the interactions of pyridine-containing diastereomeric complexes with solvent molecules have a crucial role in the complex stability and extent of enantiomeric recognition.[90] Dearden and co-workers have also found that solvents play an important role in enantiomeric recognition. In the solvent-free gas phase, the degree of enantiomeric recognition for Am**1** and Am**3** with macrocycle **4** is greater than in methanol solution and is about the same as is observed in weakly solvating solvents such as 4:6 MeOH/DCE.[65,89]

In different homogeneous solvent systems, the degrees of enantiomeric recognition toward Am**1** by (*S*,*S*)-**25** change from $\Delta(\log K) = 0.12$ in MeOH to $\Delta(\log K) = 0.72$ in 3:7 MeOH/DCE (Table 2). Ligands (*S*,*S*)-**4** and (*S*,*S*)-**27** show significant changes in the extent of enantiomeric recognition toward Am**1** in different solvents [$\Delta(\log K) = 0.41$ in MeOH to $\Delta(\log K) = 0.65$ in 4:6 MeOH/DCE for (*S*,*S*)-**4** and $\Delta(\log K) = 0.10$ in 1:9 $CD_3OD/CDCl_3$ to $\Delta(\log K) = 0.58$ in 5:5 EtOH/DCE for (*S*,*S*)-**27**, Tables 1 and 2].

In binary solvent mixtures of MeOH/DCE and $CD_3OD/CDCl_3$, the change in extent of enantiomeric recognition with solvent components is not linear. The degrees of enantiomeric recognition toward Am**1** by **4**, **25**, and **27** in the solvent mixtures having a moderate methanol component is higher than that in the solvent mixtures having either a high or a low methanol component. When the volumetric percentage of methanol in the solvent mixtures decreases from 100% to 10%, the degree of enantiomeric recognition in terms of $\Delta(\log K)$ values first increases to a peak value, then decreases. The highest degree of recognition for (*S*,*S*)-**4** interactions with (*R*)- and (*S*)-Am**1** is observed in both 4:6 $CD_3OD/CDCl_3$ and 4:6 MeOH/DCE solvents (Table 2).[83] In the case of (*S*,*S*)-**27**, the peak recognition is also found in the 4:6 $CD_3OD/CDCl_3$ mixture. However, the best recognition of enantiomers of Am**1** by (*S*,*S*)-**25** occurs in a 3:7 MeOH/DCE solvent mixture. On the basis of an analysis of thermodynamic quantities ($\log K$, ΔH, and ΔS), these changes in chiral recognition have been attributed to a conformational modification of diastereomeric complexes by different binary solvent systems.[83,84]

Different solvent molecules have different effects on enantiomeric recognition. In four alcohol/DCE (MeOH/DCE, EtOH/DCE, iPrOH/DCE, and tBuOH/

DCE) binary solvents, (*S*,*S*)-**4** and (*S*,*S*)-**25** show different degrees of enantiomeric recognition toward (*R*)- and (*S*)-Am**1**. Ligand (*S*,*S*)-**25** displays better recognition toward Am**1** enantiomers in the solvent mixture of 5:5 MeOH/DCE [$\Delta(\log K) = 0.59$] than in 5:5 iPrOH/DCE ($\Delta(\log K) = 0.36$), while (*S*,*S*)-**4** shows a better recognition toward Am**1** enantiomers in the 5:5 MeOH/DCE and EtOH/DCE [$\Delta(\log K)$ values of 0.60 in each case] than in 5:5 tBuOH/DCE [$\Delta(\log K) = 0.43$]. The degree of chiral recognition toward the enantiomer pair of Am**1** by (*S*,*S*)-**25** in 3:7 tBuOH/DCE [$\Delta(\log K) = 0.54$] is smaller than that in 3:7 MeOH/DCE [$\Delta(\log K) = 0.72$]. These results show that large solvent molecules (such as iPrOH and tBuOH) decrease the enantiomeric recognition. The solvent EtOH/DCE has the same effect as MeOH/DCE on enantiomeric recognition, i.e., the chiral macrocycles (**4**, **27**, and **28**) exhibit the same degrees of recognition in both MeOH/DCE and EtOH/DCE binary solvents. It is concluded that enantiomeric recognition is optimized in solvents consisting of small molecule(s).[84]

A baseline resolution of Am**1** enantiomers by silica gel-bound (*S*,*S*)-**10** has been observed.[22] Because (*S*,*S*)-**10** interacts more strongly with (*R*)-Am**1**, (*S*)-Am**1** passes through the column more rapidly than (*R*)-Am**1**.

F. Enantiotopic Group Recognition

A recent ^{1}H and ^{13}C NMR spectroscopic study reveals that (*S*,*S*)-**5** has the ability to distinguish between the two NH_3^+ groups (enantiotopic group recognition) in a bis-ammonium salt (A_2cH or A_2cP, Chart 2).[91,92] The NMR spectroscopy results clearly demonstrate the formation of two diastereomeric 1:1 complexes of (*S*,*S*)-**5** with either A_2cH or A_2cP. In the case of A_2cH, the ratio of the complex in which the ligand binds with one NH_3^+ to the complex in which the ligand binds with the other NH_3^+ is *ca.* 5:1 at room temperature in CD_3CN/CD_2Cl_2, indicating a significant preference of the host molecule for one of the enantiomeric conformers of A_2cH. For A_2cP this ratio is *ca.* 2.5:1.[91]

IV. Dimethoxyphenyl-Containing Macrocycles

Sawada and co-workers examined chiral recognition toward a series of organic ammonium cations with dimethoxyphenyl-containing macrocycles by a FAB/MS procedure.[39,60,93−99] Two methodologies, i.e., enantiomer-labeled guest (EL) and relative peak intensity (RPI), were used in their studies. Both methods used the peak intensity ratios of two diastereomeric host−guest complex ions, I_R/I_{S-d_3} and $RPI_{(R)}/RPI_{(S)}$, to evaluate the extent of chiral recognition. It has been demonstrated that the enantioselective results obtained by these methods are reasonably correlated with the relative thermodynamic stabilities for the corresponding host−guest complexation in solution.[94,98] The more the values of I_R/I_{S-d_3} and $RPI_{(R)}/RPI_{(S)}$ deviate from unity, the higher the degree of chiral recognition. On the other hand, I_R/I_{S-d_3} and $RPI_{(R)}/RPI_{(S)}$ values of 1.0 ± 0.1 indicate nonenantioselectivity. Enantiomeric recognition data indicated by I_R/I_{S-d_3} and $RPI_{(R)}/RPI_{(S)}$ are summarized in Tables 3 and 4, respectively, and equilibrium constants for the interactions of some dimethoxyphenyl macrocycles with several ammonium cations in solutions are listed in Table 5.

Among the six dimethoxyphenyl-containing macrocycles, the chiral recognition ability for most ammonium guests studied has the sequence **35** > **3** > **34** > **36** > **37** ∼ **2** (Chart 5). Ligand (*R*,*R*,*R*,*R*)-**35** shows excellent enantiomeric recognition toward most ammonium cations (Table 3). The ammonium

Table 3. Chiral Recognition Data Indicated by (I_R/I_{S-d_3}) Values[a] Determined by FAB/MS[b]

	ligand					
cation	(*S*,*S*,*S*,*S*)-**2**	(*R*,*R*,*R*,*R*)-**3**	(*S*,*S*)-**34**	(*R*,*R*,*R*,*R*)-**35**	(*S*,*S*,*S*,*S*)-**36**	(*S*,*S*)-**37**
Am**2**	ca. 0.8	1.98	1.40	1.16	1.12	0.81
Am**5**		1.58		4.00	1.59	
Am**7**	ca. 0.8	1.90	1.60	4.37	1.03	0.83
Am**8**		1.53		3.49	1.35	
Am**9**		2.69		5.03	1.14	
Am**10**		2.07		3.62	1.12	
Am**11**		2.77		ND	1.12	
Am**12**		0.89		0.65	1.02	
Am**13**		2.25		5.03	1.04	
Am**14**		1.67		3.66	1.16	
Am**15**		1.71		5.44	1.33	
Am**16**	ca. 0.8	1.57	1.60	5.35	1.50	0.80
Am**17**		1.27		3.16	1.39	

[a] The values were corrected by the natural abundance of the corresponding (M + 3) isotope. ND means that the cation−macrocycle complex ion peaks were not detected. [b] From ref 98.

Table 4. Chiral Recognition Data Indicated by ($RPI_{(R)}/RPI_{(S)}$) Values Determined by FAB/MS

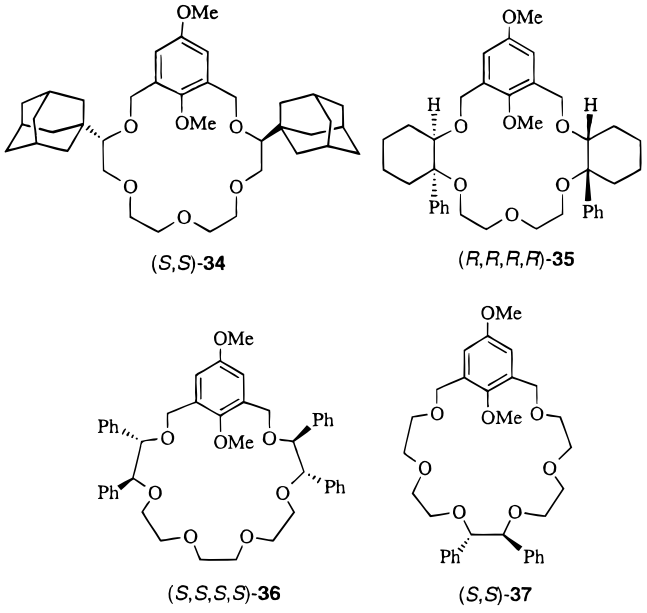
	ligand					
cation	(*S*,*S*,*S*,*S*)-**2**	(*R*,*R*,*R*,*R*)-**3**	(*S*,*S*)-**34**	(*R*,*R*,*R*,*R*)-**36**	(*S*,*S*)-**37**	ref
Am**1**		1.2		1.0	1.2	93, 94
Am**2**	ca. 0.8	1.90, 1.6	1.33	1.05	0.78	60, 95
Am**3**					1.1	94
Am**7**		1.6, 1.90	1.50	1.1, 0.98	0.9, 0.81	60, 94
Am**16**		1.56	1.47	1.36	0.76	60
Am**18**					1.0	93

Table 5. Chiral Recognition Data Indicated by Δ(log *K*) Values[a] for Ammonium Cations with Dimethoxyphenyl- and Triazole-Containing Macrocycles

ligand	cation	log *K*	Δ(log *K*)	solvent[b]	ref
(*R*,*R*,*R*,*R*)-**3**	(*R*)-Am**1**	1.52		aceton-d_6	94
	(*S*)-Am**1**	1.22	0.30	aceton-d_6	94
	(*R*)-Am**2**	0.30		10M/1C	98
	(*S*)-Am**2**	0	0.30	10M/1C	98
(*S*,*S*)-**34**	(*R*)-Am**16**	2.20		C	96, 98
	(*S*)-Am**16**	2.08	0.12	C	96, 98
(*R*,*R*,*R*,*R*)-**35**	(*R*)-Am**16**	1.90		10M/1C	98
	(*S*)-Am**16**	1.20	0.70	10M/1C	98
(*S*,*S*)-**38**	(*R*)-Am**1**	2.70		C	101
	(*S*)-Am**1**	*c*		C	101
(*S*,*S*)-**39**	(*R*)-Am**1**	2.32		C	101
	(*S*)-Am**1**	*c*		C	101
	(*R*)-Am**3**	2.22		C	101
	(*S*)-Am**3**	1.75	0.47	C	101
(*S*,*S*)-**40**	(*R*)-Am**1**	2.91		C	101
	(*S*)-Am**1**	2.38	0.53	C	101
	(*R*)-Am**3**	2.67		C	101
	(*S*)-Am**3**	2.21	0.46	C	101

[a] Values were determined by ^{1}H NMR titration at 25 °C (for **3**, **34**, and **35**) and 21 °C (for **38**-**40**). $\Delta(\log K) = |\log K_{(R)} - \log K_{(S)}|$. [b] See note *c* of Table 1. [c] The Am**1** signal shift upon complexation was too small to allow accurate curve fitting.

Chart 5. Macrocycles 34−37



guests studied, expressed as RCH(COOMe)NH_3^+, can be classified into the following four categories according to their chiral recognition behavior with (*R*,*R*,*R*,*R*)-**35**:[98] (1) a high degree of (*R*)-enantiomer preference (I_R/I_S = 3.2−5.4) when R is a primary or secondary alkyl group (Am**5**, Am**7**−Am**10**, and Am**13**−Am**17**); (2) a low degree of (*S*)-enantiomer preference (I_R/I_S = 0.65) when the guest is a secondary ammonium ion (Am**12**); (3) almost no enantioselectivity (I_R/I_S = 1.16) when R is a phenyl group (Am**2**); and (4) almost no complexation when R is a tertiary alkyl group (Am**11**).

Compared with **35**, **3** shows a different structure-dependent pattern: (1) a moderate degree of (*R*)-enantiomer preference (I_R/I_S = 1.5−2.8) for primary ammonium cations (Am**2**, Am**5**, Am**7**−Am**11**, and Am**13**−Am**16**) and (2) almost no enantiomer preference (I_R/I_S = 0.9) for a secondary ammonium ion (Am**12**). The higher degree of enantioselectivity for ammonium guests by **35** than by **3** probably results from two factors. First, the presence of two cyclohexyl groups in **35** causes **35** to be more rigid than **3**. Second, the four phenyl groups attached to the chiral centers of **3** cause it to be less sterically complementary with the guest ammonium cations than **35**, which has only two chiral phenyl groups.

Although **34** has two bulky adamantyl groups as its chiral barriers, it shows lower degrees of enantiomeric recognition toward Am**7** and Am**16** than does **35** (Table 3) and toward Am**2** and Am**7** than does **3** (Tables 3 and 4). The high conformational flexibility of **34** is probably a reason for the low extent of chiral recognition by this ligand. Less-complementary structures of **2**, **36**, and **37** with the ammonium guests could be the main reason that these macrocyclic receptors show a low degree of or no chiral recognition. Ligands **36** and **37** have one more ethyleneoxy unit in their macroring and **2** has a missing ethyleneoxy unit. Also, positions of the chiral centers of **37** are apparently too remote from the dimethoxyphenyl group to be effective in causing chiral recognition.

Binding constants for the interactions of the chiral macrocycles with ammonium enantiomers in homogeneous solutions gives the same results of enantiomeric recognition as those obtained by the FAB/MS method. The degree of enantiomeric recognition of Am**16** by (*R*,*R*,*R*,*R*)-**35** [Δ(log *K*) = 0.70, Table 5] is much higher than that by (*S*,*S*)-**34** [Δ(log *K*) = 0.12]. Ligand (*R*,*R*,*R*,*R*)-**3**, on the other hand, exhibits the Δ(log *K*) value of 0.30 for both enantiomer pairs of Am**1** and Am**2** in acetone-d_6 and 10:1 $CD_3OD/CDCl_3$, respectively.[94] All three chiral receptors bind the (*R*) forms of the enantiomers of the guests in preference to the (*S*) forms.

Sawada and co-workers recently demonstrated good enantiomeric recognition of Am**7**, Am**9**, and Am**16** by macrocyclic receptors **3** and **35** in MeOH and other solutions using electrospray ionization mass spectrometry.[99] The peak intensity ratios of the diastereomeric host−guest complex ions were found to be 1.1−1.9. It is believed that the primary binding forces between dimethoxyphenyl-containing macrocycles and guest ammonium cations are intermolecular hydrogen bonding and charge−dipole interaction between RNH_3^+ and the host oxygen atoms.[98] The secondary binding interaction is expected to be of the π-acid and π-base type between the COOR group of the ammonium guest and the dimethoxyphenyl group of the macrocycle. As seen in Table 3, chiral recognition abilities of **3** and **35** toward Am**14**, which has a larger and more branching $CH(CH_3)_2$ group, drop to about 70% when compared with those toward ammonium guest Am**13**. This decrease in extent of chiral recognition could be attributed to a less effective $\pi-\pi$ interaction due to the large alkyl group of Am**14**.[98]

V. Triazole-Containing Macrocycles

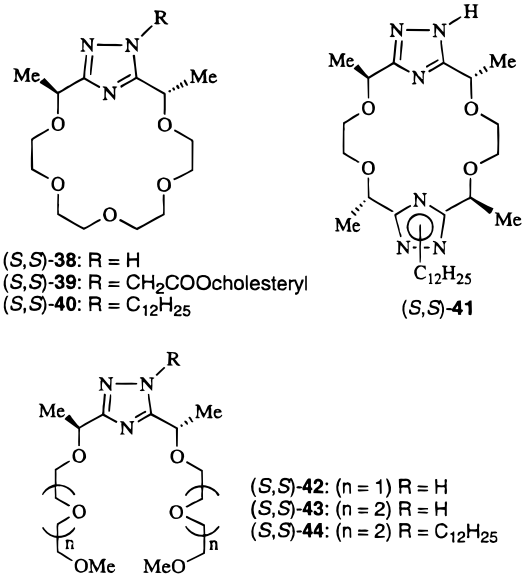
The chiral recognition behavior of a triazole-containing macrocycle for enantiomers of Am**1** was reported by Bradshaw and his co-workers in 1985.[100] Later, Echegoyen, de Mendoza, and their co-workers

Table 6. Enantioselective Data Studied by Bulk and Supported Liquid Membrane Transport and Solvent Extraction for Racemic Ammonium Salts with Triazole-Containing Macrocycles and Podands

ligand	cation	method[a]	time (h)	major enantiomer	enantiomeric excess (%)	ref
(*S*,*S*)-**38**	Am**1**	BLM	5	*R*	25	102
	Am**2**	BLM	26	*S*	24	102
(*S*,*S*)-**40**	Am**1**	BLM	3	*R*	9	102
	Am**2**	BLM	3.3	*S*	23	102
	Am**1**	SLM	24	*R*	26	103
	Am**1**	SE		*R*	32	103
	Am**2**	SE		*S*	26	103
	Am**3**	SE		*R*	17	103
	Am**7**	SE		*S*	15	103
	Am**8**	SE		*S*	16	103
(*S*,*S*)-**41**	Am**1**	SLM	24	*R*	12	103
	Am**1**	SE		*R*	11	103
(*S*,*S*)-**42**	Am**1**	BLM	5.5	*R*	15	102
	Am**2**	BLM	26	*S*	11	102
(*S*,*S*)-**43**	Am**1**	BLM	5.5	*R*	14	102
	Am**2**	BLM	23.5	*S*	13	102
(*S*,*S*)-**44**	Am**1**	BLM	5.5	*R*	12	102
	Am**1**	SLM	24	*R*	6	103
	Am**2**	BLM	23	*S*	11	102
	Am**1**	SE		*R*	7	103
	Am**2**	SE		*S*	13	103

[a] BLM = bulk liquid membrane; SLM = supported liquid membrane; SE = solvent extraction.

Chart 6. Macrocycles and Podands 38−44



synthesized several new triazole-containing macrocycles and podands and studied their chiral recognition properties (Tables 5 and 6).[101−104] As seen in Tables 5 and 6, chiral ligand **40** (Chart 6) shows a higher degree of enantiomeric recognition toward Am**1** than toward Am**3**, probably due to the large naphthyl group of Am**1**. The values of Δ(log *K*) and ee (enantiomeric excess) for **40**−Am**1** systems are 0.53 (Table 5) and 32% (Table 6, solvent extraction result), respectively, while those for **40**−Am**3** systems are 0.46 and 17%, respectively. Receptor **39** displays the same degree of chiral recognition toward Am**3** (Δ(log *K*) = 0.47) as **40** (Δ(log *K*) = 0.46), indicating that the substituents of the triazole ring have little effect on chiral recognition.

Studies on liquid membrane transport indicate that **38** shows better enantioselectivity for Am**1** (25% ee) than either **40** (9% ee) or **41** (12% ee). Both **38** and **40** show good enantioselectivity for Am**2** (24% and 23% ee values, respectively). The low enantioselectivity ability of **41** is probably due to a low degree of steric complementarity. An extra triazole group of **41** may prevent an optimal three-dimensional arrangement of the donor sites for binding of the host ammonium cations.

On the whole, all triazole-containing podands and macrocycles studied exhibited moderate enantiomeric recognition toward several racemic ammonium salts. The better results were observed for the more preorganized macrocyclic receptors **38** and **40**. The open-chain receptors **42**−**44** that are conformationally flexible generally showed a lower extent of enantioselectivity than the macrocyclic ligands.

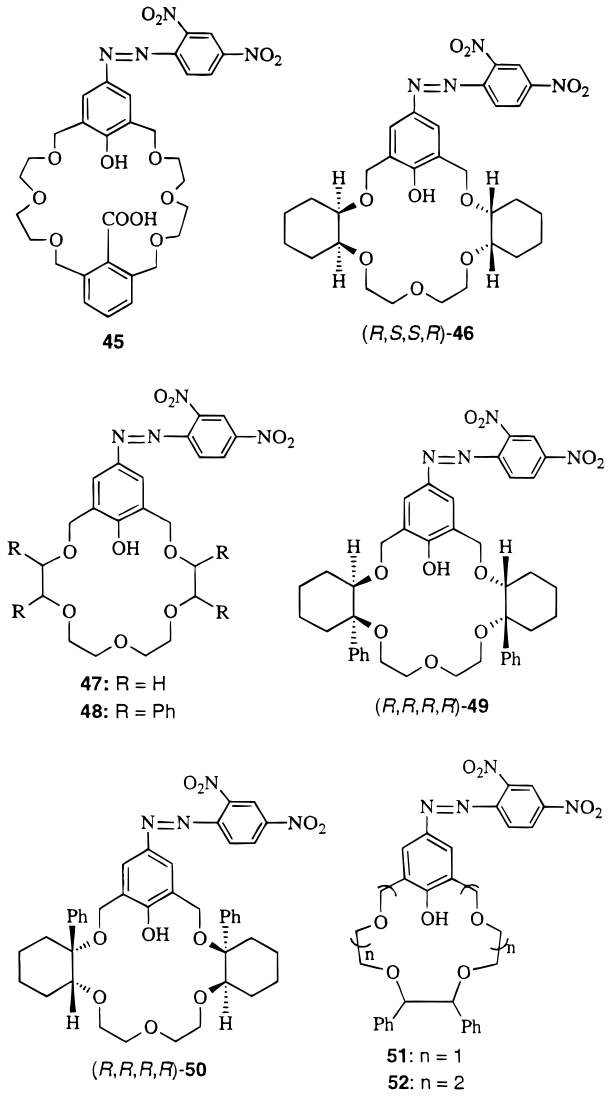
As shown in Table 5, **40** exhibits stronger binding (larger log *K* values) toward Am**1** and Am**3** cations than either **38** or **39**. It has been rationalized that the triazolo hydrogen of **38** and bulk cholesteryl chain of **39** reduce the cation binding abilities of the macrocyclic ligands.[101] In the case of **40**, the Am**3** complexes are less stable than the corresponding Am**1** complexes (Table 5). The stronger binding of the Am**1** complexes is due to an increased $\pi-\pi$ interaction caused by the larger aromatic groups of the guests.[101]

VI. Azophenol-Containing Macrocycles

Naemura, Kaneda, and their co-workers synthesized a series of azophenol-containing macrocycles (**14, 15, 45-52**, Chart 7).[72,105−116] These ligands have an interesting property of color change on complexation.[33,105−107] As the macrocycles interact with some neutral amines, tripod hydrogen bonding forms through the interaction of an amine with the phenol group and two macroring oxygen atoms of the ligand resulting in the change from phenol to phenolate. Since the phenol proton is transferred to the amine, a salt complex is formed from the neutral macrocycle and neutral amine. The resulting phenolate, together with a 2,4-dinitrophenylazo group attached, causes a synchronous coloration. It has been pointed out that not only is the 2,4-dinitrophenylazo group at the *para* position of the phenol moiety an effective chromophore but it also increases the acidity of the phenolic OH group and thereby increases its bonding ability toward neutral amines.[113,116] Macrocycles **45** and **46** show absorption maxima at 400 and 408 nm in $CHCl_3$, respectively.[105,110] When **45** and **46** form complexes with amines, large red shifts of their UV−visible spectra can be observed. The λ_{max} of **45** at 400 nm is shifted to 531−568 nm in the **45**−piperazine complex[105] and that of **46** at 408 nm is shifted to 557−588 nm in **46**−amine complexes.[110]

Formation of the salt complexes was confirmed by X-ray crystal analysis. In both **45**−piperazine[105] and **47**−piperidine[107] complexes, strong $N^+-H\cdots O^-$ hydrogen bonds are formed between the phenolic oxygen atoms of **45** and **47** and the nitrogen atoms of the piperazine and piperidine guests. Both **45** and **47** are in their anionic form and the amines are protonated upon formation of the complexes. Since the reactants (amine and macrocycle) are both neu-

Chart 7. Macrocycles 45−52



tral but the complex is a salt in nature, these acidic azophenol-containing ligands can be considered as "saltex" (salt complex) precursors.

A. Enantioselective Coloration

Interaction of an enantiomeric pair of azophenol-containing macrocycles with a chiral amine usually results in different shifts of the UV−visible spectra. Thus, chiral azophenolic macrocycles display enantioselective coloration changes upon complexation with guest enantiomers. Significant differences (more than 10 nm[106,115]) in λ_{max} values between diastereomeric complexes ($\Delta\lambda_{max}$) have been observed for several chiral amine−macrocycle systems.[72,106,108,110,112,113,115]

The differential complexation of enantiomers with chiral azophenol ligands was examined either by the interaction of an (*S*)- or (*R*)-amine (not both) with an enantiomeric pair of the ligands (**46**, **49**, and **50**) or by the interaction of a chiral macrocycle (**53**−**64**) with (*S*)- and (*R*)-amines using a UV−visible or ^{1}H NMR spectroscopic method. Enantiomeric recognition data indicated by $\Delta(\log K)$ and $\Delta\lambda_{max}$ values are summarized in Table 7. In many cases, significantly

Chart 8. Amine Compounds: Am19−Am26

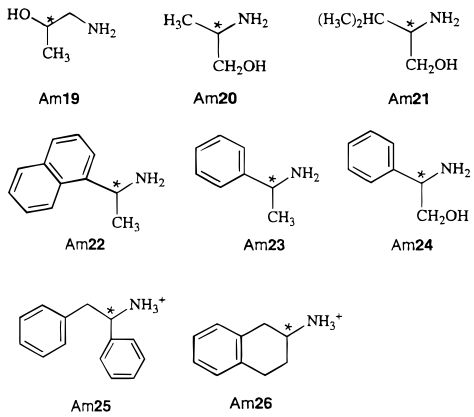
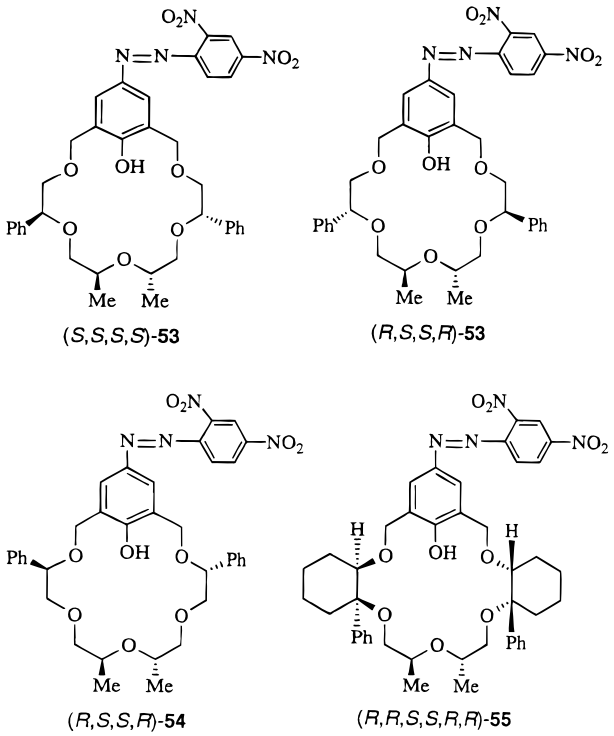


Chart 9. Macrocycles 53−55



different stabilities are observed for diastereomeric amine−macrocycle complexes [$\Delta(\log K)$ values > 0.5]. Receptors (*S*,*S*,*S*,*S*)- and (*R*,*S*,*S*,*R*)-**53** show an excellent recognition toward Am**20**, Am**21**, and Am**24** (Chart 8). Values of $\Delta(\log K)$ and $\Delta\lambda_{max}$ for (*S*,*S*,*S*,*S*)-**53**−Am**24** system are 1.07 and 9 nm, respectively. The largest $\Delta\lambda_{max}$ values (14 nm) are observed for the Am**24** interaction with (*R*,*S*,*S*,*R*)-**53** and (*R*,*S*,*S*,*R*)-**54** (Chart 9). Significant differences in enantioselective coloration are also noted for Am**22**−**49** ($\Delta\lambda_{max}$ = 10 nm in EtOH), Am**23**−**46** ($\Delta\lambda_{max}$ = 8 nm), and **53**−Am**20** ($\Delta\lambda_{max}$ = 12 nm) systems (Table 7).

If a pair of amine−macrocycle interactions has a large $\Delta(\log K)$ value, on the whole, they show a large $\Delta\lambda_{max}$ value. Several of the amine−macrocycle interactions in Table 7 have near-zero $\Delta(\log K)$ values. In these cases the $\Delta\lambda_{max}$ values are generally small. However, a linear relationship between the $\Delta(\log K)$ and $\Delta\lambda_{max}$ values has not been observed, since in some cases a large $\Delta(\log K)$ does not correspond to a large $\Delta\lambda_{max}$ value (see Table 7).

Table 7. Chiral Recognition Data[a] for Azophenol-Containing Macrocycles (46−60) and Analogues (61−65) in $CHCl_3$ or in $CDCl_3$ (except as indicated) at 25 °C

amine (ligand)	ligand (amine)	log *K*	Δ(log *K*)	λ_{max}	$\Delta\lambda_{max}$	λ_{max}[b]	$\Delta\lambda_{max}$[b]	ref
(*S*)-Am**19**	(*R*,*S*,*S*,*R*)-**46**	2.26		569				110
	(*S*,*R*,*R*,*S*)-**46**	2.27	0.01	567	2			110
	(*R*,*R*,*R*,*R*)-**49**	2.29		583		570		108, 113
	(*S*,*S*,*S*,*S*)-**49**	2.43	0.14	577	6	565	5	108, 113
	(*R*,*R*,*R*,*R*)-**50**	2.77		589				113
	(*S*,*S*,*S*,*S*)-**50**	2.70	0.07	588	1			113
(*S*)-Am**20**	(*R*,*S*,*S*,*R*)-**46**	2.18		562				110
	(*S*,*R*,*R*,*S*)-**46**	1.97	0.21	558	4			110
	(*R*,*R*,*R*,*R*)-**49**	1.89		577		575		108, 113
	(*S*,*S*,*S*,*S*)-**49**	1.95	0.06	578	1	573	2	108, 113
	(*R*,*R*,*R*,*R*)-**50**	2.10		583				113
	(*S*,*S*,*S*,*S*)-**50**	1.95	0.15	585	2			113
(*S*)-Am**21**	(*R*,*S*,*S*,*R*)-**46**	1.59		572				110
	(*S*,*R*,*R*,*S*)-**46**	1.42	0.17	572	0			110
	(*R*,*R*,*R*,*R*)-**49**	1.27		574		575		108, 113
	(*S*,*S*,*S*,*S*)-**49**	1.29	0.02	574	0	575	0	108, 113
	(*R*,*R*,*R*,*R*)-**50**	0.99		579				113
	(*S*,*S*,*S*,*S*)-**50**	1.05	0.06	580	1			113
(*S*)-Am**22**	(*R*,*S*,*S*,*R*)-**46**	0.96		564				110
	(*S*,*R*,*R*,*S*)-**46**	1.18	0.22	560	4			110
	(*R*,*R*,*R*,*R*)-**49**	0.63		586				113
	(*S*,*S*,*S*,*S*)-**49**	0.92	0.29	584	2			113
	(*R*,*R*,*R*,*R*)-**50**	0.89		595				113
	(*S*,*S*,*S*,*S*)-**50**	0.75	0.12	598	3			113
(*R*)-Am**22**	(*R*,*R*,*R*,*R*)-**49**	0.92		584		561		108
	(*S*,*S*,*S*,*S*)-**49**	0.63	0.29	586	2	571	10	108
(*S*)-Am**23**	(*R*,*S*,*S*,*R*)-**46**	1.17		566				110
	(*S*,*R*,*R*,*S*)-**46**	1.38	0.21	558	8			110
	(*R*,*R*,*R*,*R*)-**49**	0.72		588		571		108, 113
	(*S*,*S*,*S*,*S*)-**49**	1.05	0.33	585	3	564	7	108, 113
	(*R*,*R*,*R*,*R*)-**50**	1.27		599				113
	(*S*,*S*,*S*,*S*)-**50**	1.00	0.27	597	2			113
(*S*)-Am**24**	(*R*,*S*,*S*,*R*)-**46**	1.52		557				110
	(*S*,*R*,*R*,*S*)-**46**	1.04	0.48	558	1			110
(*S*,*S*,*S*,*S*)-**53**	(*R*)-Am**19**	3.77		560				115
	(*S*)-Am**19**	3.41	0.36	564	4			115
	(*R*)-Am**20**	3.98		558				115
	(*S*)-Am**20**	3.19	0.79	570	12			115
	(*R*)-Am**21**	3.20		564				115
	(*S*)-Am**21**	2.49	0.71	569	5			115
	(*R*)-Am**24**	3.68		558				115
	(*S*)-Am**24**	2.61	1.07	567	9			115
(*R*,*S*,*S*,*R*)-**53**	(*R*)-Am**19**	3.18		565				115
	(*S*)-Am**19**	3.49	0.31	562	3			115
	(*R*)-Am**20**	3.23		565				115
	(*S*)-Am**20**	3.67	0.44	562	3			115
	(*R*)-Am**21**	2.34		567				115
	(*S*)-Am**21**	2.98	0.64	566	1			115
	(*R*)-Am**24**	3.67		573				115
	(*S*)-Am**24**	3.44	0.77	559	14			115
(*S*,*S*,*S*,*S*)-**54**	(*R*)-Am**19**	3.60		565				115
	(*S*)-Am**19**	3.23	0.37	563	2			115
	(*R*)-Am**20**	3.67		561				115
	(*S*)-Am**20**	3.44	0.23	565	4			115
	(*R*)-Am**21**	2.94		569				115
	(*S*)-Am**21**	2.86	0.08	566	3			115
	(*R*)-Am**24**	3.10		564				115
	(*S*)-Am**24**	2.61	0.49	561	3			115
(*R*,*S*,*S*,*R*)-**54**	(*R*)-Am**19**	2.78		564				115
	(*S*)-Am**19**	3.15	0.37	559	5			115
	(*R*)-Am**20**	2.96		563				115
	(*S*)-Am**20**	3.22	0.26	560	3			115
	(*R*)-Am**21**	2.29		563				115
	(*S*)-Am**21**	2.51	0.22	564	1			115
	(*R*)-Am**24**	2.43		574				115
	(*S*)-Am**24**	2.62	0.19	560	14			115
(*R*,*R*,*S*,*S*,*R*,*R*)-**55**	(*R*)-Am**19**	1.77		582				112
	(*S*)-Am**19**	1.68	0.09	588	6			112
	(*R*)-Am**20**	0.98		582				112
	(*S*)-Am**20**	1.29	0.31	580	2			112
(*S*,*S*)-**56**[c]	(*R*)-Am**19**	4.11						114
	(*S*)-Am**19**	3.43	0.68					114
	(*R*)-Am**20**	4.38						114
	(*S*)-Am**20**	3.83	0.55					114

Table 7 (Continued)

amine (ligand)	ligand (amine)	log *K*	Δ(log *K*)	λ_{max}	$\Delta\lambda_{max}$	λ_{max}[b]	$\Delta\lambda_{max}$[b]	ref
(*S*,*S*)-**57**	(*R*)-Am**19**	4.92						114
	(*S*)-Am**19**	4.49	0.43					114
	(*R*)-Am**20**	4.54						114
	(*S*)-Am**20**	3.88	0.66					114
(*S*,*S*)-**58**	(*R*)-Am**19**	3.72						114
	(*S*)-Am**19**	3.49	0.23					114
	(*R*)-Am**20**	3.85						114
	(*S*)-Am**20**	3.49	0.36					114
(*R*,*R*)-**59**[c]	(*R*)-Am**19**	3.54						114
	(*S*)-Am**19**	3.66	0.12					114
	(*R*)-Am**20**	4.88						114
	(*S*)-Am**20**	4.11	0.77					114
(*S*,*S*)-**60**	(*R*)-Am**19**	3.89						116
	(*S*)-Am**19**	3.34	0.55					116
	(*R*)-Am**20**	3.92						116
	(*S*)-Am**20**	3.41	0.51					116
(*S*,*S*)-**61**	(*R*)-Am**19**	3.73						116
	(*S*)-Am**19**	3.30	0.43					116
	(*R*)-Am**20**	3.87						116
	(*S*)-Am**20**	3.32	0.55					116
(*S*,*S*)-**62**	(*R*)-Am**19**	2.79						116
	(*S*)-Am**19**	2.49	0.30					116
	(*R*)-Am**20**	2.94						116
	(*S*)-Am**20**	2.38	0.56					116
(*S*,*S*)-**63**	(*R*)-Am**19**	1.23						116
	(*S*)-Am**19**	0.94	0.29					116
	(*R*)-Am**20**	1.52						116
	(*S*)-Am**20**	0.88	0.64					116
(*S*,*S*)-**64**	(*R*)-Am**19**	0.59						116
	(*S*)-Am**19**	0.49	0.10					116
	(*R*)-Am**20**	0.70						116
	(*S*)-Am**20**	*d*						116
(*S*,*S*)-**65**	(*R*)-Am**19**	*d*						116
	(*S*)-Am**19**	*d*						116
	(*R*)-Am**20**	*d*						116
	(*S*)-Am**20**	*d*						116

[a] The Δ(log *K*) value is the difference between log *K* values for the interactions of an enantiomer pair of the macrocycles with a given amine or of an enantiomer pair of amines with a given macrocycle. Similarly, the $\Delta\lambda_{max}$ value (in nm) is the difference between λ_{max} values (in nm) for the interactions of an enantiomer pair of the macrocycles with a given amine or of an enantiomer pair of amines with a given macrocycle. [b] In EtOH. [c] At −40 °C. [d] The log *K* value was too small to be accurately determined.

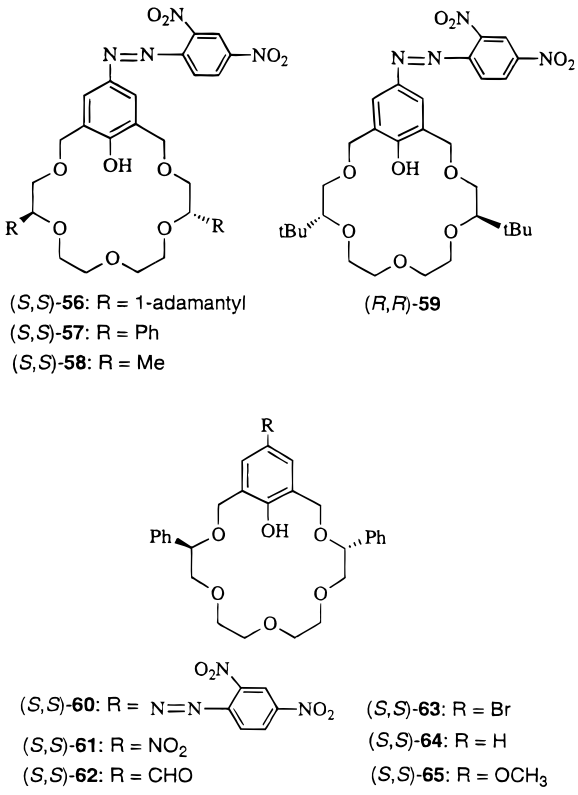
B. Structural Effects on Enantiomeric Recognition

Am**19** and Am**20** are structural isomers with the chiral centers occupying different positions. No enantioselectivity is observed for the **46**−Am**19** interaction]Δ(log *K*) = 0.01], but the **46**−Am**20** complexes show a moderate degree of chiral differentiation]Δ(log *K*) = 0.21]. Ligands **53**, **55**, and **57**−**59** (Chart 10) display larger Δ(log *K*) values for the interactions with Am**20** than with Am**19**. This difference is due to structural complementarity. CPK models showed that in either the (*R*,*S*,*S*,*R*)-**46**−(*S*)-Am**19** or the (*S*,*R*,*R*,*S*)-**46**-(*S*)−Am**19** complex significant steric interactions were not found between the chiral barriers of the amine and the macrocyclic ligands.[110] The cyclohexane moiety of **46** did not function as an effective chiral barrier in complexation with 1-substituted 2-aminoethanol (Am**19**). However, in the case of complexation with 2-substituted 2-aminoethanols (Am**20**, Am**21**, and Am**24**), **46** exhibited enantioselectivity due to an effective steric repulsion between the chiral barriers, as shown by CPK molecular models.[110] Ligand **49** has a phenyl group attached to the cyclohexane ring. The enantioselective behavior of **49** is different from that of **46**. The moderate differences in stabilities of diastereomeric complexes of **49** with Am**19**, Am**22**, and Am**23** [Δ(log *K*) values 0.14−0.33] are observed but the diastereomeric complexes of **49** with Am**20** and Am**21** have almost the same stabilities (Table 7).[108,113]

Macrocycle **50** is a structural isomer of **49**. As compared with **49**, **50** has a different placement of the phenyl barriers with respect to the phenolate binding site. The log *K* values in Table 7 show that **49** and **50** demonstrate a reversal of enantioselectivity in complexation with amines. For example, (*S*)-Am**23** forms a more stable complex with (*S*,*S*,*S*,*S*)-**49** than with (*R*,*R*,*R*,*R*)-**49**, but the same amine forms a more stable complex with (*R*,*R*,*R*,*R*)-**50** than with (*S*,*S*,*S*,*S*)-**50**.

The structures of chiral azophenol-containing macrocycles have an effect on the extent of enantiomeric amine-selective coloration. Among three chiral ligands (**48**, **51**, and **52**), **48** showed a higher degree of enantioselective coloration for Am**23**.[106] The differences in the absorption maxima of the visible spectra between diastereomeric complexes of Am**23** with the enantiomeric pair of **48** were larger than those with enantiomeric pairs of either **51** or **52**, indicating that the 18-membered-ring **48** had a better recognition for Am**23** than did the 15-membered-ring **51** and 21-membered-ring **52**. In the cases of the other amines studied, however, **48** did not show significantly larger $\Delta\lambda_{max}$ values than **51** and **52**.[106]

Chart 10. Macrocycles 56−65



As seen in Table 7, Δ(log *K*) values for the interaction of **53** with Am**20**, Am**21**, and Am**24** are larger than those for **54**, indicating that arrangement of chiral barriers on the macroring affects enantioselectivity. Location of the phenyl barriers near the diethylene glycol bridge in ligand **53** results in higher degrees of enantiomeric recognition than is the case when those barriers are located near the phenol moiety, as in ligand **54**.[115]

C. Effect of Temperature

Enantioselectivity of Am**19** and Am**20** by macrocyclic receptors **56**−**59** in chloroform solution was examined at different temperatures (−40 to 30 °C).[114] All log *K* values increased with decreasing temperature, and in most cases the enantioselectivities increased also with decreasing temperature. As temperature deceased from 45 to 15 °C, for example, the Δ(log *K*) values for the interactions of Am**19** and Am**20** enantiomers with receptors **57** and **58** increased from 0.29 to 0.43 (**57**−Am**19**), 0.47 to 0.78 (**57**−Am**20**), 0.16 to 0.26 (**58**−Am**19**), and 0.29 to 0.44 (**58**−Am**20**). Ligand (*S*,*S*)-**56** exhibited also an increased degree of enantiomeric recognition toward Am**19** with a decrease in temperature from 30 to −40 °C. It was interesting that the temperature dependent reversal of the enantioselectivity was found in the complexation of (*S*,*S*)-**56** with Am**20**. Receptor (*S*,*S*)-**56** recognized (*R*)-Am**20** at −40 °C over the (*S*)-Am**20** (Table 7), but it recognized (*S*)-Am**20** over (*R*)-Am**20** at 30 °C with a Δ(log *K*) value of 0.19. Ligand (*R*,*R*)-**59** showed higher Δlog *K* values for complexation with (*R*)- and (*S*)-Am**20** at −40 °C (0.77) and at 30 °C (0.14) than at 0 °C.[114]

Table 8. Differential Transport of Racemic Ammonium Salts through Bulk $H_2O/CHCl_3$ Liquid Membranes Containing Chiral Macrocycles and Dipodands Incorporated with Small Cyclic Subunits at 20 °C

ligand	cation	time (h)	transport (%)	dominant enantiomer	optical purity (%)	ref
no	Am**2**	72	1			124
no	Am**25**	10	4			124
(+)-**22**	Am**2**	24	9.3	*R*	8	78, 123
	Am**25**	3	10.8	*S*	24	78, 123
(+)-**66**	Am**2**	180	5.0	*R*	4	124
	Am**25**	10	7.0	*S*	37	124
(+)-**66**[a]	Am**2**	44	11	*R*	6	124
	Am**25**	12	10	*S*	36	124
(−)-**67**	Am**2**	180	5.0	*R*	4	124
	Am**25**	2.2	10	*S*	33	124
(−)-**68**	Am**2**	52	11	*R*	8	124
	Am**25**	1.5	11	*S*	84	124
(−)-**69**	Am**2**	48	11	*R*	3	124
	Am**25**	1.6	10	*S*	30	124
(+)-**70**	Am**2**	8.5	10	*R*	25	124
	Am**25**	2.4	10	*S*	67	124
(+)-**71**	Am**2**	24	11	*R*	11	124
	Am**25**	1.7	10	*S*	80	118, 124
(−)-**72**	Am**2**	70	4.7	*R*	4	119
(−)-**73**	Am**2**	36	10		0	118, 124
	Am**25**	2.5	10	*S*	69	124
(+)-**74**	Am**2**	36	12		0	124
	Am**25**	2.2	10	*S*	32	124
(+)-**75**	Am**2**	4	5.5	*R*	13	119
(−)-**76**	Am**2**	6	18	*R*	19	117
	Am**25**	8	16	*S*	53	117
(−)-**77**	Am**2**	17	10.0	*R*	7	121
	Am**25**	0.5	11.2	*S*	23	121
	Am**26**	2.0	9.5	*R*	10	121
(+)-**78**	Am**2**	3.4	10.0	*R*	15	121
	Am**25**	4.0	10.5	*S*	40	121
	Am**26**	9.0	9.8	*R*	22	121
(−)-**79**	Am**2**	25	9.9	*R*	20	78, 123
	Am**25**	2.5	10.7	*S*	21	78, 123
(−)-**80**	Am**2**	8.5	10.2	*S*	3	125, 126
	Am**25**	3.0	9.3	*S*	38	125, 126
(−)-**81**	Am**2**	6.0	9.9	*S*	14	125, 126
	Am**25**	4.8	9.6	*S*	81	125, 126
(−)-**82**	Am**2**	8.0	10.0	*S*	16	125, 126
	Am**25**	7.3	9.8	*S*	70	125, 126
(−)-**83**	Am**2**	74	10.0	*R*	13	78
	Am**25**	4.8	10.1	*S*	24	78
(+)-**84**	Am**2**	3	3.1	*R*	18	120
	Am**25**	3	10.5	*R*	28	120
	Am**26**	4	8.2	*S*	25	120
(+)-**85**	Am**2**	3	7.3		0	120
	Am**25**	2	9.0	*R*	19	120
	Am**26**	4	12	*S*	31	120
(−)-**86**	Am**2**	11	3.0	*R*	12	120
	Am**25**	2	12.0	*S*	13	120
	Am**26**	4	11.5	*R*	8	120
(−)-**87**	Am**2**	3	3.8		0	120
	Am**25**	2	5.0	*S*	2	120
	Am**26**	3	4.8		0	120
(+)-**88**	Am**2**	4	3.7		0	120
(+)-**89**	Am**2**	42	11	*R*	5	118, 124
	Am**25**	1.5	12	*S*	53	118, 124
(+)-**90**	Am**2**	12	11.0	*R*	16	122
	Am**25**	3	10.1	*S*	46	122
	Am**26**	5	10.3	*R*	25	122

[a] The $CHCl_3$ solution contained (+)-**66** (0.005 M) and 18-crown-6 (0.0005 M).

D. Effect of *para*-Substituents of the Phenol Group

As mentioned above, the *para*-substituents on the phenol (2,4-dinitrophenylazo) increase the acidity of the phenol and thereby increase the bonding ability of the ligand. A recent study shows that, among six

chiral receptors with different *para*-substituents on the phenol group (**60**−**65**), the 2,4-dinitrophenylazo-containing **60** is the most acidic (pK_a = 7.3 in a 1:1 (v:v) dioxane/water solution[116]) and forms the most stable complexes with Am**19**−Am**23** (Table 7).[116]

The different *para*-substituents of the phenol group have an effect on enantioselectivity. As seen in Table 7, the Δ(log *K*) values for the interaction with (*R*)- and (*S*)-Am**19** decrease from macrocycle **60** (0.55) through **61**−**63** to **64** (0.10). However, the same effect is not observed for the interactions of **60**−**64** with other amines studied (Am**20**−Am**23**).[116]

VII. Macrocycles Containing Cyclic Subunits as Chiral Barriers

Naemura and co-workers incorporated various organic cyclic units into macrocycles to form chiral host molecules[78,117−126] and evaluated their chiral recognition properties using a liquid membrane transport procedure for primary ammonium salts. The differential transport data are summarized in Table 8. A chloroform solution of the optically active host molecule separated two aqueous phases. The transport rates of an ammonium salt from one aqueous phase (source phase) to the other one (receiving phase) through the chloroform layer were measured by monitoring the ammonium content in the receiving phase. When the chloroform membrane does not contain any host molecule, as is seen in Table 8, Am**2** and Am**25** (Chart 8) are scarcely transported to the receiving phase (only 1% and 4% transport rates after 3 days and 10 h, respectively).

Chart 11. Macrocycles 66−79

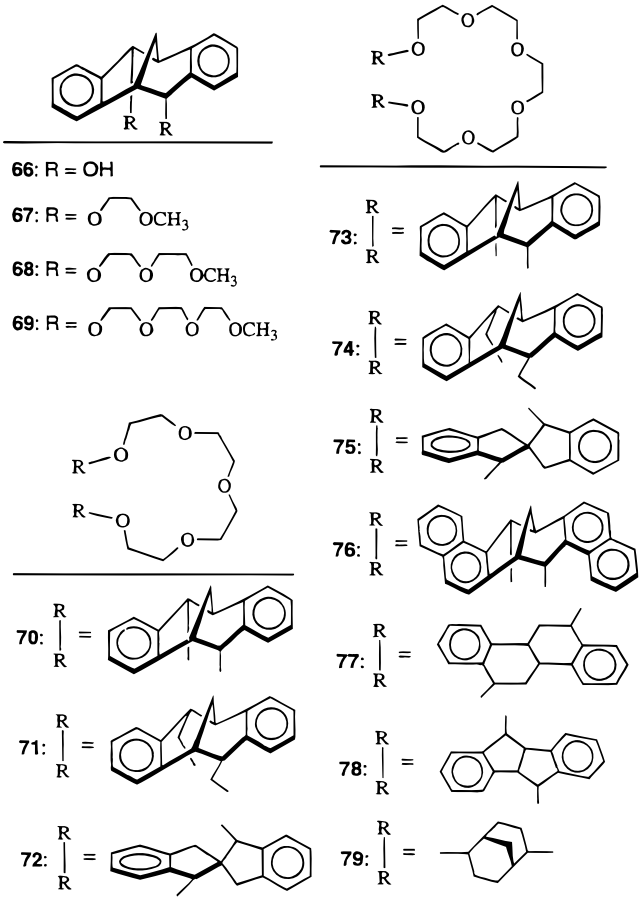
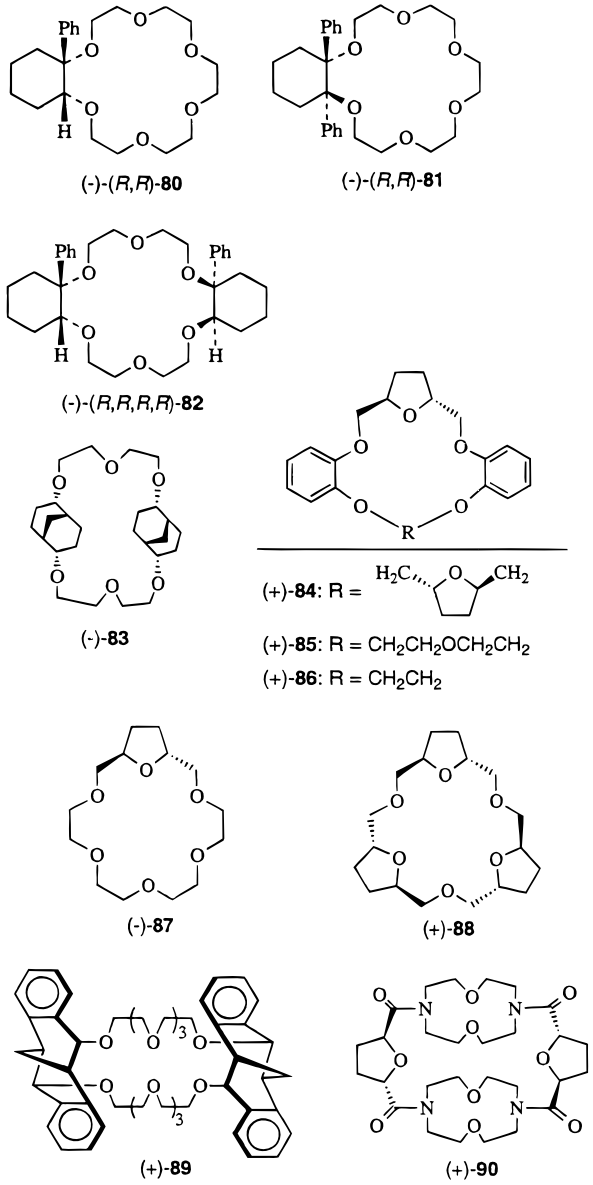


Chart 12. Macrocycles 80−90



Although chiral compound **66** (not a macrocyclic compound) (Chart 11) exhibits enantioselectivity for Am**25** (37% ee value) and Am**2** (4% ee value), its transportability is low (Table 8). When both **66** and a small amount of achiral 18-crown-6 are present in the chloroform layer, the transport rates of Am**2** and Am**25** are enhanced, but the enantioselectivity is hardly changed.[124] On the other hand, in most cases the chiral macrocycles and dipodands (open-chain polyethers) show good differential transport for three ammonium guests studied (Am**2**, Am**25**, and Am**26**). Compounds (−)-**68**, (+)-**70**, (+)-**71**, (−)-**73**, (−)-**76**, (−)-**81**, (−)-**82**, and (+)-**89** display high enantiomeric recognition toward Am**25** with >50% optical purities of the (*S*)-form in the receiving phase. The recognition for Am**2** and Am**26** by these chiral macrocycles is lower than that for Am**25**. Optical purities of ≥20% for Am**2** and/or Am**26** were observed in the cases of (+)-**70**, (+)-**78**, (−)-**79**, (+)-**84**, (+)-**85**, and (+)-**90** (Chart 12**)**.

The enantioselectivity of open-chain dipodands (**67**−**69**) is comparable to that of macrocycles. The same situations were observed in the other

cases.[78,118−120] Among (−)-**67**, (−)-**68**, and (−)-**69**, the highest enantioselectivity is found for (−)-**68**, indicating that in the case of the dipodands listed in Table 8 the 1,4,7-trioxaoctyl group (containing three oxygen atoms) is the best donor side chain subunit for differential transport of the racemic ammonium salts.[124]

A. Size of the Macroring

The size of the macroring has an effect on enantiomeric recognition. Macrocycles **70**−**72** and **73**−**75** have the same chiral barriers but different macroring sizes. The chiral recognition behavior between these two sets of macrocycles is different. The five-oxygen-containing **70** and **71** show enantiomeric recognition better than or the same as (in the case of Am**25**−(+)-**70**) the six-oxygen-containing **73** and **74**. On the other hand, six-oxygen-containing **75** exhibits higher enantioselectivity for Am**2** than does five-oxygen-containing **72**.

B. Structures of Cyclic Subunits

The structures of cyclic subunits affect the extent of enantioselectivity. Macrocycles **73**−**81** have the same macroring but different cyclic subunits. These macrocycles show different extents of enantiomeric recognition. Although both **73** and **74** have the same cyclic subunit and they exhibit good enantioselectivity for Am**25**, the ee value of (−)-**73**−Am**25** (69%) is significantly higher than that of (+)-**74**−Am**25** (32%). In the case of **74**, attachment of the cyclic subunit to the macroring through two methylene groups results in a chiral barrier remote from the macroring, providing a less complementary host structure for the substrate and causing a lower degree of enantiomeric recognition.

In contrast to **75**−**81**, which display enantioselectivity for Am**2**, **73** and **74** cannot discriminate between the enantiomers of Am**2**. This observation indicates that the 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene residue of **73** and **74** is not an effective chiral subunit for Am**2**. It has been noted that a conformationally rigid chiral subunit of these macrocycles enhances enantioselectivity.[121] Ligand **78** shows higher enantioselectivity for all of the substrates studied than does **77** due to the more rigid chiral subunit of **78**.

Because **81** has one more phenyl substituent attached to the chiral centers than does **80** (**81** is of C_2 symmetry but **80** is of C_1 symmetry, as mentioned in section II-E), **81** exhibits better enantiomeric recognition toward Am**2** and Am**25** than the latter. Similarly, **82** also displays higher enantioselectivity than **80**. CPK molecular model examination demonstrates that the phenyl groups of **80**−**82** prefer to take an axial position in the cyclohexane moiety and are fixed nearly vertical to the macroring plane.[125,126] Thus, the phenyl group provides the most effective chiral barrier and neither the axial hydrogen atom nor the cyclohexane moiety acts as such a barrier. Therefore, either **81** or **82** with two phenyl groups shows better enantioselectivity than does the one-phenyl-containing **80**.

C. Structures of Macroring

Macrocycles **84**−**86** containing two catechol residues show enantioselectivity for the three amine compounds studied (Table 8), but **87** and **88** without such moieties do not have the ability to recognize these enantiomers, indicating that the catechol units play an important role in chiral recognition. The degree of enantiomeric recognition by **84**−**88** is generally lower than that by the other macrocycles in Table 8, suggesting that the *trans*−2,5-disubstituted tetrahydrofuran incorporated into the macroring (**84**-**88**) is less effective as a chiral center than the other cyclic subunits mentioned above.

Macrocyclic **89** and macrotricyclic **90** contain two cyclic subunits as their chiral barriers. Both display good enantioselectivity for amine compounds. The cylindrical **90** is of D_2 symmetry and contains two lateral cavities and one central cavity that may bind NH_3^+. The D_2-symmetric receptors, as mentioned in section II, should display good enantiomeric recognition as C_2-symmetric macrocycles. It is suggested that the bound enantiomers interact appreciably with the chiral centers and thus be recognized by macrotricyclic **90**.[122]

VIII. Binaphthyl- and Bitetralyl-Containing Macrocycles

Chiral crown ethers and their enantiomeric recognition behavior were first reported by Cram and coworkers in 1973.[127,128] Ligands (*S*,*S*)-**12** and (*R*,*R*)-**12** were shown to recognize (*R*)-Am**3** and (*S*)-Am**3**, respectively, by EDC (enantiomer distribution constants) values of 1.78 and 1.48 at 0 and 25 °C (a unit EDC value means no chiral recognition).[128,129] Experiments were performed in which the enantiomers of racemic amine salts were distributed between an aqueous inorganic salt solution and an organic solution containing optically pure macrocycle. The EDC is defined by a term of D_A/D_B, where D_A and D_B are the distribution coefficients in the organic phase of the more and of the less complexed enantiomer, respectively.

Many binaphthyl- and bitetralyl-containing macrocycles have been synthesized and their chiral recognition properties studied.[127−151] These macrocycles show enantiomeric recognition toward amine compounds due to asymmetry of the ligands. The bulky and configurationally stable binaphthyl units constitute steric and chiral barriers as ammonium cations form complexes with the macrocycles through tripod hydrogen bonding. The naphthalene planes are perpendicular to the best plane of the oxygen atoms and form walls along the sides of the macrocycle. Thus the space above and below the oxygen planes of **12** and **13**, for example, is divided by the naphthalene walls into two chiral cavities.[69,143] These structural features have been confirmed by X-ray analyses for the crystalline compounds of **12**, **13**, **111**, and/or their complexes.[42,138,147,149] The bitetralyl unit possesses a shape similar to that of the binaphthyl unit.[143] Chiral recognition as indicated by EDC values for binaphthyl- and bitetralyl-containing macrocycles is shown in Table 9.

A. Substituents of Binaphthyl and Bitetralyl Groups

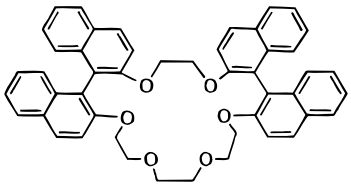
As has been mentioned in section II, an extension of the binaphthyl group by attachment of two methyl groups increases the extent of chiral recognition (compare **12** with **13**). A dramatic increase in chiral recognition provided by attachment of two methyl groups has been observed also for **100**, **101**, and **104** (Chart 13). Compared with **12** and **103**, the methyl-substituted **13**, **100**, **101**, and **104** exhibit much higher degrees of enantiomeric recognition toward Am**2**. From Table 9, the ability of several chiral macrocycles to distinguish between the enantiomers of Am**2** takes the following sequence: **13** ~ **100** > **101** > **104** > **102** > **99** > **103** > **12**. The higher degrees of enantiomeric recognition demonstrated by **13** and **100** compared to those by **101**, **102**, and **104** indicate that incorporation of two methyl groups in the binaphthyl unit has a more important effect on chiral recognition than incorporation of a bitetralyl group into the macrocycles.

Substitution of methyl groups into both binaphthyl barriers (**98**) results in a decrease in chiral recognition. Ligand (*S*,*S*)-**98** has a lower EDC value at −10 °C (1.5) for distribution of racemic Am**16** than (*R*,*R*)-**13** at −5 °C (2.2). A similar situation is observed for **108** and **109** (Chart 14). An extra methyl group on the biphenyl unit of **109** results in a less complementary receptor and causes a decrease in the EDC value for chiral recognition of Am**29** (Chart 15). Substitutions of isopropyl (iPr) groups in the binaphthyl unit (**99**) and of bromines in the tetralin unit (**102** and **105**) diminish the chiral recognition as compared with macrocycles having the methyl substituents (**98**, **101**, and **104**, respectively). Electron-withdrawing (in the case of Br) and greater steric (in the case of iPr) effects appear to be the reasons for diminished chiral recognition.[143] However, the iPr- and bromine-substituted macrocycles (**99**, **105**, and **107**) show still better chiral recognition than the unsubstituted **12**, **103**, and **106**, respectively, due to the extension of the chiral barriers.

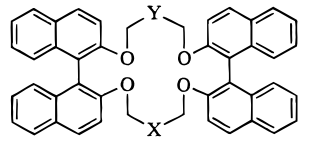
The effect of substituents in the 3,3′-positions of the binaphthyl unit can be seen also for macrocycles **110**−**119**. With an increase in the substituents of **110**−**113** (from H, Me, CH_2OCH_3, to $CH_2OC_6H_5$, successively), the EDC values for Am**9** increase from 1.1 for **110** to 6.6 for **113**. The further increase in the size of the substituents (**114**−**118**) results in a decrease in chiral recognition, probably due to a too large steric repulsion. Among this series of binaphthyl-containing macrocycles (**110**−**119**), **119** shows the highest degree of enantiomeric recognition.

Shinbo and co-workers prepared polymeric membrane electrodes by incorporating (*R*)- or (*S*)-**119** into the sensor membrane and these enantioselective membrane electrodes showed good enantioselectivities for many amino acid methyl esters.[150] The enantioselectivities by these electrodes were generally consistent with the results obtained from the liquid−liquid extraction experiments. The highest enantioselective factor was observed for Am**2**. It has been demonstrated that these enantioselective electrodes can be used to determine the concentrations of each Am**2** enantiomer in a D,L mixture of Am**2** solution.[150]

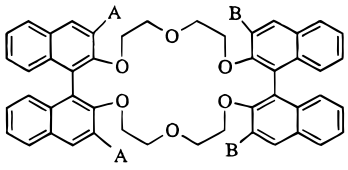
Chart 13. Macrocycles 91−105



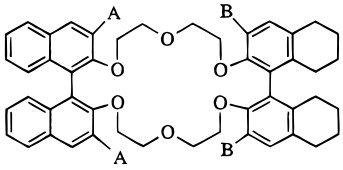
91



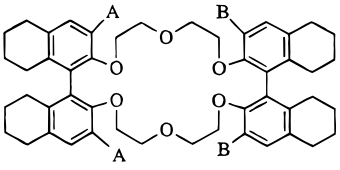
	X	Y
92:	CH_2OCH_2	$CH_2CH_2CH_2$
93:	CH_2OCH_2	
94:	CH_2OCH_2	
95:		
96:		
97:		$CH_2CH_2CH_2$



98: A = B = Me
99: A = iPr, B = H



100: A = Me, B = H
101: A = H, B = Me
102: A = H, B = Br



103: A = B = H
104: A = CH_3, B = H
105: A = B = Br

X-ray crystallographic,[42,138,147,149] ^{1}H NMR spectral,[143,146,148] and CPK molecular model[142,143,146,148] studies indicate that binaphthyl-containing macrocycles form complexes with amine compounds through

Table 9. Enantiomer Distribution Constants (EDC) for Extraction of Racemic Amine Compounds from D_2O Phase into Organic Phase Containing the Macrocyclic Ligands

ligand	cation	org phase[a]	aq phase	T, °C	dominant enantiomer	EDC	ref
(*S*,*S*)-**12**	Am**2**	C	2 M $LiClO_4$	0	S	2.4	143
	Am**2**	C	4 M $LiPF_6$	−10	S	2.8	133, 142
	Am**2**	C	4 M $LiPF_6$	−18	S	3.1	133, 142
	Am**3**	C	1 M F^-	0	—[b]		142
	Am**3**	C	1 M Cl^-	0	—[b]		142
	Am**3**	C	1 M Br^-	0	—[b]		142
	Am**3**	C	2 M PF_6^-	0	R	1.8	142
	Am**3**	C	1 M PF_6^-	0	R	1.9	142
	Am**3**	C	0.5 M PF_6^-	0	R	2.1	142
	Am**3**	C	0.4 M PF_6^-	0	R	2.1	142
	Am**3**	C	0.4 M PF_6^-, 1 M NaBr	0	R	2.0	142
	Am**3**	C	0.4 M PF_6^-, 1 M KBr	0	—[b]		142
	Am**3**	C	1 M PF_6^-, 1 M LiI	0	—	∼1.1	142
	Am**3**	C	1 M PF_6^-, 1 M NaI	0	—	∼1.0	142
	Am**3**	C	1 M PF_6^-, 1 M KI	0	—	∼1.2	142
	Am**3**	C	1 M Br^-, 1 M $NaAsF_6$	0	R	2.1	142
	Am**3**	C	1 M Br^-, 1 M $NaSbF_6$	0	R	2.1	142
	Am**3**	C	0.93 M $NaPF_6$	0	R	1.78	128, 129
	Am**3**	C	2−4 M $LiPF_6$, pH ∼4	0	?	1.8	71
	Am**9**	C	2 M $LiClO_4$	0	D	1.1	143
	Am**9**	C	4 M $LiPF_6$	−10	R	1.5	133
	Am**27**	C	4 M $LiClO_4$, pH 4	0	L	3.5	143
	Am**38**	C	0.9 M PF_6^-, 0.5 M Li^+	25	L	4.0	142
	Am**39**	C	0.7 M PF_6^-, 0.5 M Li^+	25	L	4.0	142
	Am**39**	C	0.7 M PF_6^-, 0.5 M Li^+	0	L	4.4	142
	Am**40**	C	1.4 M PF_6^-, 1.0 M Li^+	0	—	1.0	142
	Am**41**	C	0.5 M $LiClO_4$, pH 4	0	L	2.3	143
	Am**42**	C	0.5 M $LiClO_4$, pH 4	0	L	1.3	143
(*R*,*R*)-**12**	Am**2**	C	4 M $LiPF_6$, pH 4	26	D	2.5	142
	Am**2**	C	2−4 M $LiPF_6$, pH ∼4	24	?	2.5	71
	Am**2**	C	4 M $LiPF_6$, pH 4	2	D	2.8	142
	Am**2**	C	3.5 M $LiPF_6$, pH 4	0	D	2.8	143
	Am**2**	C	2−4 M $LiPF_6$, pH ∼4	−15	?	3	71
	Am**2**	C	4 M $LiPF_6$, pH 4	−18	R	3.1	142
	Am**3**	C	0.93 M $NaPF_6$	∼25	S	1.48	128, 129
	Am**5**	C	4 M $LiPF_6$, pH 4	0	—[b]		142
	Am**6**	C	2−4 M $LiPF_6$, pH ∼4	−1	?	1.8	71
	Am**7**	C	4 M $LiPF_6$, pH 4	−1	L	1.8	142
	Am**9**	C	4 M $LiPF_6$, pH 4	−10	L	1.5	71, 142
	Am**9**	C	4 M $LiPF_6$, pH 4	−26	—[b]		142
	Am**16**	C	4 M $LiPF_6$, pH 4	−5	L	1.7	71, 142
	Am**27**	C	4 M $LiPF_6$, pH 4	−6	D	3.4	71, 142
	Am**27**	C	4 M $LiPF_6$, pH 4	−15	D	5.0	71, 142
	Am**29**	23.1AN/C	4.0 M $LiClO_4$, pH 1	0	D	1.7	146
	Am**29**	23.1AN/C	2.0 M $LiClO_4$, pH 1	0	D	2.1	146
	Am**35**	C	4 M $LiPF_6$, pH 4	−11	—[b]		142
	Am**37**	C	4 M $LiPF_6$, pH 4	−3	—[b]		142
(*S*,*S*)-**13**	Am**2**	C	3.5 M $LiPF_6$, pH 4	0	L	19	143
	Am**2**	C	1.4 M $LiPF_6$, pH 4	0	L	22	143
	Am**2**	C	0.75 M $LiPF_6$, pH 4	0	L	31	143
	Am**2**	C	0.50 M $LiPF_6$, pH 4	0	L	26	143
	Am**2**	C	1.0 M $LiClO_4$, pH 4	0	L	22	143
	Am**7**	C	1.0 M $LiPF_6$, pH 4	0	L	3.8	143
	Am**28**	23.1AN/C	2.0 M $LiClO_4$, pH 1	0	L	9.4	146
	Am**29**	16.5AN/C	2.0 M $LiClO_4$, pH 1	0	L	12.9	146
	Am**29**	19.6AN/C	2.0 M $LiClO_4$, pH 1	0	L	12.4	146
	Am**29**	23.1AN/C	2.0 M $LiClO_4$, pH 1	0	L	10.3	146
	Am**29**	28.4AN/C	2.0 M $LiClO_4$, pH 1	0	L	8.8	146
	Am**29**	33.6AN/C	2.0 M $LiClO_4$, pH 1	0	L	7.1	146
	Am**30**	23.1AN/C	2.0 M $LiClO_4$, pH 1	0	L	2.13	146
	Am**31**	23.1AN/C	1.5 M $LiClO_4$, pH 1	0	L	2.61	146
	Am**32**	23.1AN/C	4.0 M $LiClO_4$, pH 1	0	L	2.3	146
	Am**33**	23.1AN/C	4.0 M $LiClO_4$, pH 1	0	L	2.3	146
	Am**36**	23.1AN/C	3.0 M $LiClO_4$, pH 1	0	L	3.8	146
(*R*,*R*)-**13**	Am**2**	C	2−4 M $LiPF_6$, pH ∼4	24	D	12	71, 143
	Am**2**	C	3.5 M $LiClO_4$, pH 4	0	D	21	143
	Am**2**	C	1.4 M $LiPF_6$, pH 4	0	D	31	143
	Am**2**	C	4 M $LiClO_4$, pH 1	0	D	21	137
	Am**2**	9.1AN/C	4 M $LiClO_4$, pH 1	0	D	23	137
	Am**2**	C	2 M $LiPF_6$, pH 4.5	0	D	31	137
	Am**7**	C	4 M $LiPF_6$	0	L	2.3	137
	Am**9**	C	4 M $LiPF_6$	0	D	5.3	137
	Am**16**	C	2−4 M $LiPF_6$, pH ∼4	−5	D	2.2	71, 137

Table 9 (Continued)

ligand	cation	org phase[a]	aq phase	*T*, °C	dominant enantiomer	EDC	ref
	Am**27**	C	2−4 M $LiPF_6$, pH ∼4	24	?	18	71
	Am**27**	C	4 M $LiClO_4$, pH 1	0	D	25	137
	Am**27**	C	4 M $LiPF_6$	0	D	38	137
	Am**27**	C	1.4 M $LiPF_6$, pH 4	0	D	12.4	143
	Am**27**	9.1AN/C	4 M $LiClO_4$, pH 1	0	D	24	137
	Am**28**	23.1AN/C	4 M $LiClO_4$, pH 1	0	D	48	137
	Am**29**	C	4 M $LiClO_4$, pH 1	0	−[b]		137
	Am**29**	9.1AN/C	4 M $LiClO_4$, pH 1	0	D	6.15	137
	Am**29**	16.7AN/C	4 M $LiClO_4$, pH 1	0	D	9.32	137
	Am**29**	28.6AN/C	4 M $LiClO_4$, pH 1	0	D	6.15	137
	Am**29**	33.3AN/C	4 M $LiClO_4$, pH 1	0	D	6.25	137
	Am**30**	23.1AN/C	4 M $LiClO_4$, pH 1	0	D	36	137
	Am**31**	23.1AN/C	4 M $LiClO_4$, pH 1	0	D	11	137
	Am**32**	23.1AN/C	4 M $LiClO_4$, pH 1	0	D	3.2	137
	Am**33**	23.1AN/C	4 M $LiClO_4$, pH 1	0	D	2.3	137
	Am**34**	23.1AN/C	4 M $LiClO_4$, pH 1	0	−	1	137
	Am**36**	23.1AN/C	4 M $LiClO_4$, pH 1	0	L	3.5	137
(*S*,*S*)-**91**	Am**2**	C	2 M $LiClO_4$, pH 4	0	D	1.8	143
	Am**2**	C	4 M $LiPF_6$, pH 4	−10	R	2.21	132
	Am**2**	C	4 M $LiPF_6$, pH 4	−17	D	2.16	132, 143
	Am**9**	C	4 M $LiClO_4$, pH 4	0	D	1.3	143
(*S*,*S*)-**92**	Am**2**	C	4 M $LiPF_6$	−15	−[b]		133, 142
	Am**9**	C	4 M $LiPF_6$	−16	−[b]		133, 142
(*S*,*S*)-**93**	Am**2**	C	4 M $LiPF_6$	−10	S	1.7	133, 142
	Am**9**	C	4 M $LiPF_6$	−10	S	1.24	133, 142
(*S*,*S*)-**94**	Am**2**	C	4 M $LiPF_6$	−14	−[b]		133, 142
	Am**9**	C	4 M $LiPF_6$	−16	−[b]		133, 142
(*S*,*S*)-**95**	Am**2**	C	4 M $LiPF_6$	−16	S	2.0	133, 142
	Am**9**	C	4 M $LiPF_6$	−16	S	1.3	133, 142
(*S*,*S*)-**96**	Am**2**	C	4 M $LiPF_6$	−17	−	1.0	133, 142
	Am**9**	C	4 M $LiPF_6$	−16	−[b]		133, 142
(*S*,*S*)-**97**	Am**2**	C	4 M $LiPF_6$	−13	S	1.35	133, 142
	Am**9**	C	4 M $LiPF_6$	−16	−[b]		133, 142
(*R*,*R*)-**98**	Am**16**	C	3.5 M $LiPF_6$, pH 4	−10	D	1.5	143
(*R*,*R*)-**99**	Am**2**	C	3.5 M $LiPF_6$, pH 4	24	−[b]		143
	Am**2**	C	3.5 M $LiPF_6$, pH 4	−16	D	5.0	143
(*R*,*R*)-**100**	Am**2**	C	1.4 M $LiPF_6$, pH 4	0	D	31	143
(*R*,*R*)-**101**	Am**2**	C	1.4 M $LiPF_6$, pH 4	0	D	20	143
(*R*,*R*)-**102**	Am**2**	C	3.5 M $LiPF_6$, pH 4	27	D	7.4	143
	Am**2**	C	3.5 M $LiPF_6$, pH 4	−17	D	11.5	143
	Am**9**	C	3.5 M $LiPF_6$, pH 4	−10	D	4.8	143
(*R*,*R*)-**103**	Am**2**	C	2 M $LiClO_4$, pH 4	0	D	3.1	143
	Am**9**	C	4 M $LiClO_4$, pH 4	0	D	1.2	143
	Am**27**	C	4 M $LiClO_4$, pH 4	0	D	6.6	143
	Am**41**	C	0.5 M $LiClO_4$, pH 4	0	D	3.6	143
	Am**42**	C	0.5 M $LiClO_4$, pH 4	0	D	2.1	143
(*S*,*S*)-**104**	Am**2**	C	0.75 M $LiPF_6$, pH 4	0	L	13.6	143
	Am**2**	C	2 M $LiClO_4$, pH 4	0	L	10.2	143
	Am**7**	C	0.75 M $LiPF_6$, pH 4	0	L	2.38	143
(*R*,*R*)-**104**	Am**2**	C	3.5 M $LiPF_6$, pH 4	0	D	8	143
(*S*,*S*)-**105**	Am**2**	C	4 M $LiClO_4$, pH 4	0	L	1.5	143
(*S*,*S*)-**106**	Am**2**	C	2 M $LiClO_4$, pH 4	0	D	1.1	143
	Am**9**	C	4 M $LiClO_4$, pH 4	0	−[b]		143
(*S*,*S*)-**107**	Am**2**	C	2 M $LiClO_4$, pH 4	0	D	1.8	143
(*S*)-**108**	Am**29**	23.1AN/C	2.0 M $LiClO_4$, pH 1	0	L	4.1	146
(*S*)-**109**	Am**29**	23.1AN/C	2.0 M $LiClO_4$, pH 1	0	L	1.7	146
(*R*)-**110**	Am**2**	C	0.003 M ClO_4^-	0	L	1.6	148
	Am**9**	C	0.003 M ClO_4^-	0	L	1.1	148
(*R*)-**111**	Am**9**	C	0.003 M ClO_4^-	0	D	3.3	148
(*S*)-**112**	Am**9**	C	0.003 M ClO_4^-	0	L	3.7	148
(*S*)-**113**	Am**2**	C	0.003 M ClO_4^-	0	L	3.4	148
	Am**9**	C	0.003 M ClO_4^-	0	L	6.6	148
(*S*)-**114**	Am**9**	C	0.003 M ClO_4^-	0	L	5.7	148
(*S*)-**115**	Am**9**	C	0.003 M ClO_4^-	0	L	4.5	148
(*S*)-**116**	Am**9**	C	0.003 M ClO_4^-	0	L	3.5	148
(*S*)-**117**	Am**9**	C	0.003 M ClO_4^-	0	L	3.7	148
(*S*)-**118**	Am**2**	C	0.003 M ClO_4^-	0	L	1.3	148
(*R*)-**119**	Am**2**	C	0.003 M ClO_4^-	0	D	19.5	148
	Am**2**	12.5AN/C	0.003 M ClO_4^-	0	D	13.2	148
	Am**2**	27.6AN/C	0.003 M ClO_4^-	0	D	7.5	148
	Am**5**	C	0.003 M ClO_4^-	0	D	3.9	148
	Am**7**	C	0.003 M ClO_4^-	0	D	4.4	148
	Am**8**	C	0.003 M ClO_4^-	0	D	7.9	148
	Am**9**	C	0.003 M ClO_4^-	0	D	7.7	148

Table 9 (Continued)

ligand	cation	org phase[a]	aq phase	*T*, °C	dominant enantiomer	EDC	ref
	Am**16**	C	0.003 M ClO_4^-	0	D	6.0	148
	Am**29**	6.1AN/C	0.003 M ClO_4^-	0	D	19.9	148
	Am**29**	12.5AN/C	0.003 M ClO_4^-	0	D	21.1	148
	Am**29**	19.6AN/C	0.003 M ClO_4^-	0	D	23.4	148
	Am**29**	27.6AN/C	0.003 M ClO_4^-	0	D	23.3	148
	Am**29**	23.1AN/C	2.0 M $LiClO_4$	0	D	19.2	148
	Am**30**	23.1AN/C	2.0 M $LiClO_4$	0	D	5.1	148
	Am**31**	23.1AN/C	2.0 M $LiClO_4$	0	D	8.1	148
	Am**32**	23.1AN/C	2.0 M $LiClO_4$	0	D	13.5	148
	Am**33**	23.1AN/C	2.0 M $LiClO_4$	0	D	6.4	148
(*S*)-**119**	Am**36**	23.1AN/C	2.0 M $LiClO_4$	0	L	6.4	148

[a] C = $CDCl_3$, AN = CD_3CN. Solvent mixtures are indicated by wt % of CD_3CN in $CDCl_3$. [b] No significant amount of the ammonium salts was extracted into the organic phase.

Chart 14. Macrocycles 106−119

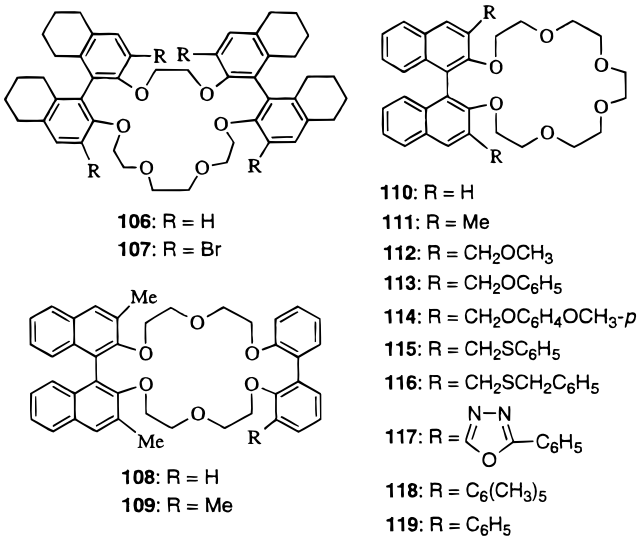
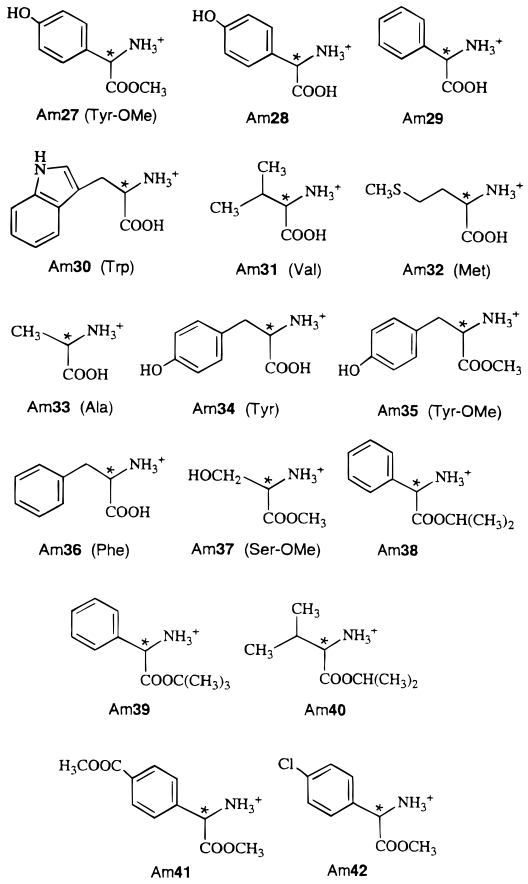


Chart 15. Amino Compounds: Am27−Am42



tripod hydrogen bonding and that the naphthaleneoxy group can act as a π-base and the $COOCH_3$ group as a π-acid so that a π-acid−π-base interaction provides an additional contribution to the complex stability. These attractive interactions result in a rigid conformation of the diastereomeric complexes. The dramatic increase in chiral recognition when two methyl groups are present in **13**, **100**, **101**, and **104**, as mentioned above, is due to a greater steric repulsion of the methyl groups with one enantiomer of ammonium cations in the less stable diastereomeric complexes.

B. Structures of Chiral Barriers

Macrocycles having two binaphthyl units (**12** and **13**) show a higher degree of enantiomeric recognition than those having only one (**110** and **111**) or three (**21**) such unit(s). At 0 °C, (*R*,*R*)-**12** and (*R*,*R*)-**13** display better chiral recognition toward Am**2** (EDC value of 2.8 and 21, respectively) than does (*R*)-**110** (EDC value of 1.6, Table 9) and (*R*,*R*)-**13** displays better chiral recognition toward Am**9** (EDC value of 5.3) than does (*R*)-**111** (EDC value of 3.3). Interaction between tris(binaphthyl)-substituted **21** and ammonium cations was too weak to be detected, resulting in no chiral recognition.[24,134]

Positions of attachment of the chiral barriers to the macroring have an effect on enantiomeric recognition. For chiral recognition of Am**2**, (*R*,*R*)-**12** and (*R*,*R*)-**103**, which have two chiral units symmetrically attached, demonstrate higher EDC values (2.5−3.1 and 3.1, respectively) than (*S*,*S*)-**91** and (*S*,*S*)-**106** (EDC values of 1.8−2.21 and 1.1, respectively). The two chiral units of (*S*,*S*)-**91** and (*S*,*S*)-**106** are separated by one ethylene glycol unit on one side and by a triethylene glycol unit on the other, instead of by a diethylene glycol unit on both sides, as in (*R*,*R*)-**12** and (*R*,*R*)-**103**.

Tetralyl-containing macrocycles **100** and **103** show no significant change in chiral recognition from binaphthyl-containing **12** and **13**. At 0 °C for recognition of Am**2**, both (*R*,*R*)-**100** and (*R*,*R*)-**13** have an EDC value of 31 (1.4 M $LiPF_6$ in D_2O phase) and (*R*,*R*)-**103** and (*R*,*R*)-**12** have EDC values of 3.1 (2 M $LiClO_4$) and 2.8 (3.5 M $LiPF_6$), respectively. How-

ever, the methyl groups attached to the bitetralyl unit result in a less significant increase in the degree of enantiomeric recognition as compared with those attached to the binaphthyl group. For example, **101** and **104** display lower EDC values of recognition for Am**2** than do **13** and **100**. Bitetralyl-substituted **106** exhibits diminished chiral recognition toward Am**2** than does the binaphthyl-substituted **91**. Similarly, the biphenyl-containing **108** and **109** show a decreased degree of enantiomeric recognition compared to the binaphthyl-containing **13**.

C. Structures of Crown Rings

Macrocycles **92**−**97** differ from **12** in that one or both CH_2OCH_2 units of the crown ring of **12** are replaced by other groups. The absence of the sixth donor atom in **92**, **94**, **96**, and **97** results in very weak interaction of the ligands with ammonium cations. **92** and **94** cannot extract either Am**2** or Am**9** and **96** and **97** cannot extract Am**9** into the organic phase. Ligand **96** shows no, and **97** a low, degree of chiral recognition toward Am**2**. Replacement of one or both CH_2OCH_2 unit(s) by pyridyl group(s) (**93** and **95**) decreases the extent of chiral recognition toward Am**2** (EDC value of 2.8 at −10 °C in the case of **12** to EDC values of 1.7−2.0 in the cases of **93** and **95**) and toward Am**9** (EDC value of 1.5 at −10 °C in the case of **12** to EDC values of 1.2−1.3 in the cases of **93** and **95**). Therefore, a six-oxygen-containing crown ring plays an important positive role in chiral recognition.

D. Effects of Inorganic Salts in D_2O Phase

Inorganic salts in the D_2O phase have been used to "salt out" hydrophilic amine salts.[142] Different types and concentrations of inorganic salts have effects on the extraction of amine compounds and on chiral recognition. In the presence of PF_6^-, ClO_4^-, AsF_6^-, and SbF_6^-, ammonium cations can be effectively extracted into an organic phase by macrocyclic ligands, and roughly the same degrees of complexation and chiral recognition have been observed for these anions. On the other hand, no extraction of Am**3** by (*S*,*S*)-**12** was observed when F^-, Cl^-, or I^- was used as the counterion in the aqueous phase (Table 9). In the presence of LiI, NaI, or KI (1 M), Am**3**·PF_6^- can be extracted into $CDCl_3$ by (*S*,*S*)-**12**, but the chiral recognition of the ammonium cation disappears (EDC 1.0−1.2). When the aqueous phase contains 1 M KBr, Am**3**·PF_6^- cannot be extracted by (*S*,*S*)-**12**, indicating that K^+ competes with NH_4^+ for the ligand.[142] Therefore, in most cases studies of chiral recognition by the extraction method was performed using PF_6^- and ClO_4^- as the counterions in the aqueous phase.

The concentration of $LiPF_6$ has an effect on the extent of chiral recognition. As can be seen in Table 9, with a decrease in $LiPF_6$ concentrations from 3.5 to 0.50 M, the EDC values for the Am**2**-(*S*,*S*)-**13** system increase from 19 to 31 and then decrease to 26. The highest EDC value is observed at 0.75 M $LiPF_6$. Receptor **104** shows a larger EDC value at 0.75 M $LiPF_6$ than at either 2 M $LiClO_4$ or 3.5 M $LiPF_6$. In the presence of 2 M $LiClO_4$, (*R*,*R*)-**12** shows better chiral recognition toward Am**29** than in the presence of 4 M $LiClO_4$. In the case of the Am**27**−(*R*,*R*)-**13** system, however, the highest EDC value was found in 4 M $LiPF_6$.

E. Effects of Solvents and Temperature

Extractions of amine compounds by binaphthyl-containing macrocycles were studied by using single $CDCl_3$ or mixed $CD_3CN/CDCl_3$ solvents as organic phases. The composition of the organic phase had a significant effect on chiral recognition. In the case of the Am**29**−(*R*,*R*)-**13** system, no extraction was observed when the organic phase was $CDCl_3$. However, when the solvent mixture $CD_3CN/CDCl_3$ was used, (*R*,*R*)-**13** displayed a good enantiomeric recognition toward Am**29**. As the CD_3CN content of the organic phase increased from 9.1 to 33.3 wt %, the EDC values increased from 6.15 to a maximum of 9.32 in 16.7 wt % CD_3CN solvent and decreased to a constant value of 6.2 in the solvents containing the higher composition of CD_3CN. Receptor (*S*,*S*)-**13** shows the highest EDC value for chiral recognition of Am**29** in 16.5 wt % CD_3CN solvent (EDC = 12.9, Table 9). No data are available for this system in low-content CD_3CN solvents. These observations are consistent with the solvent effect on enantiomeric recognition of pyridine-containing systems (section III-E). The recognition of Am**29** by (*R*)-**119** in mixtures of $CD_3CN/CDCl_3$ showed a similar behavior. With increasing CD_3CN content of the organic phase from 6.1 to 19.6 wt %, the EDC values increased from 19.9 to 23.4 and then decreased to 19.2 in 23.1 wt % CD_3CN solvent.

Chiral recognition of Am**2** by (*R*)-**119** exhibited a different solvent dependence than that of Am**29** by (*R*,*R*)-**13**. When the CD_3CN content of the organic phase increased from 0 to 27.6 wt %, the EDC values decreased from 19.5 to 7.5. However, a small increase in the EDC value (EDC = 23) was observed in 9.1 wt % CD_3CN for the Am**2**−(*R*,*R*)-**13** system in the presence of 4 M $LiClO_4$ as compared with that in pure $CDCl_3$ (EDC = 21, Table 9). These results indicate that, in general, the solvent mixtures of $CD_3CN/CDCl_3$ favor enantiomeric recognition over the single solvent $CDCl_3$.

The effect of temperature on chiral recognition can be seen for several macrocyclic ligands (**12**, **13**, **91**, and **102**) in Table 9. In every case, the lower temperature gives the higher EDC value and thus better chiral recognition.

F. Enantiomeric Resolutions

Effective enantiomeric resolutions through liquid−liquid[1,129,143] and solid−liquid[1,3,5−7,13,20,21,135,136,144] chromatography and enantiomeric differential transport through liquid membranes[131,151] were observed. An amino acid and ester resolving machine was designed, built, and tested.[23,25,145] Total enantiomer resolutions of both macrocyclic hosts and amino guests have been realized in liquid−liquid and liquid−solid chromatography with separation factors as high as 24.[23,25,144] Optical purity of amino esters by the resolving machine has been as high as 90%.[145] Shinbo and co-workers have demonstrated that almost all amino acids commonly found in proteins can

be separated into their enantiomers on chromatographic packings coated with (*R*)- or (*S*)-**119**.[8]

IX. Macrocycles Having Carbohydrates or Other Alkyl Units Attached

Natural compounds, such as carbohydrates, provide relatively inexpensive chiral starting materials for synthesis of optically active macrocycles. Syntheses and properties of chiral macrocyclic compounds having carbohydrates incorporated were summarized by Stoddart.[26,27] Among them, DD-(**120**) and (*R*)- and (*S*)-D-(**121**) (Chart 16) showed the highest degree of enantiomeric differentiation examined based on ^{1}H NMR spectroscopic data in $CDCl_3$.[26,27,152−155] Later, other macrocycles having carbohydrates attached were synthesized and studied by Pietraszkiewicz, Joly, and their co-workers.[40,156−158] The chiral recognition data involving these macrocycles are summarized in Table 10.

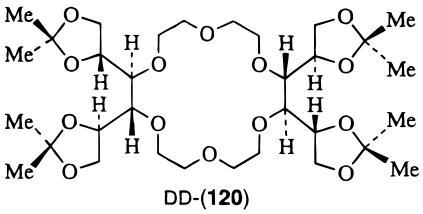
Most D-hexopyranoside-containing macrocycles (**122**−**129**, Chart 16) exhibited no enantiomeric recognition while D-mannitol-containing macrocycles (**133**−**137**) showed enantiomeric recognition. The D-mannitol-containing **120** and **121**, as mentioned above, displayed a high degree of enantiomeric differentiation. Therefore, the D-mannitol, among the other carbohydrates, is a better chiral building material for enantiomeric recognition by the macrocycles. Solvent extraction results demonstrated that **130** did

Table 10. Enantioselective Data Studied by Bulk Liquid Membrane (organic phase, $CHCl_3$) Transports (after 75 h) and Solvent Extraction (organic phase, $CDCl_3$) for Racemic Ammonium Salts with Carbohydrate-Containing Macrocycles

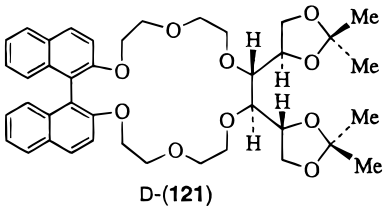
ligand	cation	method[a]	*T*, °C	(*R*)-Am/(*S*)-Am	ref
122−**128**	Am**2**	SE	20	1.0/1.0	40
129	Am**2**	SE	20	1.0/1.1	40
130	Am**2**	SE	20	*b*	40
132	Am**29**	BLM	20−23	3.29/1.0	157
	Am**30**	BLM	20−23	1.0/3.73	157
	Am**36**	BLM	20−23	1.25/1.0	157
133	Am**2**	SE	20	1.3/1.0	40, 158
136	Am**2**	SE	20	1.7/1.0	40, 158
137	Am**2**	SE	20	1.0/1.6	40
138	Am**2**	SE	20	1.0/1.0	40

[a] SE = solvent extraction, the ratio of (*R*)- to (*S*)- ammonium salts in the $CDCl_3$ phase was determined by a ^{1}H NMR spectral method. BLM = bulk liquid membrane. [b] No significant amount of the ammonium salts was extracted into the organic phase.

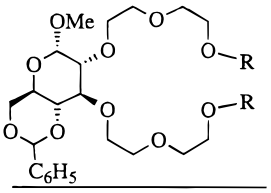
Chart 16. Macrocycles 120−138



DD-(**120**)

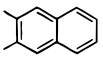


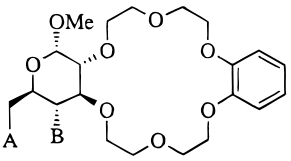
D-(**121**)



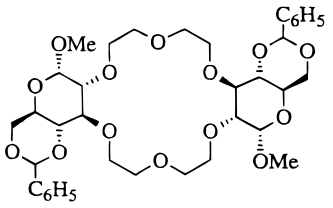
122: R, R = 

123: R, R = 

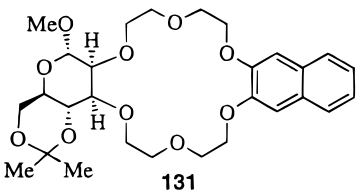
124: R, R = 



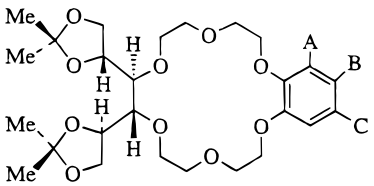
125: A = B = OH
126: A = OH, B = OMe
127: A = OH, B = O(*n*-$C_{12}H_{25}$)
128: A = OH, B = $O(CH_2CH_2O)_3CH_3$
129: A = Br, B = OBz



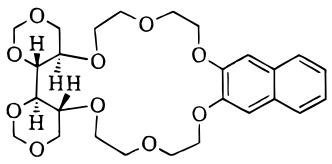
130



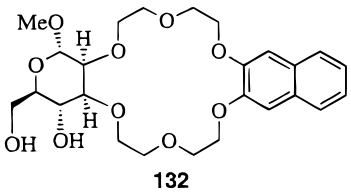
131



133: A = B = C = H
134: A = C = H, B = Me
135: A = C = H, B = NO_2
136: A = C = H, B = $C(CH_3)_3$
137: A = C = $C(CH_3)_3$, B = H



138



132

not extract a detectable amount of Am**2** into the $CDCl_3$ phase,[40] probably due to the large number of chiral centers and large degree of deformation of the ligand. In addition, the lack of a catechol residue in **130** could contribute to the weak complexing ability of the ammonium guest.[40] The same situation has been noted for macrocycles **84**−**88** (see section VII).

The difference between **125** and **132** is in the benzo (in **125**) and 2,3-naphtho (in **132**) subcyclic units on the macrorings. Receptor **132** shows good enantioselectivity toward Am**29**, Am**30**, and Am**36**, but **125** shows no enantioselectivity toward Am**2** (Table 10).[40,157] This observation suggests that the large aromatic area of **132** favors enantiomeric recognition. Small differences between the degrees of enantiomeric recognition demonstrated by **136** and **137** indicate that the positions of the *tert*-butyl substituent on the phenyl moiety have a small effect on enantiomeric recognition. On the other hand, the different positions and numbers of the *tert*-butyl substituent result in the ability of **136** to recognize (*R*)-Am**2** over (*S*)-Am**2** but of **137** to recognize (*S*)-Am**2** over (*R*)-Am**2**.

The transport experiments showed that **131** did not display enantioselectivity, probably due to weak binding.[157] Removal of the isopropylidene group at the 4,6-*O*-positions of the sugar unit of **131** to form **132** resulted in pronounced enantioselectivity. The free hydroxyl groups of **132** may act as auxiliary binding sites for hydrogen bonding with amine compounds and help to orient the guest spatially within the close proximity of the macroring.

Joly and co-workers have resolved Am**29** (phenylglycine), Am**30** (tryptophan), Am**32** (methionine), Am**36** (phenylanaline), ethionine, *p*-nitrophenylalanine, and other amino acids using a dynamic coating of D-mannitol-containing **133**−**136** on a commercial C_{18}-silica prepacked column.[10,40,158] It has been demonstrated that a chromatographic system with **131** coated onto a hydrophobic solid support can be used to separate the α-phenylglycine (Am**29**) enantiomers.[11]

Table 11. Differential Transport of Racemic Ammonium Salts through Bulk $H_2O/CHCl_3/H_2O$ Liquid Membrane Containing Chiral Macrocycles Incorporated with Twisted Aromatic Moieties at 20 °C

ligand	cation	time (h)	transport (%)	dominant enantiomer	optical purity (%)	ref
(−)-**139**	Am**2**	6.0	6.0	*S*	75	159, 165
	Am**3**	5	12	*R*	26	159, 165
	Am**25**	5.0	6.2	*R*	80	165
(+)-**139**	Am**2**	6.0	6.0	*R*	77	159, 165
	Am**3**	5	11	*S*	29	159, 165
	Am**25**	5.0	6.2	*S*	82	165
(−)-**140**	Am**2**	10.0	5.8	*R*	27	159, 165
	Am**3**	4.5	6.1	*S*	20	159, 165
	Am**25**	8.0	5.8	*S*	45	165
(+)-**140**	Am**2**	10.0	5.8	*S*	28	159, 165
	Am**3**	4.5	6.1	*R*	18	159, 165
	Am**25**	8.0	5.9	*R*	46	165
(−)-**141**	Am**2**	10.0	5.8	*S*	28	165
	Am**3**	4.5	6.0	*R*	23	165
	Am**25**	8.0	5.9	*R*	41	165
(+)-**141**	Am**2**	10.0	5.9	*R*	30	165
	Am**3**	4.5	6.1	*S*	22	165
	Am**25**	8.0	6.0	*S*	42	165
(+)-**142**	Am**2**	1.0	6.5	*R*	39	162
	Am**3**	1.5	4.6	*S*	24	162
(−)-**143**	Am**2**	1	2.8	*R*	24	160
	Am**3**	0.5	3.7	*S*	31	160
	Am**25**	0.5	2.5	*S*	32	160
	Am**43**	22	3.4	L (*R*,*R*)	18	164
	Am**44**	10	3.6	(*S*,*S*)	26	164
(+)-**144**	Am**2**	1	1.4	*R*	15	163
	Am**3**	1	3.5	*S*	19	163
	Am**25**	1	3.1	*S*	20	163
(−)-**145**	Am**2**	0.5	1.4	*S*	21	161
	Am**25**	0.5	1.6	*S*	66	161
	Am**26**	0.5	2.5	*R*	74	161
(+)-**146**	Am**2**	1.0	6.1	*R*	61	162
	Am**3**	1.5	4.5	*S*	27	162
(−)-**147**	Am**2**	1	1.8	*S*	21	163
	Am**3**	1	3.9	*R*	49	163
	Am**25**	1	4.1	*R*	88	163
(−)-**148**	Am**43**	1.0	3.5	L (*R*,*R*)	66	164
	Am**44**	0.5	3.9	(*S*,*S*)	82	164
(−)-**149**	Am**2**	24	2.6	*S*	19	160
	Am**3**	12	3.2	*R*	21	160
	Am**25**	12	3.0	*R*	20	160
(−)-**150**	Am**2**	24.0	2.7	*R*	25	161
	Am**25**	0.5	1.4	*R*	35	161
	Am**26**	0.5	2.1	*S*	42	161

X. Macrocycles Incorporating Twisted Aromatic Moieties

Yamamoto and co-workers synthesized a series of macrocyclic compounds incorporating twisted aromatic groups as chiral centers.[159−165] The twisted structure of the [7]circulene has been confirmed by X-ray analysis.[166] Enantiomeric recognition by these macrocycles was examined by liquid membrane transport through a bulk $CHCl_3$ phase. As seen in Table 11, the results generally show good enantioselectivity. The highest degree of enantiomeric recognition is found for **139**−Am**2**, **139**−Am**25**, **147**−Am**25**, and **148**−Am**44** systems. The optical purity of transported ammonium salts by these macrocycles are as high as 80%.

The pentaheliceno macrocycle **139** (Chart 17) showed a higher degree of enantioselectivity than the hexaheliceno macrocycle (**140**) and the hexa[7]-circuleno macrocycle (**141**), especially toward Am**2** and Am**25**.[165] It was believed that the better enantiomeric recognition of **139** was due to the larger chiral barrier of the ligand. An inspection of the CPK space-filling molecular models suggested that the inner methyl groups of the pentahelicene substituent of **139** provided a more effective steric barrier for guest salts than did the hexahelicene and hexa[7]-circulene groups of **140** and **141**.[165]

Five-oxygen-containing **146** and **147** (Chart 17) exhibit higher degrees of enantiomeric recognition than the corresponding six-oxygen-containing **142** and **144**, probably due to the more rigid structure of the small crown ring of **146** and **147**. In section VII-A, a similar effect was noted. Receptors **143** and **144** have the same aromatic group, but this group is attached to **144** by two methylene units. The different way that the aromatic group is attached to the macroring results in lower enantioselectivity for **144** than for **143** for Am**2**, Am**3**, and Am**25.** The greater distance of the chiral center from the macroring of **144** is probably a primary reason for the lower enantioselectivity. The same effect was observed for macrocyclic receptors **73** and **74** (see section VII-B).

An increase in the number of twisted aromatic chiral centers decreases enantiomeric recognition.

Chart 17. Macrocycles 139−153

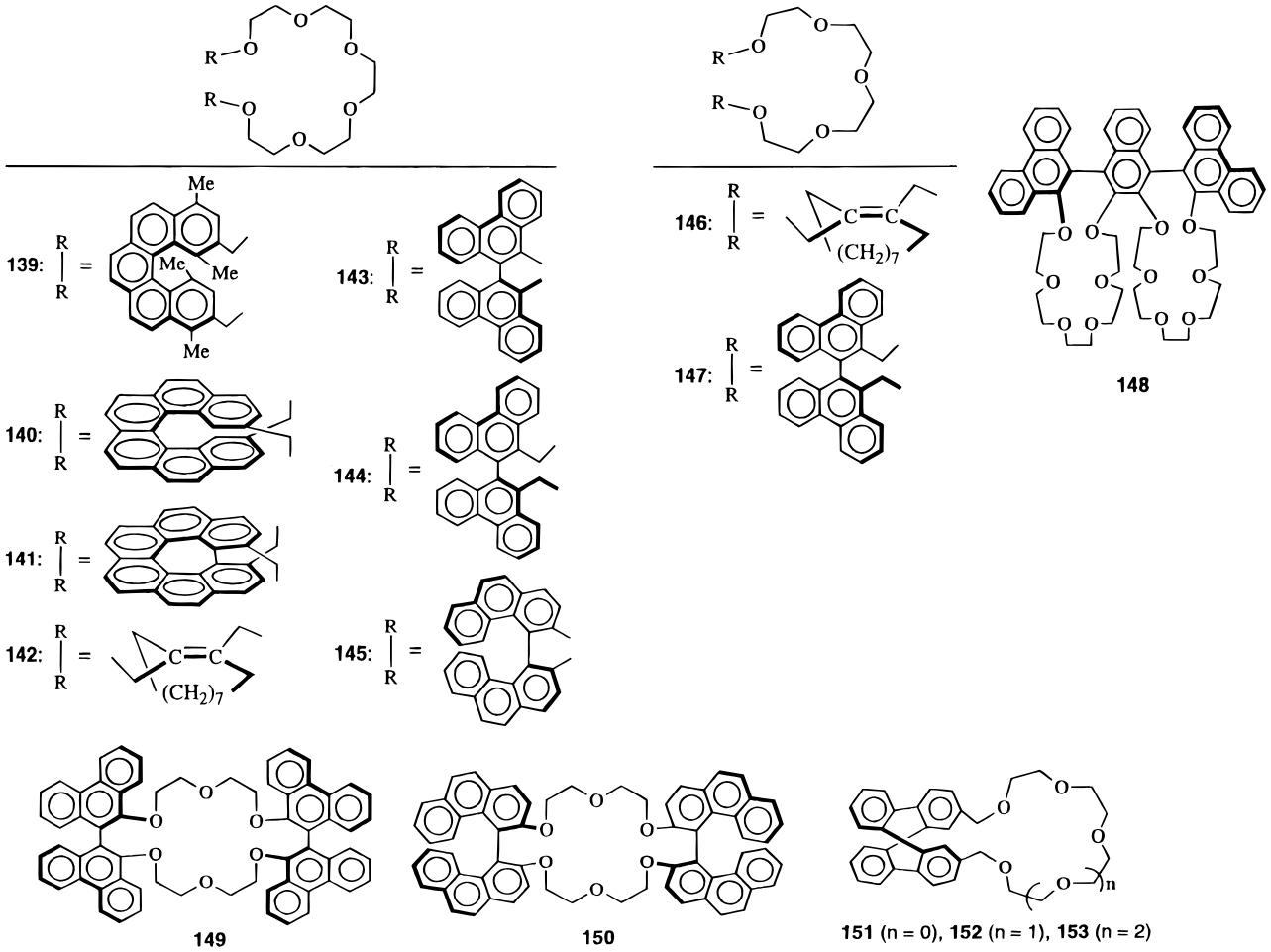
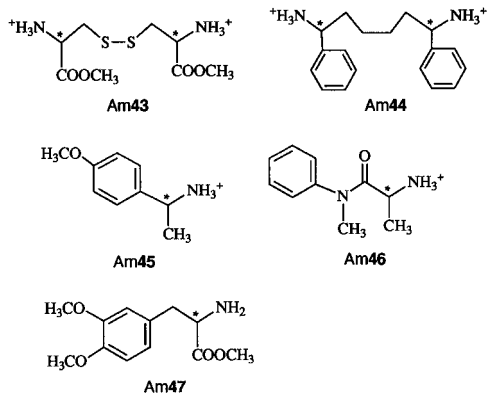


Chart 18. Amine Compounds: Am43−Am47



Macrocycle **149**, having the twisted aromatic groups on both sides of the crown ring, exhibits a lower degree of enantioselectivity toward Am**2**, Am**3**, and Am**25** than does **143**, which has a chiral substituent on one side of the crown ring. Macrocycle **150** shows also a lower degree of enantiomeric recognition toward Am**25** and Am**26** than its analogue **145**. The two-macroring-containing **148** shows significantly higher degrees of enantiomeric recognition toward two diammonium salts (Am**43** and Am**44**, Chart 18) than does the one-macroring-containing **143**. An examination of CPK molecular models has shown that two bindable functional groups of the ammonium guests can be located in two binding sites of **148** in a complementary manner.[164]

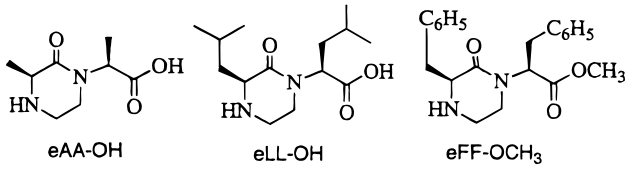
Of three macrocycles each containing a 9,9′-spirobifluorene group (**151**−**153**), the five-oxygen-containing **152** had the highest degree of enantioselectivity.[163,167,168]

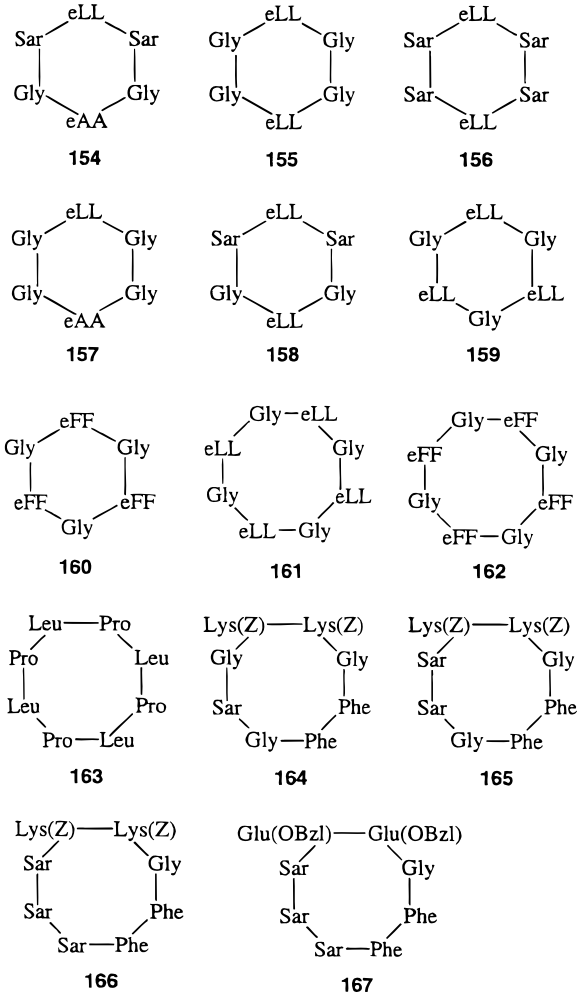
XI. Macrocyclic Peptides

Enantiomeric differentiation of D- and L-amino acid salts with macrocyclic peptides was first reported by Deber and Blout in 1974.[169] They observed that ^{13}C NMR spectra of $CDCl_3$ solutions containing macrocyclic peptide cyclo(Pro-Gly)$_3$ or cyclo(Pro-Gly)$_4$ and a D,L mixture of an amino acid salt displayed separate resonances for several carbons of the D- and L-enantiomers of Pro-OBn·HCl, Phe-OMe·HCl, and Val-OMe·HCl. Such spectra resulted from the formation of diastereomeric pairs of the complexes.[169] Circular dichroism spectra of the complexes with D- and L-tryptophan methyl esters suggested that the side chain of the complexed amino acid might be limited to a few specific orientations relative to the macrocyclic peptide.[170]

Kojima and co-workers recently synthesized a series of macrocyclic pseudopeptides and studied their ability to differentiate between enantiomers of Am**3**, Am**45**, and Am**46** (Chart 18).[171−176] Primary amino acids, sarcosine (*N*-methylglycine), and three synthesized dipeptides, (2*S*,3′*S*)-2-(2′-oxo-3′-methyl-1′-piperazinyl)propanoic acid (eAA-OH), (2*S*,3′*S*)-4-methyl-2-(2′-oxo-3′-isobutyl-1′-piperazinyl)pen-

Chart 19. Dipeptides eAA-OH, ELL-OH, and eFF-OCH$_3$ and Macrocyclic Peptides 154−167





(Sar = sarcosine; Z = benzyloxycarbonyl)

tanoic acid (eLL-OH), and (2*S*,3′*S*)-3-phenyl-2-(2′-oxo-3′-benzyl-1′-piperazinyl)propanoate (eFF-OCH$_3$) (Chart 19), were used to prepare the macrocyclic pseudopeptides. The study suggests that the interaction between amine compounds and macrocyclic peptides may be attributed mainly to the effects of the hydrogen bonding between the amidocarbonyl groups of the peptides (see Figure 9 for an example) and the ammonium or amine groups of the substrates.[169−171,177] The ammonium or amine groups of the guest molecules are located predominantly in the cavities of the macrocyclic peptides. In addition, a hydrophobic interaction between the host and guest molecules has been proposed.[177] The side chains of amino acid residues of the macrocyclic peptides can sterically interact with guest amine compounds, resulting in members of an enantiomer pair having different binding energies.

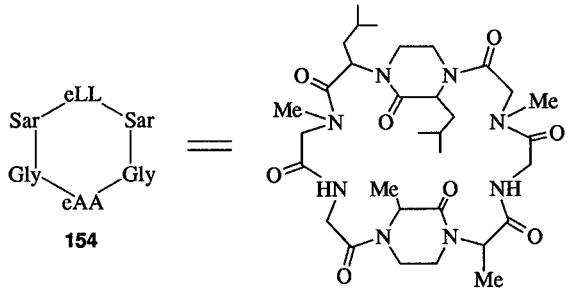


Figure 9. Macrocyclic pseudopeptides.

As enantiomers of Am**3** formed complexes with macrocyclic pseudopeptides **154-162** (Chart 19), the methyl groups of (*R*)- and (*S*)-Am**3** showed distinguishable ^{13}C NMR spectra in CDCl$_3$.[171−174] These results suggested that there were differences between binding constants of (*R*)- and (*S*)-enantiomers to the macrocyclic pseudopeptides. ^{1}H and ^{13}C NMR measurements showed that 36-membered-ring **161** exhibited a higher enantiodifferentiating ability toward Am**3** and Am**45** than do the 24- and 27-membered-ring ligands **155** and **159**.[174] On the other hand, the 24- and 27-membered-ring compounds **155** and **159** distinguished (*R*)- and (*S*)-enantiomers of Am**46**, while the 36-membered-ring compound **161** differentiated Am**46** less effectively than either **155** or **159**.

Macrocyclic pseudopeptides **155**, **159**, **161**, and **163** were shown to act as effective carriers of Am**2**, Am**7**, Am**8**, and Am**27** in CHCl$_3$ and CH$_2$Cl$_2$ liquid membrane systems.[175] Among the examined pseudopeptides, 27-membered **159** exhibited the highest transport rates and 36-membered **161** displayed the most effective transport for (*S*)-amino acid ester salts over their corresponding (*R*)-enantiomers. In the CH$_2$Cl$_2$ liquid membrane system these macrocyclic carriers exhibited higher transport rates and extents of enantioselectivity than those found in the CHCl$_3$ liquid membrane system.[175]

Katagi and co-workers determined binding constants for interactions of four macrocyclic pseudopeptides with Am**7** (Phe-OMe) and Am**17** (Leu-OMe) in chloroform by a solvent extraction method (Table 12).[177,178] As can be seen in Table 12, the structure of macrocyclic pseudopeptides has a significant effect on enantiomeric recognition. Macrocycle **166** shows essentially no chiral recognition toward Am**7** and Am**17**. On the other hand, macrocycles **164** and **165** show good chiral recognition toward D-Am**7** over L-Am**7** [Δ(log *K*) values 0.31 and 0.60, respectively] while **164** and **167** recognize L-Am**17** over the D-form by Δ(log *K*) values of 0.45 and 0.37, respectively. Liquid membrane experiments indicated that the macrocyclic pseudopeptides **164** and **165** transported D-Am**7** through a CHCl$_3$ liquid membrane more efficiently than the L-enantiomer. The ee values showed that **164** and **165** exhibited higher degrees of enantioselectivity for Am**7** than did **166** and **167**. Both binding constant and liquid membrane transport data demonstrated the poor chiral recognition properties of **166** for amino acid methyl esters. When the guest enantiomers were Am**3**, Am**17**, and Am**29**, the selective transport abilities of these macrocyclic compounds were low.[177]

Table 12. log *K* and Δ(log *K*) Values[a] for the Interactions of Ammonium Cations with Macrocyclic Pseudopeptides in $CHCl_3$ ca. at 25−26 °C[b]

ligand	cation	log *K*	Δ(log *K*)
164	D-Am**7**	3.67	
	L-Am**7**	3.36	0.31
	D-Am**17**	2.34	
	L-Am**17**	2.79	0.45
165	D-Am**7**	4.23	
	L-Am**7**	3.63	0.60
	D-Am**17**	3.20	
	L-Am**17**	3.34	0.14
166	D-Am**7**	3.53	
	L-Am**7**	3.51	0.02
	D-Am**17**	3.34	
	L-Am**17**	3.32	0.02
167	D-Am**7**	3.46	
	L-Am**7**	3.32	0.14
	D-Am**17**	2.78	
	L-Am**17**	3.15	0.37

[a] $\Delta(\log K) = |\log K_{(D)} - \log K_{(L)}|$. [b] From ref 177.

XII. Cyclophanamide-Type Macrocycles

Still,[34,35,77,179−189] Kilburn,[179,190−192] Chamberlin,[193] and their co-workers synthesized a series of macrocyclic, macrobicyclic, and macrotricyclic cyclophanamide-type compounds. These macrocycles are of C_2, D_2, or C_3 symmetry. A general characteristic of these compounds is the amide functionality incorporated around the macroring to provide hydrogen-bonding interactions with the guest molecules. This includes both hydrogen-bond donors (amide hydrogen N−H) and acceptors (carbonyl C═O) which result in host−guest complexes. The formation of intermolecular hydrogen bonds has been rationalized to be the driving forces of the binding of these macrocycles with peptide guests in organic solvents.[77] Differences in chiral centers, macroring sizes, cavity shapes, and substituents on the molecules create different chiral environments that cause enantiomeric recognition. Excellent chiral recognition by these macrocycles toward certain enantiomers of polypeptides, amino acid derivatives, and amides has been observed.[179−184,186−189,191−193] Of the macrocycles synthesized by Still and co-workers, >99% ee values were observed in many cases.[182,184,186] Recognition data indicated by differences in free energy changes for enantiomeric pair interactions ($\Delta\Delta G$) are summarized in Table 13.

A. Rigidity of the Host Macrocycles

Macrocycle **172** is more flexible than **170** due to three additional methylene groups built into the apolar bottom of the **172** (Chart 20). It is believed that the absence of these methylenes in **170** is particularly significant since it opens the cavity and disfavors transannular hydrogen bonds.[34] In every case, the less rigid **172** binds peptides with significantly less enantioselectivity (smaller $\Delta\Delta G$ values) than does the more rigid **170** (larger $\Delta\Delta G$ values, see Table 13). This reduction in enantiomeric recognition for binding L-peptides is even greater for the peptidic ethyl amides (*N*-Boc-Ala-NHEt and *N*-Boc-Ser-NHEt), whose more sterically demanding C-terminal substituents should project more deeply into the ligand's binding site. A molecular mechanics study and ^{13}C spin−lattice relaxation time measurements provide evidence for the conformational flexibility of **172**.[183] While **170** exists in a single family of closely related conformations, **172** has many more significantly distinct conformers.

It was found that protected peptides such as N-Ac-Leu-NHMe, Boc-Leu-Phe-OMe, and Cbz-Gly-NHMe, as well as numerous other small peptides and acyclic amides did not show any detectable binding affinities with macrocyclic hosts **177** and **178** (Chart 20).[193] Extents of enantiomeric recognition of these two macrocycles for two cyclic dipeptides are not high (Table 13). These facts indicate that the macrocyclic **177** and **178** show lower degrees of chiral recognition than do macrobicyclic (**168**, **169**, and **175**) and macrotricyclic (**170**-**174**) hosts due to the conformational flexibility of **177** and **178**. Although extents of enantioselectivity by **168**, **169**, and **175** are not directly comparable with those by **170**−**174** due to different guest molecules studied, the generally lower $\Delta\Delta G$ values involving **168**, **169**, and **175** (0.46−5.48 kJ/mol) than those involving **170**−**174** (as high as 20 kJ/mol) indicate that the more rigid macrotricycles (**170**-**174**) show better enantioselectivity than do the less rigid macrobicycles (**168**, **169**, and **175**).

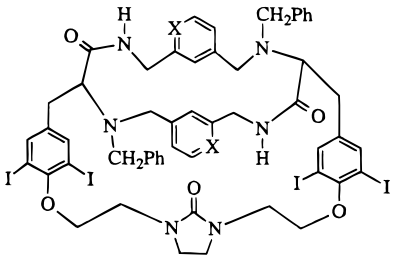
B. Structural Complementarity

In every case, macrocycle **170** shows better enantioselectivity for *N*-Boc-Am-NHMe (Am = Ala, Val, Leu, and Ser) than does **171**. The sulfur atoms of **170** must play a role in better recognition. A high extent of enantioselectivity with sulfur-containing **173** has been observed also. The large size of the sulfur atom may interfere with the formation of hydrogen bonds for one of the guest enantiomers, increasing the differences in the complex stabilities ($\Delta\Delta G$) between the two enantiomers. A favorable effect of sulfur atoms on enantiomeric recognition has been noted also for pyridine-containing macrocycles (see section III-B).

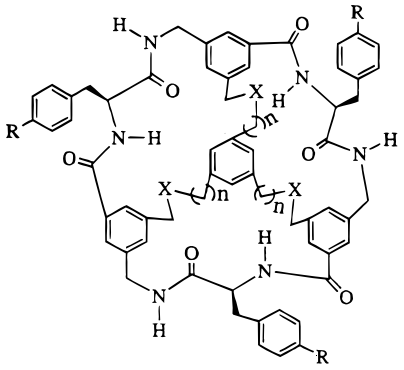
Macrocycle **174** has essentially the same structure as **173** but has three naphthalene groups replaced by benzene groups. The macrocycles **170**, **171**, and **173** have a cup-like shape with an ~6 Å diameter cavity.[182,189] Replacement of benzene by naphthalene enlarges the cavity diameter of the cup-like shape of **174** to ~8 Å.[189] This enlargement results in the host **174** exhibiting high enantioselectivity for large polypeptide substrates, such as the enantiomer pair iPrCO-L-Ala-(L,D)-Pro-L-Ala-$NHC_{12}H_{25}$ ($\Delta\Delta G$ = 13.0 kJ/mol, Table 13).

D_2-symmetric macrocycles $\mathbf{A_4B_6}$ (Chart 21), $\mathbf{A_4C_6}$, and $\mathbf{A_4D_6}$ are cyclooligomers formed from trimesic acid $\mathbf{A}(OH)_3$ and diamines $H_2\mathbf{B}$, $H_2\mathbf{C}$, or $H_2\mathbf{D}$. These macrocycles not only display a high enantioselectivity for N-acylated and Boc-protected peptides but also can be synthesized easily by a simple one-step coupling.[184,186,194] In most cases, $\mathbf{A_4B_6}$ and $\mathbf{A_4C_6}$ show higher degrees of enantioselectivity for the L-configuration of peptide derivatives than does $\mathbf{A_4D_6}$. It is seen in Table 13 that these three hosts bind most D-amino acid substrates with approximately the same binding energies ($-\Delta G$ values: 10.0 ± 0.5, 8.8 ± 0.4, and 9.2 ± 0.4 kJ/mol for $\mathbf{A_4B_6}$, $\mathbf{A_4C_6}$, and $\mathbf{A_4D_6}$, respectively). Therefore, the different extents of enantioselectivities result from different binding energies for L-amino acid substrates. A general

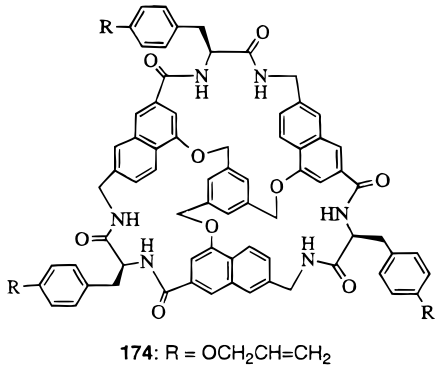
Chart 20. Macrocycles 168−178



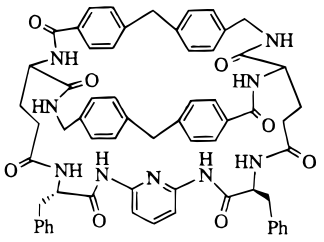
168: X = CH
169: X = N



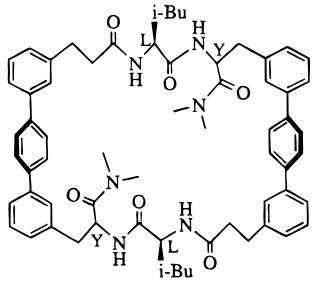
170: X = S, n = 0, R = H
171: X = O, n = 0, R = H
172: X = S, n = 1, R = H
173: X = S, n = 0, R = $OCH_2CH{=}CH_2$



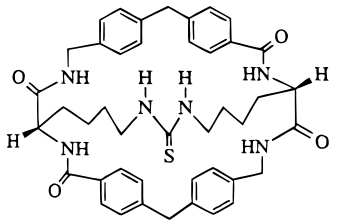
174: R = $OCH_2CH{=}CH_2$



175

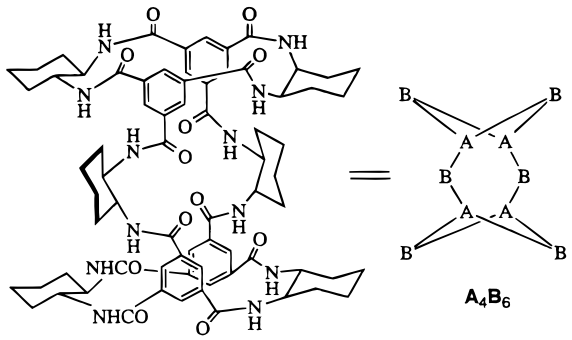


177: LLLL (Y = L)
178: DLDL (Y = D)

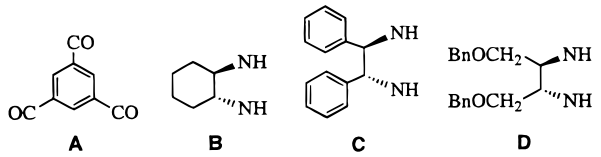


176

Chart 21. Macrocycles A_4B_6



A_4B_6



A B C D

binding model[184,186] illustrates that, by binding with the amino acid substrates through four hydrogen bonds, $\mathbf{A_4B_6}$, $\mathbf{A_4C_6}$, and $\mathbf{A_4D_6}$ can project L-amino acid side chains into the central cavity of the host molecules but project D-amino acid side chains away from the binding site and into the solvent. Thus, the binding energies of D-amino acid guests with the host are roughly the same and the different sizes and shapes of the L-amino acid side chains result in different binding energies.

Still and co-workers used a combinatorial library method to find the most tightly binding substrates with the macrocyclic receptors.[35,187−189] The approach dealt with a solid-phase color assay employing an encoded combinatorial library of ~50 000 acylated tripeptide substrates. The libraries were prepared on 50−80 μm polystyrene beads and each library bead carried only one type of tripeptide substrate. Then the libraries were screened for binding by treatment with solutions of a dye-linking analogue of the macrocycle. After equilibration, a fraction of the beads became colored. The most deeply colored beads were picked and decoded to reveal the most tightly binding substrates. With this method, **173** and **174** were found to most tightly bind tripeptides containing cyclopropanoyl-L-Ala and L-Pro, respectively, over the other substrates studied.[188,189] As is seen in Table 13, excellent enantiomeric recognition toward several tripeptide substrates by **173** and **174** is observed. Receptor **173** exhibits a $\Delta\Delta G$ value of larger than 20 kJ/mol for an enantiomer pair of tripeptides. This difference in binding energies corresponds to a $\Delta(\log K)$ value of 3.5 at 25 °C, which is the largest degree of enantiomeric recognition observed so far for tripeptides.

Still and co-workers have recently studied sequence-selective peptide binding by receptors **170**, **174**, $\mathbf{A_4B_6}$, and other related macrocycles and podands using encoded combinatorial libraries.[35,195−200] The results demonstrate that these macrocyclic receptors bind peptides with significant sequence-selectivity, indicating that many polyfunctional and enantioselective host molecules have also significant sequence-selective peptide-binding properties.

An amidopyridine unit of **175** and a thiourea moiety of **176** were shown to be strong binding sites

Table 13. Binding Energies (kJ/mol) of Chiral Macrocycles (hosts) and Amine Compounds (guests)[a] in $CDCl_3$ (except those indicated in note *c*)

host	guest	$-\Delta G$	$\Delta\Delta G^b$	*T*, °C	ref
168[c]	PhCHMeNHCOMe	12.72 (*S*), 10.96 (*R*)	1.76	?	179
	PhCHMeNHCOH	13.31 (*S*), 11.92 (*R*)	1.39	?	179
	PhCHMeNHCOEt	7.53 (*S*), 6.49 (*R*)	1.04	?	179
	1-NpCHMeNHCOMe	10.71 (*S*), 9.67 (*R*)	1.04	?	179
	BnOAlaNHCOMe	9.58 (*S*), 7.57 (*R*)	2.01	?	179
	MeOPGlyNHCOMe	7.99 (*S*), 8.62 (*R*)	0.63	?	179
169	Ac-Ala-NHBn	9.87 (L), 5.69 (D)	4.18	25	180
	PhAc-Ala-NHMe	8.45 (L), 7.99 (D)	0.46	25	180
	Ac-Ala-OBn[c]	14.48 (L), 12.26 (D)	2.22	25	180
	Ac-Ala-L-Ala-OBn	10.75 (L), 6.99 (D)	3.76	25	180
	Ac-Ala-D-Ala-OBn	9.37 (L), 6.19 (D)	3.18	25	180
	Ac-Ala-NH-tBu	9.83 (L), 4.35 (D)	5.48	25	180
	Ac-Ala-NH-tBu[c]	18.33 (L), 13.85 (D)	4.48	25	180
170	*N*-Boc-Ala-NHMe	16.3 (L), 7.1 (D)	9.2	25	181, 182
	N-Boc-Ala-NHEt	15.5 (L), 7.1 (D)	8.4	25	183
	N-Ac-Ala-NHMe	16.3 (L), 11.3 (D)	5.0	25	181
	N-Ac-Ala-NHtBu	12.6 (L), 8.4 (D)	4.2	25	181
	Pr-Ala-OtBu	15.9 (L), 9.6 (D)	6.3	23	182
	Ac-Ala-OtBu	12.6 (L), 6.3 (D)	6.3	23	182
	Boc-Ala-OMe	6.3 (L), 5.0 (D)	1.3	23	182
	MeO_2C-Ala-OtBu	20.1 (L), 9.6 (D)	10.5	23	182
	Boc-Ala-Ala-NHMe	12.1 (L,L), 8.4 (D,D)	3.7	23	182
	MeO_2C-Ala-Ala-OtBu	19.7 (L,L), 9.2 (D,D)	10.5	23	182
	N-Boc-Val-NHMe	18.4 (L), 6.3 (D)	12.1	25	181, 182
	MeO_2C-Val-OtBu	15.5 (L), 6.3 (D)	9.2	23	182
	N-Boc-Leu-NHMe	17.2 (L), 6.3 (D)	10.9	25	181, 183
	N-Boc-Ser-NHMe	>25.5 (L), 15.9 (D)	>9.6	25	181, 182
	N-Boc-Ser-NHEt	>25.5 (L), 15.9 (D)	>9.6	25	183
	N-Ac-Ser-NHtBu	17.6 (L), 12.6 (D)	5.0	25	183
	MeO_2C-Ser-OtBu	>29.3 (L), 19.7 (D)	>9.6	23	182
	Boc-Ser-OMe	19.7 (L), 12.1 (D)	7.6	23	182
	N-Boc-Thr-NHMe	>25.9 (L), 13.4 (D)	>12.5	25	181
	Boc-Thr-OMe	19.7 (L), 13.0 (D)	6.7	23	182
	Boc-His-OMe	14.6 (L), 11.3 (D)	3.3	23	182
	Boc-Asn-OMe	13.0 (L), 9.2 (D)	3.8	23	182
	Boc-Gln-OMe	17.6 (L), 9.2 (D)	8.4	23	182
	Boc-Glu(OMe)-OMe	12.1 (L), 5.9 (D)	6.2	23	182
171	*N*-Boc-Ala-NHMe	15.9 (L), 8.8 (D)	7.1	25	181
	N-Boc-Val-NHMe	16.7 (L), 6.3 (D)	10.4	25	181
	N-Boc-Leu-NHMe	15.9 (L), 6.7 (D)	9.2	25	181
	N-Boc-Ser-NHMe	>25.9 (L), 18.4 (D)	>7.5	25	181
172	*N*-Boc-Ala-NHMe	11.7 (L), 8.8 (D)	2.9	25	183
	N-Boc-Ala-NHEt	7.5 (L), 8.8 (D)	1.3	25	183
	N-Ac-Ala-NHtBu	13.4 (L), 9.6 (D)	3.8	25	183
	N-Boc-Val-NHMe	13.0 (L), 7.5 (D)	5.5	25	183
	N-Boc-Leu-NHMe	13.0 (L), 10.5 (D)	2.5	25	183
	N-Boc-Ser-NHMe	23.0 (L), 18.4 (D)	4.6	25	183
	N-Boc-Ser-NHEt	18.8 (L), 18.4 (D)	0.4	25	183
	N-Ac-Ser-NHtBu	16.3 (L), 18.0 (D)	1.7	25	183
	N-Boc-Thr-NHMe	19.7 (L), 14.2 (D)	5.5	25	183
173	cPrCO-L-Ala-OtBu	27.6 (L), 13.4 (D)	14.2	?	188
	cPrCO-L-Ala-L-Pro-L-Ala-$NHC_{12}H_{25}$	23.8		?	188
	cPrCO-D-Ala-L-Pro-L-Ala-$NHC_{12}H_{25}$	*d*	>20	?	188
174	iPrCO-L-Ala-L-Pro-L-Ala-$NHC_{12}H_{25}$	31.0		?	189
	iPrCO-D-Ala-L-Pro-L-Ala-$NHC_{12}H_{25}$	23.0	8.0[e]	?	189
	iPrCO-L-Ala-D-Pro-L-Ala-$NHC_{12}H_{25}$	18.0	13.0[e]	?	189
	iPrCO-D-Ala-L-Pro-D-Ala-$NHC_{12}H_{25}$	18.4	12.6[e]	?	189
	iPrCO-L-Pro-L-Pro-L-Ala-$NHC_{12}H_{25}$	25.1		?	189
	iPrCO-L-Pro-L-Pro-D-Ala-$NHC_{12}H_{25}$	22.6	2.5	?	189
175	Cbz-Ala	15.6 (L), 17.6 (D)	2.0	?	191
	Boc-Val	12.6 (L), 10.7 (D)	1.9	?	191
	Boc-Phe	14.6 (L), 15.8 (D)	1.2	?	191
	Boc-Ser	17.6 (L), 14.8 (D)	2.8	?	191
	Cbz-Gly-Ser	19.2 (L), 15.4 (D)	3.8	?	191
	Cbz-Ala-Ala	14.6 (L,L), 17.7 (D,D)	3.1	?	191
	Cbz-β-alanyl-Ala	19.1 (L), 22.8 (D)	3.7	?	191
177	cyclo-Gly-Leu	18.8 (L), 14.7 (D)	4.1	23	193
	cyclo-Leu-Leu	15.6 (L,L), 10.5 (D,D)	5.1	23	193
178	cyclo-Gly-Leu	15.4 (L), 16.1 (D)	0.7	23	193
	cyclo-Leu-Leu	13.8 (L,L), 14.2 (D,D)	0.4	23	193
$\mathbf{A_4B_6}$	*N*-Ac-Ala-NHMe	14.6 (L), 9.2 (D)	5.4	25	184
	N-Ac-Val-NHMe	20.9 (L), 10.0 (D)	10.9	25	184
	N-Boc-Val-NHMe	11.7 (L), 7.1 (D)	4.6	25	184
	N-Boc-Val-NH_2	20.5 (L), 15.5 (D)	5.0	25	184

Table 13 (Continued)

host	guest	$-\Delta G$	$\Delta\Delta G^b$	T, °C	ref
	N-Ac-Ile-NHMe	18.0 (L), 10.0 (D)	8.0	25	184
	N-Ac-Leu-NHMe	14.2 (L), 10.0 (D)	4.2	25	184
	N-Ac-Phe-NHMe	*d* (L), 8.4 (D)	>8.4	25	184
	N-Ac-Ser-NHMe	14.6 (L), 14.2 (D)	0.4	25	184
	N-Ac-HSer-NHMe	21.3 (L), 15.5 (D)	5.8	25	184
	N-Ac-Thr-NHMe	14.6 (L), 12.1 (D)	2.5	25	184
	N-Ac-PGly-NHMe	24.7 (L), 12.1 (D)	12.6	25	184
	N-Ac-EGly-NHMe	23.8 (L), 10.0 (D)	13.8	25	186
	N-Ac-PrGly-NHMe	25.1 (L), 10.5 (D)	14.6	25	186
	N-Ac-BuGly-NHMe	16.3 (L), 10.5 (D)	5.8	25	186
	N-Boc-Gly-Val-NHMe	25.9 (L), 13.4 (D)	12.5	25	184
	N-Boc-Gly-Val-Gly-NHBn	>30.1 (L), 19.2 (D)	>10.9	25	184
$\mathbf{A_4C_6}$	*N*-Ac-Ala-NHMe	17.2 (L), 9.6 (D)	7.6	25	186
	N-Ac-Val-NHMe	18.8 (L), 8.8 (D)	10.0	25	186
	N-Ac-Ile-NHMe	17.6 (L), 8.4 (D)	9.2	25	186
	N-Ac-Leu-NHMe	15.1 (L), 8.8 (D)	6.3	25	186
	N-Ac-Phe-NHMe	*d* (L), 6.3 (D)		25	186
	N-Ac-PGly-NHMe	23.8 (L), 7.5 (D)	16.3	25	186
	N-Ac-EGly-NHMe	23.0 (L), 8.8 (D)	14.2	25	186
	N-Ac-PrGly-NHMe	23.8 (L), 9.2 (D)	14.6	25	186
	N-Ac-BuGly-NHMe	15.9 (L), 9.2 (D)	6.7	25	186
$\mathbf{A_4D_6}$	*N*-Ac-Ala-NHMe	15.5 (L), 8.4 (D)	7.1	25	186
	N-Ac-Val-NHMe	15.9 (L), 9.6 (D)	6.3	25	186
	N-Ac-Ile-NHMe	10.9 (L), 9.2 (D)	1.7	25	186
	N-Ac-Leu-NHMe	10.5 (L), 9.2 (D)	1.3	25	186
	N-Ac-Phe-NHMe	*d* (L), 5.9 (D)		25	186
	N-Ac-PGly-NHMe	14.2 (L), 7.5 (D)	6.7	25	186
	N-Ac-EGly-NHMe	23.0 (L), 9.2 (D)	13.8	25	186
	N-Ac-PrGly-NHMe	20.1 (L), 9.0 (D)	10.5	25	186
	N-Ac-BuGly-NHMe	10.5 (L), 9.6 (D)	0.9	25	186

[a] PGly = phenylglycine; EGly = ethylglycine; PrGly = propylglycine; BuGly = butylglycine; cPr = cyclopropyl; HSer = homoserine. [b] The $\Delta\Delta G$ value is the difference between ΔG values for the interactions of an enantiomer pair with a given macrocyclic host. [c] Determined in C_6D_6. [d] No complexation observed. [e] The $\Delta\Delta G$ value is relative to iPrCO-L-Ala-L-Pro-L-Ala-$NHC_{12}H_{25}$.

for carboxylate anions of various amino acid derivatives.[191,192] It is seen in Table 13 that **175** exhibits better enantioselectivity for dipeptide substrates than for single amino acid derivatives. Binding constants in $CDCl_3$ for the interactions of **176** with various acylated amino acids (as tetrabutylammonium carboxylates) have been determined by a solvent extraction method.[192] log K values in $CDCl_3$ for **176**-L-Ala and **176**-D-Ala interactions are 4.23 and 4.16, respectively, giving a Δ(log K) value of 0.07, while **176** recognizes L-Phe (log K = 4.34) over D-Phe (log K = 4.12) by 0.22 log K unit. ^{1}H NMR spectra showed that the bound D-Ala and D-Phe substrates were in substantially different environments compared to the L-substrates.[192]

C_2-Symmetric **177** and **178** did not interact with linear flexible peptides.[193] Since **177** and **178** have an open and doughnut-like conformation and the overall dimensions of the binding sites are large, their binding sites should be complementary to rigid guests having a slightly greater distance between their hydrogen bond acceptor/donor sites. Both computer docking simulation and ^{1}H NMR experiments showed that cyclo-Gly-Leu, the cyclic diketopiperazine of the Gly-Leu peptide, fitted well in the binding sites of the hosts **177** and **178**.[193]

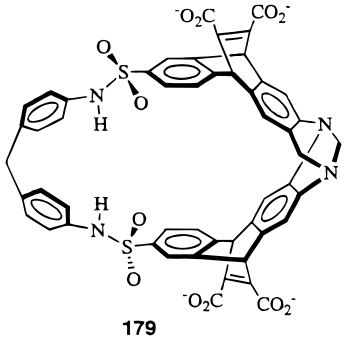
C. Solvent Effect

As shown in Table 13, most ΔG values have been determined in $CDCl_3$ and a few in C_6D_6. Chiral recognition of Ac-Ala-NH-tBu by **169** is a comparable case. In C_6D_6, the complexes are more stable (more negative ΔG values) but the degree of enantiomeric recognition ($\Delta\Delta G$ = 4.48 kJ/mol) is lower than those in $CDCl_3$ ($\Delta\Delta G$ = 5.48 kJ/mol). The higher stability of the host−guest complexes in C_6D_6 is due to the lower polarity of the solvent as compared with $CDCl_3$. The $\Delta\Delta G$ value for Ac-Ala-OBn interaction with **169** in C_6D_6 (2.22 kJ/mol) is also smaller than that for Ac-Ala-L-Ala-OBn interaction with **169** in $CDCl_3$ (3.76 kJ/mol).

D. Other Cyclophane-Type Macrocycles

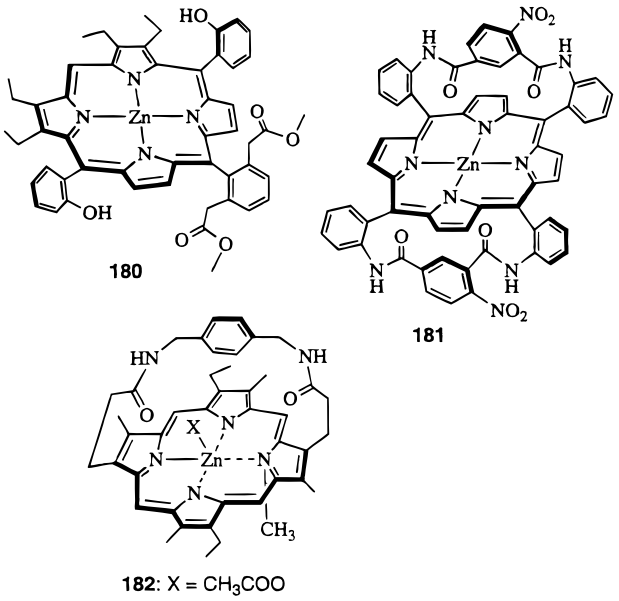
Wilcox and co-workers synthesized several water-soluble cyclophanes.[36,201−205] One of them, **179** (Chart 22), was shown to enantioselectively bind neutral aliphatic and alicyclic substrates. Because of phenyl and ethenoanthracene moieties, macrocycle **179** is highly rigid. Binding constants for the interaction of **179** with (+)- and (−)-menthols were determined in D_2O (pD = 9.0) at 20 °C by an NMR titration

Chart 22. Macrocycle 179



179

Chart 23. Zn−Porphyrin Complexes 180−182



180 **181** **182**: X = CH_3COO

procedure.[203,204] log *K* values for **179**-(+)-menthol and **179**-(−)-menthol interactions were 3.30 and 3.40, respectively, resulting in a degree of chiral recognition of 0.10 as measured by the Δ(log *K*) value. This difference in binding constants, though small, is unprecedented in the context of small alicyclic molecular recognition in aqueous media. Enantioselection was also observed for citronellol[205] and 3,3-dimethylcyclohexanol.[36]

The binding of aliphatic and alicyclic guests by **179** and related macrocycles is believed to be achieved primarily by hydrophobic interactions. Determination of binding constants at different temperatures and an examination of Δ*H* and Δ*S* values support this hypothesis.[36]

Additional chiral cyclophane hosts have been synthesized and studied for their chiral binding properties by Koga,[206] Diederich,[207−209] Collet,[210] and their co-workers. ^{1}H NMR spectroscopic studies indicate the formation of diastereomeric complexes, but a quantitative evaluation of the extent of chiral recognition has not been made in most cases.

XIII. Zn−Porphyrin-Based Macrocycles

The chiral recognition ability of porphyrins was evaluated in the late 1980s by determining association constants for the reaction of Rh(III)−porphyrin complexes and amino acid methyl esters to form adducts[211] and by examining HPLC behavior of similar diastereomeric adducts.[212] Recently, Ogoshi and co-workers observed high degrees of enantiomeric recognition of methyl esters of amino acids with Zn−porphyrin-based macrocyclic compounds (**180** and **181**, Chart 23).[213−217] In this type of host−guest interaction system, chiral recognition is accomplished by a cooperative action of three recognition groups. First, Zn metal serves as a strong coordination site for the amine groups of guests. Second, attractive hydrogen-bonding interactions between the carbonyl group of the amino acid and the amide NH group of **181** or OH groups of **180** occur. These attractive interactions result in a fixed conformation of the complexes. Chiral recognition stems from the steric interaction between the Zn−porphyrin host and the residual group of the amino acid. A stronger hydrogen-bonding interaction fixes the internal rotation of the bound guest well and results in a better enantioselection.[217,218] Because of the coordination of the Zn atom with the amine group, the Zn−porphyrins differentiate between neutral amino acid esters instead of cationic amino compounds. Therefore, the recognition mechanism of Zn−porphyrin macrocycles is different from that of chiral crown ethers, which usually form host−guest complexes with ammonium cations through hydrogen bonding.

As shown in Table 14, Zn−porphyrin-based macrocycles exhibit significant enantiomeric recognition toward amino acids. For **181**, most Δ(log *K*) values are larger than 0.5. In CH_2Cl_2, the Δ(log *K*) value for **181**−L-Leu-OMe system is as large as 0.94. Compared with **180**, **181** shows better chiral recognition due to the large size of the substituents on the porphyrin. The macrocyclic structures of the substituents of **181** also have an effect on the high extent of the recognition. This macrocyclic substitution, together with the rigid Zn−porphyrin framework, gives the host molecule a rigid conformation that favors enantiomeric recognition.

Both coordination of the amine group of the guest with the Zn metal of the host and hydrogen bonding between host and guest molecules were confirmed by ^{1}H NMR results.[216,217] On addition of the L-Val-OMe guest, the two amide protons of the (−)-**181** host experienced large downfield shifts, indicating a hydrogen-bonding interaction between these amide protons and the carbonyl group of the guest. On the other hand, an extraordinarily large upfield shift of the amine protons of the L-Val-OMe indicated a direct coordination of the amine group onto the central Zn atom of the porphyrin. It was pointed out that the nitro group on the bridged benzene ring of **181** played an important role in chiral recognition.[216] The hydrogen-bonding ability of the amide NH at the ortho position of the nitro group is enhanced by the electronic effect of the nitro group.

Determination of Δ*H* and Δ*S* values in $CHCl_3$ (containing 0.5% ethanol) for (±)-**181** interactions with amino acid methyl esters indicated that the enantiomeric recognition originated from an enthalpy effect.[216] The formation of the complexes was enthalpically favorable (negative Δ*H* values) and entropically unfavorable (negative Δ*S* values). Determination of the total free energy change for the binding of amino acid guests with reference porphyrins which lacked some of the recognition groups (hydrogen-bonding site or steric-repulsion element) confirmed that the total free energy change for macrocycle **180** interaction included three terms: metal coordination energy, hydrogen-bonding energy, and steric-repulsion energy.[215,217−219]

Ligand **180** shows essentially no chiral recognition toward Ala-OMe and Am**3**, which is a result of the small side chain of Ala-OMe and absence of a hydrogen-bonding acceptor site of Am**3**.[215] On the other hand, appreciable enantioselectivity can be observed for Am**2** due to the presence of a hydrogen-bonding site (carbonyl group). The high degree of

Table 14. log *K* and Δ(log *K*) Values[a] Determined by UV−Visible Spectrophotometric Titration for Interactions of the Zn−Porphyrin Complexes with Amine Compounds[b]

host (guest)	guest (host)	log *K*	Δ(log *K*)	*T*, °C	solvt[c]	ref
(+)-**180**	Ala-OMe	3.20 (L), 3.15 (D)	0.05	15	$CHCl_3$	214, 215
	Val-OMe	3.79 (L), 3.39 (D)	0.40	15	$CHCl_3$	214, 215
	Leu-OMe	3.79 (L), 3.39 (D)	0.40	15	$CHCl_3$	214, 215
	Leu-OBn	3.54 (L), 3.19 (D)	0.35	15	$CHCl_3$	214, 215
	Ile-OMe	3.83 (L), 3.38 (D)	0.45	15	$CHCl_3$	214, 215
	Pro-OMe	4.68 (L), 4.32 (D)	0.36	15	$CHCl_3$	215
	Phe-OMe	3.62 (L), 3.31 (D)	0.31	15	$CHCl_3$	215
	Ser-OBn	3.13 (L), 3.45 (D)	0.32	15	$CHCl_3$	214, 215
	Am**3**	2.83 (*S*), 2.85 (*R*)	0.02	15	$CHCl_3$	215
(*S*)-Am**2**	**181**	3.84 (+), 4.04 (−)	0.20	15	$CHCl_3$	213
	181	3.58 (+), 4.11 (−)	0.53	20	95.5% C	216
	181	5.20 (+), 5.30 (−)	0.10	20	CH_2Cl_2	216
L-Ala-OMe	**181**	4.64 (+), 5.26 (−)	0.62	20	CH_2Cl_2	216
L-Val-OMe	**181**	3.59 (+), 4.34 (−)	0.75	15	$CHCl_3$	213
	181	3.69 (+), 4.38 (−)	0.69	20	95.5% C	216
	181	5.04 (+), 5.91 (−)	0.87	20	CH_2Cl_2	216
L-Leu-OMe	**181**	3.62 (+), 4.23 (−)	0.61	20	95.5% C	216
	181	4.93 (+), 5.87 (−)	0.94	20	CH_2Cl_2	216
L-Phe-OMe	**181**	3.45 (+), 4.18 (−)	0.73	15	$CHCl_3$	213
	181	3.61 (+), 4.30 (−)	0.69	20	95.5% C	216
	181	4.85 (+), 5.70 (−)	0.85	20	CH_2Cl_2	216
L-Am**47**	**181**	3.73 (+), 4.38 (−)	0.65	15	$CHCl_3$	213

[a] The Δ(log *K*) value is the difference between log *K* values for interactions of an enantiomer pair of amino acids with macrocyclic host **180** or of an enantiomer pair of **181** with a given amino guest. [b] All amino compounds are in neutral amine forms. [c] 95.5% C = $CHCl_3$ containing 0.5% ethanol as a stabilizer.

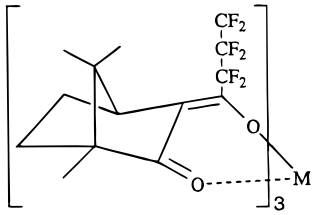
enantiomeric recognition of Ala-OMe with **181** [Δ(log *K*) = 0.62] is attributed to the large and rigid substituents on the porphyrin framework.

It was found that porphyrin **181** itself (without the complexed Zn^{2+}) specifically recognized tartaric acid derivatives with four-point hydrogen bonding.[220] Ligand **181** formed a complex with diethyl L-tartrate with the log *K* value of 3.65 in $CHCl_3$ at 15 °C, but its complex with the meso isomer of the guest had a log *K* value of only 2.72.

Inoue and co-workers showed that Zn−porphyrin complex **182** exhibited high enantioselectivity for carboxylate anions of N-protected amino acids.[221] In **182**, Zn metal is not only complexed with the porphyrin ring but also axially binds an acetate ion. Thus, this Zn−porphyrin complex is capable of undergoing axial ligand exchange with various anions. When **182** interacts with an N-protected amino acid, the amino acid replaces the acetate to form a coordination bond with Zn through its carboxylate group. In addition, two amide functionalities on the bridge of the **182** have a capability of hydrogen bonding with guest amino acids. Chiral recognition of amino acids with **182** was examined by solvent extraction of sodium salts of N-protected amino acids from aqueous solution into a $CHCl_3$ phase containing **182**.[221] In most cases, the (+)- and (−)-**182** preferentially bound the L- and D-substrates, respectively. The ratios of the major to the minor diastereoisomer pairs in the $CHCl_3$ phase were 84/16 to 96/4 for amino acid substrates having NHCO moieties.[221]

Chiral lanthanide−tris(β-diketonate) complexes (Ln(β-DK)$_3$, Chart 24) are another case in which coordination of the metal (lanthanide) ion with amino acids plays an important role in enantiomeric recognition.[222,223] A zwitterionic amino acid interacts with a Ln(β-DK)$_3$ complex through a two-point binding. Both amine and carboxylate portions of amino acids coordinate with the lanthanide ion. Discrimination

Chart 24. Ln(β-DK)$_3$



Ln(β-DK)$_3$, M = Pr, Eu, Er, Yb

between enantiomers of amino acids stems from the chirality of the β-diketonates. It has been demonstrated recently by Tsukube and co-workers that zwitterionic amino acids in neutral aqueous solutions can be enantioselectively extracted into CH_2Cl_2 solutions containing chiral Ln(β-DK)$_3$ complexes. The best enantioselectivity has been observed for phenylglycine, which shows an ee value of 49%.[222,223]

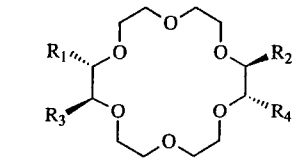
XIV. Other Chiral Macrocycles

The following chiral macrocycles have been investigated for their recognition of the enantiomers of amine compounds.

A. 18-Crown-6 (18C6) Derivatives

Attachment of substituents to the aliphatic carbons of an 18C6 molecule results in a chiral 18C6 derivative. Interaction between the 18C6 ring and an NH_3^+ group anchors the guest molecule on the macroring, and the steric interaction between the 18C6 side chains and the guest species may result in enantiomeric recognition. Lehn and Sirlin demonstrated that a chiral 18C6 derivative (**183**, Chart 25) bearing four cysteinyl residues reacted *ca.* 50−90 times faster with the *p*-nitrophenyl ester of the dipeptide Gly-L-Phe than with its D-antipode.[224] The high chiral recognition may reside in the differences in the extent of complexation or in reactivity within the complexes

Chart 25. Macrocycles 183−200



183: $R_1 = R_2 = R_3 = R_4 =$ CONH-(L)-CH(CH$_2$SH)-COOMe

184: $R_1 = R_2 = C(CH_3)_3$, $R_3 = R_4 = H$

185: $R_1 = C(CH_3)_3$, $R_2 = R_3 = R_4 = H$

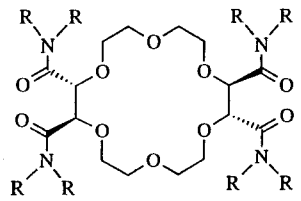
186: $R_1 = R_3 = CH_3$, $R_2 = R_4 = H$

187: $R_1 = R_2 = R_3 = R_4 =$ CONH-(L)-CH(CH$_2$-indole)-COOMe

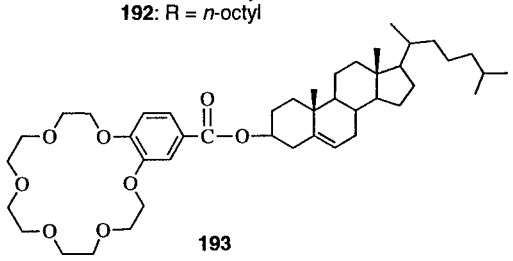
188: $R_1 = R_2 = R_3 = R_4 =$ CONH-(1-pyrenyl)

189: $R_1 = R_2 = R_3 = R_4 =$ CONH-(L)-CH(CH$_2$Ph)-COOMe

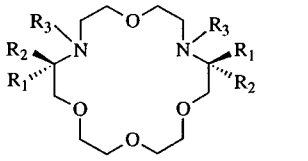
190: $R_1 = R_2 = R_3 = R_4 = CON(CH_3)_2$



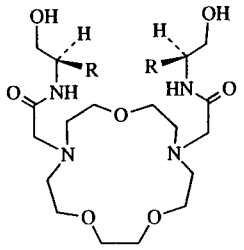
191: R = *n*-butyl
192: R = *n*-octyl



193



194: $R_1 = CHMe_2$, $R_2 = H$, $R_3 = Me$
195: $R_1 = CH_2Ph$, $R_2 = H$, $R_3 = Me$
196: $R_1 = H$, $R_2 = Ph$, $R_3 = Me$
197: $R_1 = CHMe_2$, $R_2 = H$, $R_3 = CH_2Ph$
198: $R_1 = CH_2Ph$, $R_2 = H$, $R_3 = CH_2Ph$
199: $R_1 = i$-Pr, $R_2 = H$, $R_3 = CH_2Ph$



200
R = CH_2Ph

of the two enantiomeric substrates. Both chiral centers on the macroring and in the cysteinyl residues of **183** may play a role.

A bis(*tert*-butyl)-substituted 18C6 (**184**) has been shown by a bulk liquid membrane transport experiment to have higher enantioselectivity toward Am**2**, Am**3**, and Am**25** than does either the mono(*tert*-butyl)-substituted 18C6 (**185**) or bis(methyl)-substituted 18C6 (**186**),[225] indicating an effect of the bulkiness of the chiral substituents on enantiomeric recognition.

Tundo and Fendler determined binding constants for interactions of chiral **187** and **188** with dipeptides Gly-Phe and Gly-Trp using a fluorometric method.[226] log *K* values for interaction of **187** with Gly-L-Phe and Gly-D-Phe in MeOH were 4.11 and 4.28, respectively, resulting in a degree of chiral recognition of 0.17 in Δ(log *K*) units. Interactions of Gly-L-Trp with D- and L-**188** in THF exhibited log *K* values of 5.08 and 4.70, respectively, leading to a Δ(log *K*) value of 0.38.[226]

The enantioselection ability of chiral 18C6 derivatives **189** and **190** was evaluated by a membrane electrode method.[227] A distinct difference of electrode response of **189** was observed between enantiomers of Am**3** and Am**7**. The selectivity coefficients of **189** for Am**3** and Am**7** enantiomers were 1.5 and 1.4, respectively. In the case of **190**, on the other hand, the electrode response for the (*R*) enantiomers of Am**3** and Am**7** was very similar to that for the (*S*) ones, indicating that **190** did not discriminate between Am**3** and Am**7** enantiomers. Thus, it was suggested that a chiral 18C6 needed to have bulky chiral chains to show enantioselectivity.[227]

Simon and co-workers used an electrochemical procedure to evaluate enantioselectivity of several chiral macrocyclic receptors.[167,168,228−232] A polymeric membrane electrode containing a chiral macrocycle was prepared and its potentiometric response to enantiomers of different substrates was found to be different. With this method, a chiral tetracarboxamide derivative of 18C6 (**191**, Chart 25) was shown to recognize Am**3** enantiomers by a factor of 2.7 using the potentiometric procedure.[228,231] The binaphthyl-containing (*S*,*S*)-**13** displayed a potentiometric recognition factor of 4.2 for Am**2**.[168] These investigators have developed an enantioselective optode membrane to determine enantiomeric excess.[232] A highly lipophilic chiral 18C6 derivative, (*R*,*R*,*R*,*R*)-**192** or (*S*,*S*,*S*,*S*)-**192**, was combined with a H^+-selective chromoionophore (as a sensor) in a plasticized PVC membrane. The enantiomeric recognition process was translated by this optical-response sensor into a signal that was easily measured by a conventional spectrophotometer. With this new optode membrane an enantioselective coefficient of 0.37 for Am**3** was determined. This coefficient was in agreement with the potentiometric coefficient (0.39).[232]

Chiral 18-crown-6 tetracarboxylic acid derived from tartaric acid was first synthesized by Lehn and coworkers.[45,233] This chiral 18C6 derivative was shown to exhibit high efficiency in enantiomeric resolution by capillary zone electrophoresis.[14−19]

Kawabata and Shinkai have demonstrated that cholesterol derivative **193** (Chart 25), which bears an 18C6 moiety as an NH_3^+ binding site, provides a monolayer system formed at the air−water interface for chiral discrimination of α-amino acid derivatives.[234] Ligand **193** shows chiral discrimination for enantiomer pairs of Am**5**, Am**7**, Am**8**, and Am**9**. The largest difference in chiral recognition is observed for the enantiomer pair of Am**7**. It is believed that the NH_3^+ moiety is bound to the 18C6 ring. Since the α-amino acid residue CH_2R is more hydrophobic than the CO_2Me group, the CH_2R should be trapped in the hydrophobic cholesterol stacks. As a result, the chiral plane of the cholesterol skeleton enforces the orientation of α-amino acid derivatives and they are recognized at two points (NH_3^+ by the crown ring and CH_2R by the cholesterol plane) by the **193** monolayer.[234]

B. Aza-Crown Ether Derivatives

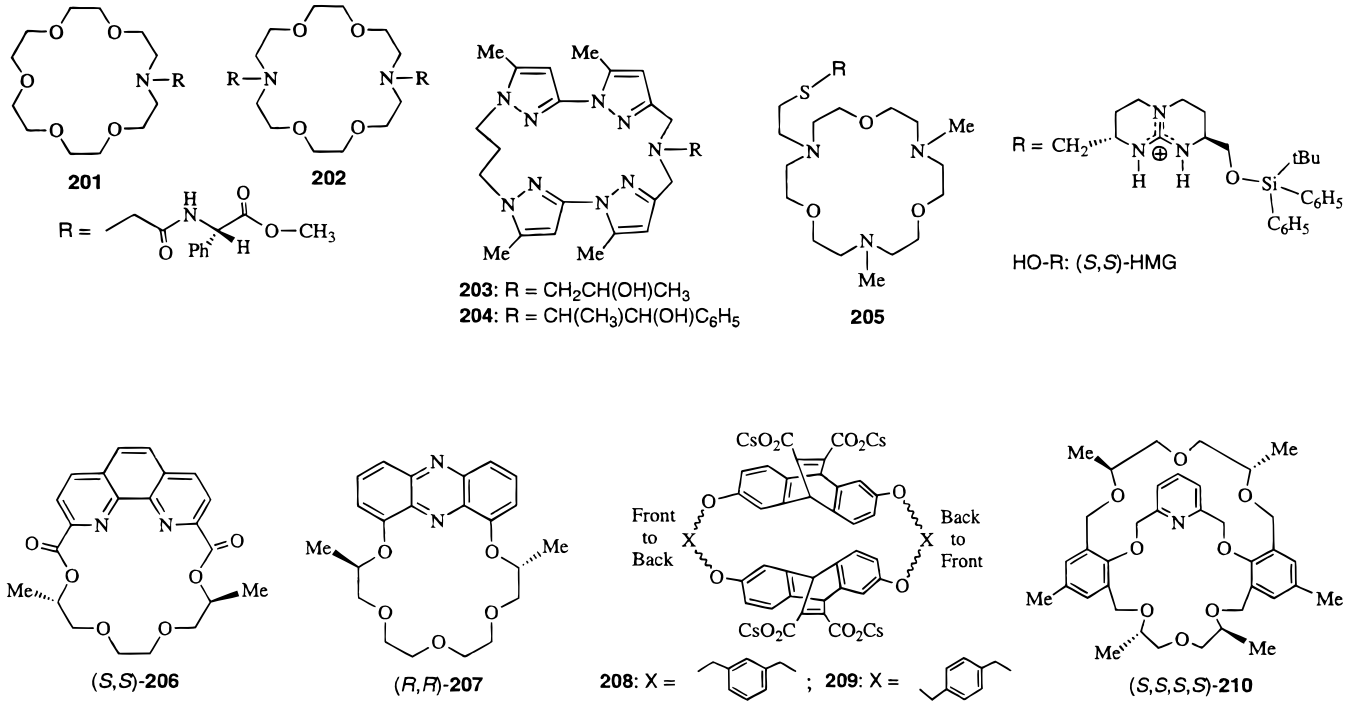
Sutherland and co-workers studied properties of enantiomeric recognition by several chiral aza-crown ether derivatives.[235,236] ^{1}H NMR spectral studies indicated that the complexes of the chiral macrocycles **194**−**199** (Chart 25) with the (*R*)- or (*S*)-Am**3** thiocyanate salts in dry $CDCl_3$ or CD_2Cl_2 gave distinctive and different NMR signals between the components of the enantiomer pair. Macrocycle **197** selectively bound the (*R*) over the (*S*) form of Am**3**. Ligand **198**, with a sterically less demanding R_1 group, showed similar NMR spectral behavior in dry $CDCl_3$ or CD_2Cl_2 but enantioselectivity in favor of the (*R*)-Am**3** was qualitatively less than that shown by **197**. This pronounced enantioselectivity was lost in the presence of water due to the formation of hydrated complexes. Thus, the solvent extraction experiments indicated only slightly selective extraction of the (*S*)-Am**3** thiocyanate salt by (*S*,*S*)-macrocycles **194** and **195**[235,236] and of the (*R*)-Am**3** salt by the (*R*,*R*)-macrocycle of **196**.[235]

Determination of free energies of activation ($\Delta G^{\ddagger}$) values by a ^{1}H NMR method indicated small differences between the dynamic stabilities of the complexes of (*R*)- and (*S*)-Am**3** with **195** and **196** in spite of the considerable differences in the ^{1}H NMR spectra of the diastereomeric complexes.[236] The solvent extraction coefficients showed a slight preference of **199** for (*R*)-Am**3**. The reliability of values of the extent of enantioselectivity obtained by only a comparison of different ^{1}H NMR spectra between the diastereomeric complexes has been questioned.[237] When a chiral host molecule is combined with the individuals of an enantiomer pair of a chiral guest, one obtains diastereomeric complexes that are easily distinguishable by high field NMR. Such effects must occur and in no way indicate enantiospecificity, i.e., the preferential binding of one particular enantiomer. To demonstrate enantiospecific binding, one must independently determine the binding affinities of each enantiomer.[237]

When chiral centers are located on pendant arms instead of on the macroring, such as those in **200**, the ligand shows no chiral recognition ability. Sutherland's research group has studied other chiral aza-crown ethers and their chiral recognition behavior has been examined also by ^{1}H NMR spectroscopy.[236,238]

Gokel and co-workers described the enantioselective transport of Z-amino acids [Z = (benzyloxy)-carbonyl] and dipeptide K^+ carboxylates through a bulky chloroform membrane by two lariat ethers bearing *N*-pivot dipeptide arms.[239,240] The single- and double-armed lariat ethers **201** and **202** (Chart 26) were shown to be efficient carriers with chiral recognition properties. The single-armed **201** showed higher transport rates than the double-armed **202**, but **202** exhibited better chiral recognition than **201**. The highest enantioselectivity was observed for **202** and D,L-Z-α-phenylglycineO^-K^+ giving a ratio of

Chart 26. Macrocycles 201−210



transport rates (L/D) of 1.6. The different transport rates between lariat ethers **201** and **202** were a result of different numbers of chiral pendant arms. The study indicated that the chiral pendant arm(s) not only participated in interactions with the transported substrates but also resulted in enantiomeric recognition.[239,240]

Two other aza-macrocycles containing a chiral pendant arm were reported by Tarrago and co-workers.[241,242] These tetrapyrazolic macrocycles (**203** and **204**, Chart 26) were shown to display slight enantioselective transport through a bulk CH_2Cl_2 membrane for racemic amino acids (Trp and Phe) and Li^+ mandelate. The percentages of the D-enantiomers of Phe and Trp salts in the receiving phase were 51% and 49%, respectively. Therefore, a macrocycle having the chiral center(s) on its pendant arm(s) usually shows low enantiomeric recognition. This is not surprising, since a chiral barrier attached on a pendant arm could not display effective steric repulsion for chiral discrimination due to the spatial flexibility of the pendant arm.

Schmidtchen and co-workers recently showed that a triaza-18-crown-6 derivative **205** selectively extracted L-phenylalanine (Am**36**) over the D-form from aqueous to CH_2Cl_2 solution.[243] The ee value of 40% was almost independent of pH in the range of 9.1−10.5. Under the same conditions the (*S*,*S*)-HMG itself (chiral guanidine-containing moiety of **205**, Chart 26) exhibited no enantioselectivity. It was, therefore, the connection of the HMG to the triaza-18-crown-6 that resulted in enantiomeric recognition. An aza-18-crown-6 ligand containing a pendant guanidine moiety as chiral barrier was shown to exhibit a high degree of enantiomeric recognition toward zwitterionic amino acids containing aromatic side chains.[244] This chiral aza-crown ether was included in the review by Webb and Wilcox.[36]

C. Macrocycles Containing Polycyclic Aromatics

A macrocycle incorporating phenanthroline in its structure (**206**, Chart 26) exhibited good enantiomeric recognition toward Am**1** in solvent mixtures of $CD_3OD/CDCl_3$ [$\Delta(\log K)$ values 0.34−0.52].[245] The highest degree of enantiomeric recognition was observed in a mixed solvent containing a moderate amount of methanol [3:7 $CD_3OD/CDCl_3$, $\Delta(\log K) = 0.52$], as demonstrated by pyridine-containing macrocycles **4**, **25**, and **27** (Table 2). (*S*,*S*)-**206** exhibited a moderate recognition toward Am**3** ($\Delta(\log K) = 0.22$ in 1:1 $CD_3OD/CDCl_3$) and no recognition toward Am**4** and Am**7**. Compared with pyridine-containing ligand **4** (see Tables 1 and 2), **206** formed more stable complexes with Am**1** and Am**3** due to a more rigid and flat structure and an extensive π-system.[245] These structural features of **206** were confirmed by X-ray analysis and 2D NMR spectra. The lower degree of enantiomeric recognition by **206** than by **4** can probably be attributed to a more remote distance of the chiral centers from the phenanthroline group.

Macrocycle (*R*,*R*)-**207** has a phenazine group incorporated into the macroring. Although it shows no chiral recognition toward Am**3**, its ability to precipitate (*S*)-Am**1** but not (*R*)-Am**1** in methanol makes it a promising candidate for a simple and efficient approach to the separation of the Am**1** enantiomer.[246]

Dougherty and co-workers reported a series of macrocycles incorporating two or three 2,6-disubstituted 9,10-ethenoanthracene units.[237] These macrocycles formed host−guest complexes with water-soluble organic compounds through hydrophobic and ion−dipole interactions. Among them, two chiral macrocycles, **208** and **209** (Chart 26), were found to exhibit moderate discrimination between the opposite enantiomers of several trimethylammonium cations. The $\Delta\Delta G°$ values evaluated by a ^1H NMR method at 295 K for enantiomeric interactions ranged between 0.4 and 2.7 kJ/mol. The largest $\Delta\Delta G°$ value of 2.7 kJ/mol implied a 3:1 enantioselectivity. Although NMR shift studies demonstrated always distinguishable diastereomeric host−guest interactions, measurement of binding affinities ($\Delta\Delta G°$ values) showed no substantial chiral recognition in several cases.[237] It was concluded that both enantiomers of these nondiscriminating guests could find favorable binding orientations with the hosts studied.

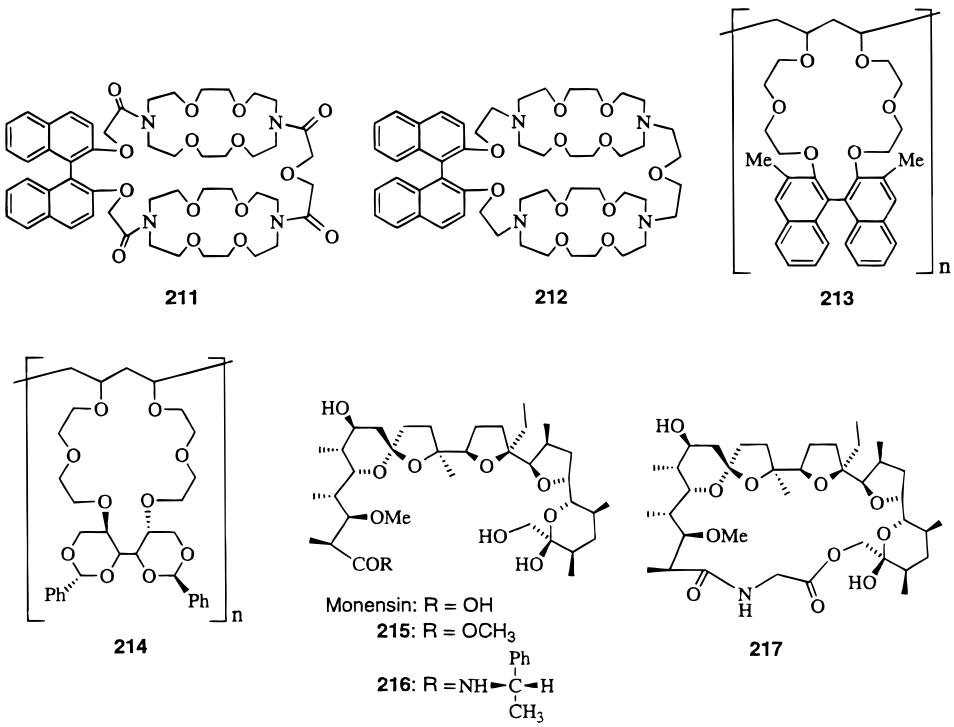
D. Macrobicyclic and Macrotricyclic Compounds

Bradshaw and co-workers recently synthesized a chiral macrobicyclic compound **210** (Chart 26) and studied its chiral recognition properties.[247] (*S*,*S*,*S*,*S*)-**210** showed a high degree of enantiomeric recognition toward Am**1** [$\Delta(\log K) = 0.85$] in a 2:8 (v/v) C_2H_5OH/ClC_2H_4Cl (2Et/8DCE) solvent mixture. This high degree of enantiomeric recognition was probably due to an increase in molecular rigidity by introducing a second macroring and two phenyl groups. Thermodynamic data provided evidence for this point. Positive values of the entropy change for **210**−Am**1** interactions suggested a small conformational change of the ligand during the complexation. The degree of enantiomeric recognition for Am**3** ($\Delta(\log K) = 0.33$ in 1:1 $CD_3OD/CDCl_3$) was much lower than that for Am**1**.

Solvent had a significant effect on enantiomeric recognition. In methanol, no complexation of macrobicyclic **210** with Am**1** and Am**3** could be detected by the ^1H NMR spectral method. Thus, chiral recognition could not be evaluated. In the solvent mixtures used, on the other hand, **210** not only formed complexes with Am**1** and Am**3** but also showed good chiral recognition.[247]

When a binaphthyl group is used as one of the bridges of a cylindrical macrotricycle, as in compounds **211** and **212** (Chart 27), the central cavity becomes chiral.[248] Compounds **211** and **212** exhibited a low degree of enantiomeric recognition.[248,249] The solvent extraction of ammonium salts (Am**1**) from water solution into chloroform by **211** resulted in an ee value about 15% for racemic Am**1**. A transport experiment through a $CHCl_3$ liquid membrane showed a 13% ee value for Am**1** and no enantioselective transport was observed for Am**3**. The fairly low ee values may arise from insufficient repulsive discriminating interactions and perhaps from some amount of external complexation of the NH_3^+ group with the macroring.[248] The observation demonstrated the importance of structural complementarity in enantiomeric recognition. When a binaphthyl group was incorporated into a monocyclic crown ether, good chiral recognition was observed (see section VIII).

Chart 27. Macrocycles 211−217



However, when the same unit was attached to the macrotricyclic compound, the resulting chiral **211** showed poor chiral recognition. The other chiral macrotricycle discussed in section VII (**90**) showed good enantiomeric recognition. In the case of **90**, two tetrahydrofuran units made up part of the macroring. This was probably the main reason that **90** showed chiral recognition.

Chiral discrimination of molecular anions by ion pairing with alkali−cation complexes of ligand **212** was observed in solvent extraction and liquid membrane transport experiments.[248] Aqueous solutions of alkali cation salts of racemic mandelic acid, C_6H_5-CH(OH)COOH, or of the corresponding naphthyl derivative (α-hydroxy-1-naphthalene acetic acid) were extracted with a $CHCl_3$ solution of **212**. Chiral ligand **212** formed a cationic complex with an alkali ion (Na^+, K^+, Rb^+, Cs^+, or NH_4^+) and the racemic anion of mandelate was enantioselectively extracted in an ion-pair form. In the cases of K^+ and Cs^+, ee values of ∼15% and ∼10%, respectively, were observed for mandelate, but no chiral discrimination of racemic mandelate was found when the cation was Rb^+ or NH_4^+.[248]

E. Polymeric Macrocycles

Yokota and co-workers synthesized a series of chiral polymeric macrocycles.[37] Chiral recognition properties of these macrocycles were studied by liquid−liquid extraction of methyl ester salts of amino acids from an aqueous into a CH_2Cl_2 phase. These polymeric macrocycles show enantiomeric recognition, and the results have been summarized.[37] Among them, a binaphthyl-containing macrocycle **213** and a D-mannitol-containing macrocycle **214** (Chart 27) exhibited the highest degrees of enantiomeric recognition toward Am**9** (EDC = 1.72 at 0 °C)[37] and Am**2** (EDC = 1.66 at 0 °C),[250−252] respectively.

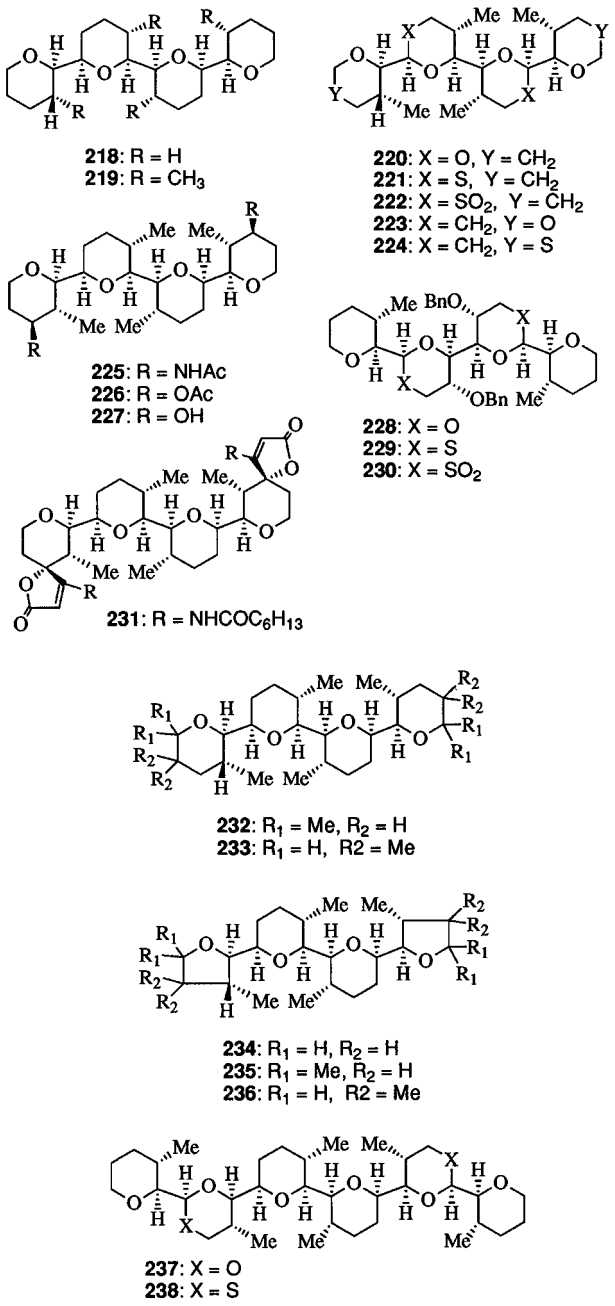
F. Monensin Derivatives and Preorganized Podands

Monensin is a typical biological ionophore and is known to accommodate a Na^+ in a pseudo-cyclic cavity and to transport it selectively across a biomembrane.[253] Although monensin itself is incapable of discriminating between enantiomers of amine compounds, its ester and amide derivatives have been shown to exhibit chiral recognition ability.[254−257] Tsukube and co-workers prepared a series of chiral receptors through a chemical modification of natural monensin.[254−257] Four macrocycle-type monensin derivatives (such as **217**, Chart 27) were synthesized. However, these macrocycles showed a low degree of or no chiral recognition toward several amine compounds.[256,257] In contrast, podand-type monensin derivatives, such as **215** and **216**, exhibited good enantioselectivity for Am**1**−Am**3**, Am**7**, Am**12**, Am**17**, Lys-OMe, and Arg-OMe.[254−257]

The chiral recognition ability of podand-type monensins strongly depended on the nature of the substituent. The larger substituent (R group) of ligand **216** resulted in a better enantiomeric recognition as compared with **215**.[257] It was shown that the monensin amide **216** exhibited higher enantioselectivity for Am**3** and Am**7** than binaphthyl macrocycle **119**.[254,257] It has been concluded that a combination of pseudo-cyclic monensin cavity, amide junction, and bulky chiral residue provides excellent chiral recognition.[254,257] Enantiomeric recognition by most podand-type monensin derivatives is comparable to that of chiral macrocyclic receptors.

Effective enantiomeric recognition demonstrated by the monensin derivatives is probably due to the homogeneous conformation of the monensin molecules. The molecules might be preorganized to have an ordered pseudo-cavity and a proper chiral environment. Acyclic podand molecules were tradition-

Chart 28. Podands 218−238



ally regarded as poor ligands when compared with analogous macrocycles. The weak binding properties of the podands stem from the conformational freedom of their acyclic chains.[258] However, Still and coworkers have shown that podands can be preorganized into binding conformations by a "locking mechanism". These preorganized podands exhibit special binding properties which are normally associated with macrocyclic structures.[258−265] Podand **218** (Chart 28), constructed of linked tetrahydropyran rings, for example, has 25 conformations within 3 kcal/mol of the ground state (the corresponding acyclic glyme ether has approximately 10^3 conformations).[258,259] However, its tetramethyl derivative **219** has only one low-energy conformation.[259] The methyl substituents of **219** serve as a conformational lock and reduce conformational flexibility to an absolute minimum so that the conformation of **219** forms a cavity linked by four oxygens resembling that found in crystal structures of the 18C6 complexes.[259,260] Solvent extraction of excess racemic ammonium hexafluorophosphate guests from D_2O into $CDCl_3$ containing a podand host indicated that podand **219** exhibited high enantioselectivity for Am**3**, Am**29**, Am**31**−Am**33**, and Am**36**.[259] The ee values for Am**3**−**219** and Am**29**−**219** systems (42% and 40%, respectively) were significantly higher than those for Am**3**−**218** and Am**29**−**218** systems (20% and 13%, respectively).

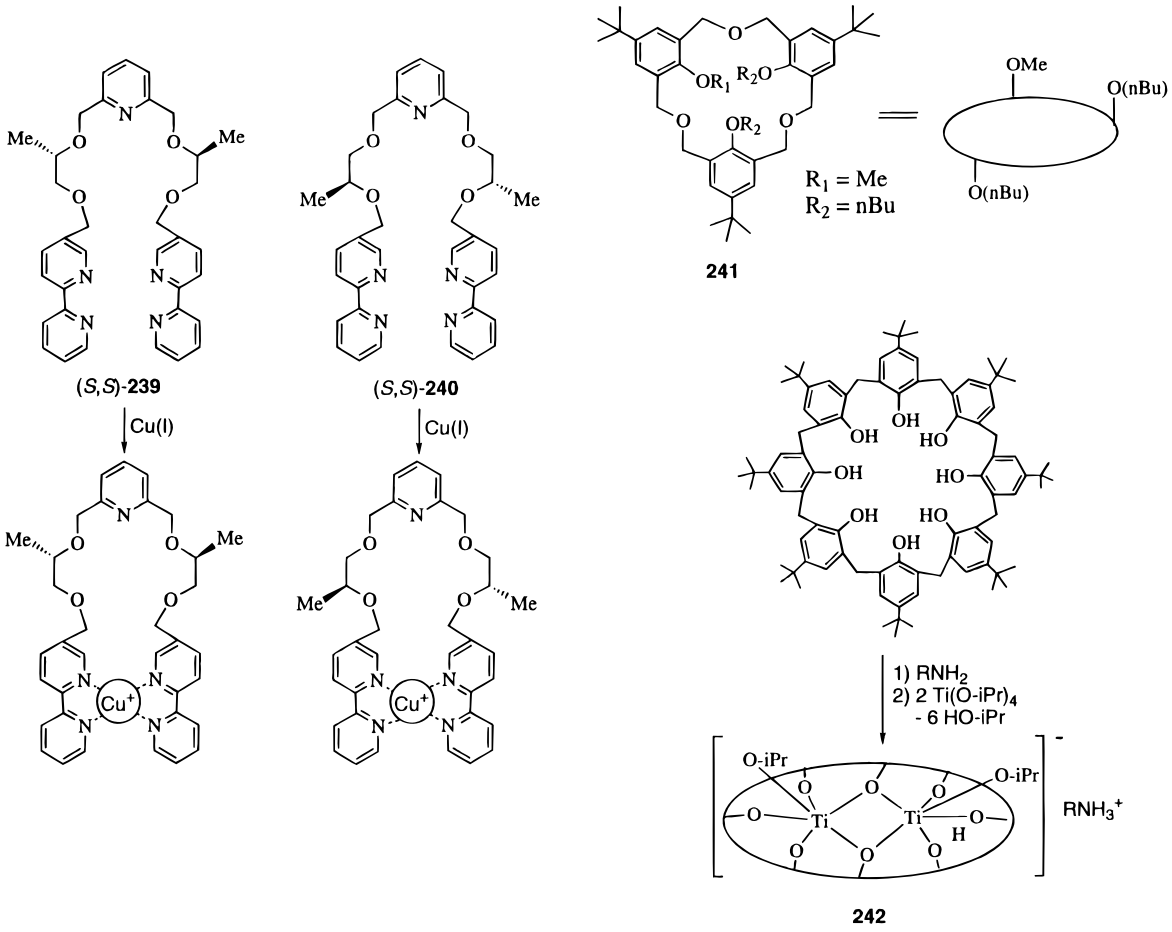
Based on the locking mechanism, Still and coworkers synthesized a series of tetracyclic (**218**−**236**) and hexacyclic (**237** and **238**) podands and studied their enantioselection properties.[258−268] These podands are conformationally locked into particular geometries and display high enantioselectivity. The sulfone podand **222** enantioselectively binds several amino acid esters and amides with ee values as high as 80%.[261] On the other hand, **220** and **221** showed negligible enantioselectivity with the same amine compounds, which may be due to the increased number of hydrogen-bond-accepting atoms (six), which give rise to more binding modes and consequently less selectivity.[261]

Podand acetamide **225** displayed markedly more enantioselective binding with amino acid methyl esters (60−80% ee values) than does the simple podand **219**.[264] Podands **228**−**230** resemble **220**−**222** but incorporate a different type of conformational lock based on benzyloxy substituents. In comparison with **222**, **230** was less enantioselective and less ionophoric for amino acid methyl esters.[267] The weak ion-binding ability of **228**−**230** may result from a remote electrostatic effect. On the other hand, **228**−**230** exhibited enantioselectivity with simple organoammonium ions with 40−50% ee values.[267] Podand **232**−**236** (Chart 28) showed moderate enantioselectivity and, in most cases, the ee values were lower than those demonstrated by **219**.[265] A possible reason for this moderate recognition was that the **232**−**236** and/or their complexes were not conformationally homogeneous. Podand **231** was designed and synthesized according to the results of free energy simulation.[268] A partitioning experiment indicated a high enantioselectivity of **231** for alaninium methylamide and benzylamide (89 ± 2% ee values). Thus, the free energy simulation can be used to find a podand receptor which turns out to be significantly more selective than any other podands studied.[268]

Hexacyclic podands **237** and **238** not only extracted more amino acid methyl esters and amides into chloroform than their tetracyclic relatives **223** and **224** but also showed an enantioselectivity similar to those of **223** and **224**.[266]

Another way to preorganize a podand is through coordination with a metal ion. Podands **239** and **240** (Chart 29) were found to have an ability of self-organization in the presence of Cu(I).[269] The two bipyridyl groups of **239** and **240** strongly complex Cu(I), and the compounds are conformationally locked to have a proper chiral environment. Both **239**−Cu(I) and **240**−Cu(I) were shown to exhibit moderate enantioselectivity for Am**3** in MeOH solution with $\Delta(\log K)$ values of 0.17 and 0.26, respectively, while the interactions of Am**3** with **239** and **240** only

Chart 29. Compounds 239−242



[without Cu(I)] were too weak to be detected by a calorimetric procedure.[269]

Good enantioselectivities with other podands have been observed also by Naemura[124] and co-workers (see section VII).

G. Calixarenes

Shinkai and co-workers recently showed that a homooxacalix[3]arene **241** (Chart 29) exhibited enantiomeric recognition ability when interacted with picrate salts of Am**1**, Am**3**, alanine ethyl ester (Ala-OEt), and phenylalanine ethyl ester (Phe-OEt).[270] Association constants for interactions of (*R*)-Am**1**, (*R*)-Am**3**, L-Ala-OEt, and L-Phe-OEt with (+)- and (−)-**241** were determined in chloroform/THF (99:1) solvent mixture at 25 °C by a spectroscopic method. The log *K* values for the interaction of (−)-**241** with the L-forms of Ala-OEt and Phe-OEt were larger than those of (+)-**241** while (*R*) forms of Am**1** and Am**3** formed more stable complexes with (+)-**241** than with (−)-**241**. The Δ(log *K*) values were 0.08, 0.13, 0.14, and 0.82 for (*R*)-Am**1**, (*R*)-Am**3**, L-Ala-OEt, and L-Phe-OEt, respectively. The largest chiral discrimination (74% ee) was observed for L-Phe-OEt.

A ^{1}H NMR spectral study indicated that **241** bound ammonium cations through hydrogen-bonding interactions with three oxygen atoms. It was believed that at least two phenolic oxygens and possibly an oxygen atom from a CH_2OCH_2 group might be involved. CPK molecular models suggested that it was sterically impossible for the oxygen atoms from all three CH_2OCH_2 units to form hydrogen bonds with the RNH_3^+ ions.[270]

A reaction between 4-*tert*-butylcalix[8]arene and 1 equiv of a base (RNH_2) followed by the addition of 2 equiv of titanium(IV) isopropoxide ($Ti(O\text{-}iPr)_4$) provided yellow crystalline complexes of the general molecular formula [4-*tert*-butylcalix[8]arene($Ti^{IV}(O\text{-}iPr)_2$)]$^-\cdot RNH_3^+$ (**242**, Chart 29).[271] The anionic complex [4-*tert*-butylcalix[8]arene($Ti^{IV}(O\text{-}iPr)_2$)]$^-$ was chiral as a result of the conformation adopted by the macrocycle upon wrapping around the two titanium atoms. Hence this anionic complex showed a chiral recognition ability. When (*R*)-α-(1-naphthyl)ethylamine was used as the base, a 3:1 mixture of diastereomers of **242** (RNH_3^+ = Am**1**) was obtained. A 10:1 mixture of diastereomers was observed upon changing the α-methyl substituent in Am**1** to an isopropyl group.[271]

Chiral recognition in these systems has been proposed to result from two attractive and one repulsive interactions.[271] Hydrogen bonding between an ammonium hydrogen and a phenolate oxygen and the π-stacking of one calixarene aryl ring with the naphthyl ring lead to the formation of a salt complex, while steric repulsion between the metallacalixarene frame and the α-alkyl substituent on the chiral ammonium would account for chiral recognition.

XV. Acknowledgments

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XVI. References

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