Host-Guest Complexation. 11. Survey of Chiral Recognition of Amine and Amino Ester Salts by Dilocular Bisdinaphthyl Hosts[1,2]

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Abstract: Eight optically pure, 22-membered macrocycles incorporating two chiral 1,1′-dinaphthyl units (D) attached at their 2,2′ positions to bridges have been studied as hosts in complexation with chiral recognition of enantiomers of alkylammonium salts as guests. The bridges were composed of combinations of oxygen (O), CH_2CH_2(E), $(CH_2)_5$, 1,3-disubstituted benzene (B), and 2,6-disubstituted pyridine (P) units. Two D units in the same host were always of the same configuration. The structures and compound numbers were as follows: $D(OEOEO)_2D$ (**1**), $D(OEOEO)(OECH_2EO)D$ (**2**), $D(OEOEO)(OCH_2BCH_2O)D$ (**3**), $D(OEOEO)(OCH_2PCH_2O)D$ (**4**), $D(OCH_2PCH_2O)_2D$ (**5**), $D(OCH_2PCH_2O)(OCH_2BCH_2O)D$ (**6**), $D(OCH_2PCH_2O)(OECH_2EO)D$ (**7**), and D(OEO)(OEOEOEO)D (**8**). The structures in $CDCl_3$ solution of the diastereomeric complexes between host (*RR*)-**1** and the enantiomers of guest α-phenylethylammonium hexafluorophosphate (**10**·HPF_6) were distinctly different as shown by their ^1H NMR spectra. A condition for observing diastereomers with different spectra was that X^- of $RNH_3^+X^-$ be unable to hydrogen bond strongly with NH_3^+. The PF_6^-, AsF_6^-, and SbF_6^- ions fulfilled this condition, whereas F^-, Cl^-, Br^-, I^-, SCN^-, and $CCl_3CO_2^-$ did not. The $CF_3CO_2^-$ and picrate anions gave salts too insoluble to examine. The ^1H NMR chemical shifts of the CH_3, NCH, and *o*-C_6H_5 protons of the guests in the diastereomeric complexes yielded information as to their locations with respect to the magnetic fields of the naphthalenes. The chemical shifts of the host's CH_2OCH_2 protons located them with respect to the magnetic field of the C_6H_5. The chemical shifts of the $ArOCH_2$ protons located them with respect to the magnetic fields of the naphthalene. These results correlated well with predictions based on molecular models of the two diastereomeric complexes. The complexes appear held together by three O··· HN^+ hydrogen bonds in a tripod arrangement, with the axis of the N–C* bond and the planes of two of the naphthalene rings protruding at approximately right angles from the best plane of the macrocycle. The naphthalene "walls" of the host divide the space available to the L, M, and S substituents of the guest ($LMSC^*NH_3^+$) into two cavities (hosts are dilocular) that are identical and chiral. Models suggest that L (the large group) distributes in one cavity and M and S (the medium and small groups) in the other. The more stable diastereomer in model **9** involves S contacting one naphthalene wall and M oriented along the side of the second. This model was tested by extracting D_2O solutions of racemic $LMSC^*NH_3PF_6$ salts with $CDCl_3$ solutions of optically pure hosts **1–8.** The amount of guest extracted was controlled by "salting out" with Li^+, Na^+, F^-, or Cl^- ions added to the D_2O layer. Ions such as K^+ or I^- were competitively extracted. Typically, the layers were equilibrated, the guest was isolated from each layer, and the optical rotations were taken. In a few cases, the relative concentrations of the enantiomeric guests in the $CDCl_3$ layer were determined from the ^1H NMR spectra of their diastereomeric complexes. From the results, the configurations of the more stable diastereomeric complexes were identified, their enantiomer distribution constants (EDCs) determined, and their free-energy differences ($\Delta(\Delta G°)$ values) estimated. The EDC and $\Delta(\Delta G°)$ values measure the chiral recognition, and the direction of the configurational bias in complexation provides structural information. Model **9** predicted the more stable diastereomeric complex for the following combinations: for **1** complexing the PF_6^- salts of $C_6H_5CH(CH_3)NH_3^+$, $C_6H_5CH(CO_2CH_3)NH_3^+$, $C_6H_5CH[CO_2CH(CH_3)_2]NH_3^+$, $C_6H_5CH[CO_2C(CH_3)_3]NH_3^+$, *p*-$HOC_6H_4CH(CO_2CH_3)NH_3^+$; for **4, 5,** and **7** complexing $C_6H_5CH(CO_2CH_3)NH_3PF_6$; and for **4** and **5** complexing $(CH_3)_2CHCH(CO_2CH_3)NH_3PF_6$. No chiral recognition (EDC = 1) was observed with **1** complexing $(CH_3)_2CHCH[CO_2CH(CH_3)_2]NH_3PF_6$, or **6** complexing $C_6H_5CH(CO_2CH_3)NH_3PF_6$. Host **1** failed to extract the more hydrophilic guests, $CH_3CH(CO_2CH_3)NH_3PF_6$, $HOCH_2CH(CO_2CH_3)NH_3PF_6$, and *p*-$HOC_6H_4CH_2CH(CO_2CH_3)NH_3PF_6$. Weakly binding hosts **2** and **3** failed to extract $C_6H_5CH(CO_2CH_3)NH_3PF_6$ or $(CH_3)_2CHCH(CO_2CH_3)NH_3PF_6$. Model **9** could not be unambiguously used as a basis for predicting the more stable diastereomeric complex between **1** and $C_6H_5CH_2CH(CO_2CH_3)NH_3PF_6$ or $CH_3SCH_2CH_2CH(CO_2CH_3)NH_3PF_6$ (which is M and which is S?). The results involving all the methyl ester guests were rationalized in terms of a refined model compatible with the x-ray structure of the complex between (*SS*)-**1** and D-$C_6H_5CH(CO_2CH_3)NH_3PF_6$ and the chemical shifts in the ^1H NMR spectra of the diastereomeric complexes. In the refined model, a fourth binding site is invoked between the CO_2CH_3 group acting as a π acid and a naphthalene as a π base. The highest chiral recognition was observed for (*RR*)-**1** complexing the D enantiomer of *p*-HO-$C_6H_4CH(CO_2CH_3)NH_3PF_6$ by a factor of 5 better than the L enantiomer (EDC = 5, $\Delta(\Delta G°) = -820$ cal/mol), and for (*SS*)-**1** complexing the L enantiomer of $C_6H_5CH[CO_2C(CH_3)_3]NH_3PF_6$ better than the D by a factor of 4.4 (EDC = 4.4, $\Delta(\Delta G) = -810$ cal/mol). Lower temperatures (down to −18 °C) favored complexation and produced higher chiral recognition. General conclusions are drawn about the design of highly structured host-guest relationships with regard to the complementary placements of binding sites and steric barriers.

This series of papers has dealt with the design and synthesis of host compounds with convergent and complementary binding sites and steric barriers that complex selectively, those guest organic compounds with divergent binding sites and steric barriers. Parts 1–5[4a–e] treated the relationships between the placement and character of binding sites, binding energies, and the structures of complexes in solution. Parts 6–9[4f–i] described the design and synthesis of hosts containing steric and chiral barriers and, in some cases, examined steric effects on binding potential.[4f,i]

This paper is concerned with chiral recognition in structured complexation between hosts and guests in solution. At one extreme, a guest might contain an asymmetric center from which radiate four different groups, each of which possesses unique binding properties. A chiral host might be designed with four convergent binding sites uniquely complementary to the four binding sites of the guest. The degree of chiral recognition in complexation between such partners might be enormous. Few guests possess four distinguishable polar groups, but many contain three, such as the amino acids serine, leucine, Dopa, and aspartic acid. At the other extreme, a guest might contain an asymmetric center from which radiated four different

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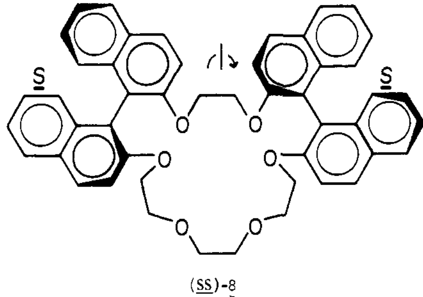
groups of largely differing sizes and shapes with little polarity and no specific binding potential. A host might be designed whose chiral cavity was shaped to accommodate one enantiomer of this guest but not the other, so that differentiation in complexation would depend on one complex possessing many, and the other few, weak van der Waals attractive forces. Although many hydrocarbon guests of this type can be envisioned (e.g., 1-adamantyl-1-*tert*-butylethane), the problems in designing and synthesizing a nonfolding host that might accommodate such a guest are prohibitive. As with enzymes and substrates, differentiation in designable host–guest relationships depends on combining specific binding sites and chiral barriers.

Part 10 of this series provided the first detailed account of chiral recognition of guest by host, and of host by guest, in solution.[4j] Valine was the standard guest, and the hosts were designed to bind both the ammonium and carboxyl groups of the protonated amino acid. Chiral recognition arose from the complementary vs. the noncomplementary placements of a single 1,1′-dinaphthyl chiral barrier in the host, and of the hydrogen and isopropyl groups attached to the asymmetric center of the valine guest.

Since the appearance of our first papers on chiral recognition in molecular complexation between multiheteromacrocycles containing 1,1′-dinaphthyl units and primary amine salts,[2a,b,5] others have reported similar studies. Lehn et al.[6] incorporated a 1,1′-dinaphthyl unit into a macrobicyclic and macrotricyclic polyether–polyamine and reported complexation leading to ~10% optically pure guests. Stoddart et al.[7] with monosaccharide and (or) 1,1′-dinaphthyl units incorporated into macrocyclic ethers carried out extraction experiments with racemic α-phenylethylammonium hexafluorophosphate similar to ours.[2a] Diastereomeric complexes were formed with chiral recognition factors as high as 1.7 representing free-energy differences as high as 300 cal/mol.

This paper describes the chiral recognition properties of hosts **1–8** toward guests of the type $LMSC^*NH_3^+ \bar{X}$, where L, M, and S are large, medium, and small groups, respectively. Each host contains two chiral 1,1′-dinaphthyl units separated by a central macrocyclic binding site containing inward-turning oxygens or nitrogens positioned to hydrogen bond, in a tripod arrangement, the NH_3^+ groups of the guests. Hosts **1–7** are very similarly shaped in Corey–Pauling–Koltun (CPK) molecular models with respect to the locations of the binding sites, chiral cavities, and barriers. Host **8** possesses a similarly

Compd. no.	X	Y
(SS)-1	CH_2OCH_2	CH_2OCH_2
(SS)-2	CH_2OCH_2	$CH_2CH_2CH_2$
(SS)-3	CH_2OCH_2	
(SS)-4	CH_2OCH_2	
(SS)-5		
(SS)-6		
(SS)-7		$CH_2CH_2CH_2$


(SS)-8

shaped central hole, but a different placement of the two chiral 1,1′-dinaphthyl units with respect to one another.

Structure **9** was envisioned prior to experiment as the more stable diastereomeric complex between prototype host (*SS*)-**1** and $LMSC^*NH_3^+ \bar{X}$ guests. In the CPK molecular model of **9**, the six oxygens of the macrocycle roughly define a plane.

(SS)-1

9

Perpendicular to this plane is the N–C* bond axis. Also perpendicular are the planes of the four naphthalene rings, cross sections of which are shown in **9**. Two naphthalene rings and the LMSC* portion of the guest protrude from one of the two faces of the macroring, and the other two naphthalene rings from the other. All the hosts contain at least one C_2 axis (symbolized by ⌒ or ⊣), so the same complexes are formed by attachment of a guest to either face of the host. In **9**, the naphthalene rings resemble walls tangent to the macroring that divide the space available to substituents L, M, and S into chiral cavities. The large substituent (L) is placed in one of the two identical chiral cavities, and M and S in the second. The smallest group (S) is placed against one naphthalene wall which provides the medium-sized group (M) with space and with an orientation parallel to the opposite wall. The alternate, and presumably higher energy, diastereomer would be formed by simply inverting the positions of S and M, or by more profound reorganization. The four cavities on the two faces of (*SS*)-**1** are identical, since the host contains three mutually perpendicular C_2 axes (overall D_2 symmetry).

Hosts containing one cavity on the binding face are referred to as *monolocular*, those containing two are *dilocular*, and those containing three are *trilocular*.[4g] The hosts of part 10[4j] were monolocular, whereas hosts **1–8** are dilocular. The chiral cavities of **1–7** all appear in models to resemble one another in shape. Therefore, **9** serves as a prototype for the more stable diastereomeric complexes of these hosts. In **8**, however, one of the cavities on each face is smaller than the other, and molecular model examination provides no secure prediction as to the generalized structure of the more stable diastereomeric complex.

The syntheses, absolute configurations, maximum rotations, and optical stabilities of hosts **1–8** have been reported in part

7.[4g] The current paper describes the chiral recognition properties of hosts **1–8** toward primary amine salts, particularly those of α-amino esters. Guests were selected to maximize the differences in sizes of the three substituents attached to the asymmetric center. Also considered was the availability of the compounds, and a knowledge of their maximum rotations and of their absolute configurations.

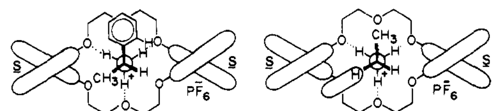
The first of the following sections (A) describes the structures of the diastereomeric complexes between **1** and α-phenylethylammonium hexafluorophosphate (**10**·HPF_6). Section B provides two methods of determining the chiral recognition by host **1** towards guest **10**·HPF_6. Section C provides a method of estimating the relative stabilities of the diastereomeric complexes from chiral recognition experiments. Section D reports the results of a survey of the effect of counterion and competing cation on chiral recognition by host **1** towards guest **10**·HPF_6. In section E is discussed the structures of the diastereomeric complexes between (*SS*)-**1** and D- or L-methyl ester hexafluorophosphate salts of phenylglycine. Section F describes the results of a survey of chiral recognition of (*RR*)-**1** toward enantiomers of esters of various α-amino acid hexafluorophosphate salts. In section G, models for chiral recognition of (*SS*)-**1** toward the amino esters are discussed. The results of a survey of the chiral recognition properties of hosts (*SS*)-**2** through (*SS*)-**7** are discussed in section H, and section I deals with the less symmetrical host, (*SS*)-**8**. Section J presents the general conclusions derived from these studies.

Results and Discussion

A. Structures of the Diastereomeric Complexes between 1 and α-Phenylethylammonium Hexafluorophosphate. Salts of α-phenylethylamine (**10**) were selected as guests in an initial survey of the ability of (*RR*)-**1** to give diastereomeric complexes whose structures were distinguishable experimentally. This amine possesses several virtues. The three groups attached to the asymmetric center differ greatly in bulk with $C_6H_5 > CH_3 > H$. All three groups contain protons whose ^1H NMR chemical shifts are likely to change when placed by complexation in the magnetic fields of the naphthalene rings of the host. The absolute configurations and maximum rotations of the enantiomers of the amine are known.[8] The lipophilicity–hydrophilicity balance of salts of this amine is subject to wide variation by anion manipulation.

The technique initially used to detect complexation involved changes in 100-MHz ^1H NMR spectra when two potential complexing partners were mixed. Compounds of maximum rotation were employed throughout this paper. **Spectrum 1** of (*RR*)-**1** in $CDCl_3$ (0.5 M) exhibited the following four well-defined and very roughly symmetrical multiplets with baseline separation: δ 3.18 (2.9–3.4), CH_2OCH_2, 8 H; 3.81 (3.6–4.1), $ArOCH_2$, 8 H; 7.20 (6.9–7.4), ArH, 16 H; 7.83 (7.6–8.1, ArH, 8 H. **Spectrum 2** in $CDCl_3$ (0.5 M) of (*R*)- was the same as that of (*S*)-**10**·HBr, and gave the signals δ 1.71, d, J = 7 Hz, CH_3, 3 H; 4.45, q, J = 7 Hz, NCH, 1 H; 7.40 (7.2–7.6), m, C_6H_5, 5 H; 8.2, m, NH_3, 3 H. **Spectra 3** and **4** were identical and were taken of mixtures of solutions of (*RR*)-**1** and (*R*)-**10**·HBr (0.5 M in each component), and of (*RR*)-**1** and (*S*)-**10**·HBr, respectively: δ 1.63, d, J = 7 Hz, CH_3, 3 H; 1.64, d, J = 7 Hz, CH_3, 3 H; δ 3.10 (2.8–3.4), m, CH_2OCH_2, 8 H; 3.72 (3.5–4.0), m, $ArOCH_2$, 8 H; 4.34, q, J = 7 Hz, NCH; 7.2 (6.9–7.4), m (overlapping somewhat with next multiplet), naphthyl ArH, 16 H; 7.2–7.6, m (overlapping somewhat with last multiplet), C_6H_5, 5 H; 7.81 (7.6–8.1), m, naphthyl ArH, 8 H. Since **spectra 3** and **4** were virtually superimposable and were close to being the product of addition of **spectra 1** and **2**, there is no evidence for complexation between (*RR*)-**1** and the enantiomers of **10**·HBr. Molecular models (CPK) of possible complexes involving *three* or *two* NH···O hydrogen bonds between

Chart I



^1H NMR δ	(*SS*)·(*R*)-**11**	(*SS*)·(*S*)-**11**	(*SS*)-**1** + (*R*) or (*S*)-**10**·HBr
CH_3	1.37	1.08	1.63
NCH	~4.1	~4.1	4.34
C_6H_5 (ortho H)	6.68	>7.0, <7.4	7.2–7.5
CH_2OCH_2	3.0	3.1	3.1
$ArOCH_2$	3.50, 3.9	3.56, 3.9	3.72

host and guest clearly place the CH_3 and NCH protons in the shielding region of the naphthalene rings. If complexed at all, only one NH···O hydrogen bond is involved, and the complex has little discrete structure. Thus **spectra 3–4** serve as a standard for spectral comparisons of mixtures of **1** and salts of **10** that do complex one another.

Attempts to isolate **10**·HPF_6 led to **10**·HF, so the former salt was formed by ion exchange in D_2O solution of **10**·HBr and the NaF impurity in the $NaPF_6$. For **spectrum 5,** 0.80 mL of D_2O–0.94 M in $NaPF_6$ and in (*R*)-**10**·HBr was shaken for 1 min at 24 °C with 0.80 mL of (*RR*)-**1** in $CDCl_3$ (0.16 M). The organic layer was dried ($MgSO_4$) and the spectrum taken. Integration of the CH_3 against the OCH_2CH_2O protons indicated that [**10**]/[**1**] = 0.5. The spectrum showed major changes in chemical shifts and multiplicity compared to **spectra 3–4.** In the most striking change in the host, the $ArOCH_2$ multiplet centered at δ 3.72 in **spectra 3–4** split into two nearly mirror image multiplets, one centered at δ 3.56 (3.4–3.7) and the other at δ 3.9. The CH_2OCH_2 proton signal did not move. Both the methyl and methine signals of the guest moved, the former from δ 1.71 (**spectra 3–4**) to 1.08 and the latter from δ 4.34 to ~4.1, where half of the quartet was obscured by the lower field multiplet of the $ArOCH_2$ protons. The C_6H_5 protons moved slightly upfield under the downfield portion of the upfield naphthalene multiplet, the combined multiplet reaching from δ 6.8 to 7.4. Dilution of the spectral solution by a factor of 2 with $CDCl_3$ produced essentially no spectral change.

The solution for **spectrum 6** was produced identically with that of **spectrum 5** except that the configuration of the **10** salt was changed from *R* to *S*. Extraction gave a [**10**]/[**1**] value of 0.7. The host's $ArOCH_2$ multiplet split as in **spectrum 5,** but the center of the CH_2OCH_2 resonance moved upfield from δ 3.1 to 3.0. The guest's CH_3 doublet moved less far upfield than in **spectrum 5** to δ 1.37, and the NCH signal remained upfield at ~δ 4.1 as in **spectrum 5.** Interestingly, the two ortho protons of the C_6H_5 group moved upfield from under the upfield ArH multiplet to form a well-defined doublet of doublets centered at δ 6.68 (J = 3 and 1 Hz). The multiplicity of both the naphthyl's ArH multiplets changed, but not their positions compared to **spectrum 5.** Dilution of the spectral solution by a factor of 2 or addition of 14% more (*RR*)-**1** to the $CDCl_3$ solution to produce [**10**]/[**1**] = 0.5 gave little change in the spectrum.

Spectral solutions were prepared identically with those for **spectra 5** and **6** except that the $NaPF_6$ component was omitted from the D_2O layer. No detectable amount of **10**·HBr was extracted into the $CDCl_3$ layer. Examination of the D_2O layers from the extractions to prepare the $CDCl_3$ solution for this and **spectra 5** and **6** showed the absence of (*RR*)-**1**.

Chart I summarizes the most important chemical shifts observed in **spectra 3–4, 5,** and **6.** Hypothetical structures,

$(SS)(R)$-**11** and $(SS)(S)$-**11**, for the enantiomers of the diastereomeric complexes studied are formulated as well. Undoubtedly each complex is an equilibrating mixture of structures that involve different conformations, and so each of these structures is meant to represent an average of these conformations. That the complexes and their components are equilibrating rapidly on the ^1H NMR time scale was demonstrated by experiments described later in this section. The structures suggested in Chart I for the diastereomeric complexes correlate what is derived by CPK molecular model building and what is revealed about their actual structure by the spectral comparisons.

In molecular models of these structures, the shielding portions of the magnetic fields of the naphthalene rings converge on many of the protons of the guest, particularly on those of the CH_3, NCH, and C_6H_5 groups. In both diastereomeric complexes, these protons are moved upfield by 0.1–0.55 ppm. Thus the guests are certainly nesting between the "naphthalene walls", as anticipated. The NCH protons of the two diastereomeric complexes are moved upfield from uncomplexed components by the same amount (0.24 ppm), and are placed in identical positions in the two hypothetical structures. This placement coupled with that of the three NH···O hydrogen bonds locates the C_6H_5 group alone in the top cavity in $(SS)(R)$-**11**, and the CH_3 group alone in the top cavity in $(SS)(S)$-**11**.

In $(SS)(R)$-**11**, the most stable conformation in CPK models places the C_6H_5 group in a plane roughly parallel to that of the macroring, locating one ortho proton directly against a naphthalene wall. Consistent with this placement, the average chemical shift of the ortho protons in $(SS)(R)$-**11** is moved upfield, upon complexation, by 0.26 ppm. The methyl group in $(SS)(R)$-**11** is in the bottom cavity, with the CH_3–C bond running parallel to the plane of the lower left naphthalene wall. The protons of this methyl group are in the shielding region of the naphthalene ring, and consequently are moved 0.26 ppm upon complexation. *Two* of the *eight* CH_2OCH_2 protons lie directly in the shielding region of the C_6H_5 group in $(SS)(R)$-**11** and are moved upfield ~0.1 ppm in the spectrum of the complex.

In $(SS)(S)$-**11**, the CH_3 group located in the upper cavity in CPK models lies in the shielding region of the right naphthalene ring. In the spectrum of the complex, these protons are moved upfield by 0.55 ppm. In models of $(SS)(S)$-**11**, the left naphthalene and C_6H_5 groups occupy roughly parallel planes, placing one meta and one ortho proton of the C_6H_5 in the shielding region of the left naphthalene ring. The multiplet of the five C_6H_5 protons moves upfield in the complex by an average of ~0.15 ppm, remaining obscured by the 16-proton naphthalene multiplet. The CH_2OCH_2 protons of this complex remain as they were in the uncomplexed host. The chemical shift of these protons in (RR)-**1** remains essentially unchanged in the spectra of complexes $(RR)(S)$-**11** and $(RR)(R)$-**11** and of the mixture of (RR)-**1** and (R)-**10**·HBr.

The fact that the CH_3 protons of the $(SS)(S)$ complex are moved further upfield than those of the $(SS)(R)$ complex by 0.29 ppm requires comment. Both complexes are hindered, particularly where the left naphthalene and the $CH_3CC_6H_5$ groups meet. Models indicate that the strain can be relieved in two ways: by the guest moving somewhat to the right toward the right naphthalene ring, and by the left naphthalene ring broadening the lower cavity by rotating away from the $CH_3CC_6H_5$ group. Less steric constraints are imposed on the right naphthalene ring. Thus the CH_3 in the $(SS)(S)$ complex probably penetrates more deeply into the shielding region of the right naphthalene than the CH_3 group in the $(SS)(R)$ complex penetrates into the shielding region of the left naphthalene.

In the above discussion, the effect of the magnetic field of the C_6H_5 group on the CH_3 has been ignored. In models of both $(SS)(R)$-**11** and $(SS)(S)$-**11**, the dihedral angles between the planes of the C_6H_5 and C–C–CH_3 groups appear to be similar and not far from 30°. Thus whatever effect is present is assumed to be about the same in the two complexes.

B. Chiral Recognition in Complexation by (*SS*)- or (*RR*)-1 of the Enantiomers of α-Phenylethylammonium Hexafluorophosphate. Extraction and spectral measurements similar to those of the last section were performed to determine which diastereomeric complex was the most stable. The $CDCl_3$ solution for **spectrum 7** was prepared exactly as those for **spectra 5** and **6** except that racemic **10**·salt replaced the enantiomeric salts used in the former extractions. Thus the enantiomeric guests were placed in competition with one another for complexation by (RR)-**1**. The D_2O acted as a reservoir for the uncomplexed salt. The $CDCl_3$ solution produced gave a spectrum that was essentially a composite of **spectra 5** and **6**, except that the enantiomeric guests were extracted differentially. Integration of the well-separated methyl doublets against the OCH_2 multiplets (corrected for NCH) gave a (R)-**10**/(RR)-**1** value of 0.30 and a (S)-**10**/(RR)-**1** value of 0.44. Thus the diastereomeric complexes gave a chiral recognition factor (CRF)[4j] of 1.46, the expected $(RR)(S)$ complex being the more stable.

Spectrum 8 was similarly produced from $(RR)(SS)$-**1** and (R)-**10** salt. The host's spectrum was radically different from that of uncomplexed material, and in detail markedly different from **spectra 5–7**. The [**10**]/[**1**] value was 0.67, and the chemical shift of the one methyl doublet was δ 1.30, between that in **spectra 5** and **6**, but closer to that of **6**. **Spectrum 9** was obtained the same way from $(RR)(SS)$-**1** and $(R)(S)$ salt. The [**10**]/[**1**] value was 0.64, and the single methyl doublet occurred at δ 1.34. These experiments demonstrate that the complexes and their components rapidly equilibrate on the ^1H NMR time scale.

Unlike the other extractions, that used to generate the $CDCl_3$ solution for **spectrum 10** was conducted at 0 °C and made use of (SS)-**1** and $(R)(S)$-**10** salt (other conditions were the same as those used to obtain **spectra 5–9**). The [**10**]/[**1**] value increased to 0.93, and the (R)-CH_3 doublet appeared at δ 1.41 and that of (S)-CH_3 at δ 1.16. The ratio of the integrals of the (R)-CH_3 to the (S)-CH_3 doublet was 1.63 (CRF value).

The above CRF value was confirmed by a classical extraction, isolation, and rotation experiment. A solution of racemic α-phenylethylammonium chloride and $NaPF_6$ was shaken with a $CHCl_3$ solution containing (SS)-**1** at 0 °C. The layers were carefully separated, and the amine was isolated from the $CHCl_3$ layer to give the amine (65% yield based on host = 100%). Rotations showed the material to be composed of 62% (R)-**10** and 38% (S)-**10**, values which give a CRF of 1.63.

C. Relative Stabilities of the Diastereomeric Complexes between 1 and α-Phenylethylamine Hexafluorophosphate (10·HPF_6). Had an infinitely large reservoir of racemic **10**·HPF_6 been extracted in the above experiment, the CRF values would have been slightly larger. Such maximum CRF values have been termed EDCs or enantiomer distribution constants.[4j] Values of EDC can be calculated from CRF values as follows. Equations 1 and 2 involve the following definitions: G_A is the more and G_B the less soluble guest enantiomer in the $CHCl_3$ layer, leaving the H_2O layer enriched in G_B; $[G_A]_{CHCl_3}$, $[G_A]_{H_2O}$, $[G_B]_{CHCl_3}$, and $[G_B]_{H_2O}$ are the concentrations at equilibrium of the enantiomeric guests in the two phases; K_A and K_B are the distribution constants between the two phases of enantiomers A and B; CRF is the chiral recognition factor in the $CHCl_3$ phase; EDC is the enantiomer distribution constant, in this case, for the guest between the two phases. Equations 1 and 2 relate these parameters.

Table I. The Effect of Various Ions on the $(Guest/Host)_{CDCl_3}$ Ratios, and EDC Values Observed at 0 °C in the Extractions of α-Phenylethylammonium Salts (**10**·HX) by (*SS*)-**1**

Run no.	Initial D_2O Phase: Amine salt[a] Anion	Amine salt[a] Concn, M	Inorg salt	In $CDCl_3$ at equil [**10**]/[**1**][b]	CRF in $CDCl_3$[c]	EDC[d]	Δ between diast CH_3 doublets, Hz
1	F^-	1	None	0.0			
2	Cl^-	1	None	0.0			
3	Br^-	1	None	0.0			
4	PF_6^-	2	None	1.0	1.7	1.8	22
5	PF_6^-	1	None	1.0	1.8	2.0	23
6	PF_6^-	1	None	1.0	1.7	1.9	21
7	PF_6^-	0.5	None	0.8	1.8	2.1	23
8	PF_6^-	0.4	None	0.6	1.8	2.1	29
9	PF_6^-	0.4	NaBr	0.6	1.7	2.0	25
10	PF_6^-	0.4	KBr	0.0			
11	PF_6^-	1	KPF_6	1.0	1.6	1.7	23
12	PF_6^-	1	LiI	1.2	~1.1	~1.1	12
13	PF_6^-	1	NaI	1.5	~1.0	~1.0	12
14	PF_6^-	1	KI	1.2	~1.2	~1.2	13
15	F^-	1	$LiPF_6$	1.0	1.6	1.7	21
16	F^-	1	$NaPF_6$	1.0	2.0	2.2	20
17	F^-	1	KPF_6	0.8	1.7	1.8	23
18	Br^-	1	$LiPF_6$	1.0	1.7	1.9	20
19	Br^-	1	$NaPF_6$	0.9	1.7	1.8	20
20	Br^-	1	KPF_6	0.5	2	2.1	22
21	Br^-	1	$NaAsF_6$	1.0	1.9	2.1	18
22	Br^-	1	$NaSbF_6$	1.0	1.75	1.9	22

[a] Racemic **10**·HX. [b] Ratio of the ^1H NMR integrals of two CH_3 doublets to the integrals of the OCH_2CH_2O multiplets (corrected for NCH). [c] Ratio of integral of (*R*)-**10** CH_3 to integral of (*S*)-**10** CH_3 (doublets were well separated). [d] Estimated error ±0.2.

$$K_A = \frac{[G_A]_{CHCl_3}}{[G_A]_{H_2O}} \quad K_B = \frac{[G_B]_{CHCl_3}}{[G_B]_{H_2O}} \quad CRF = \frac{[G_A]_{CHCl_3}}{[G_B]_{CHCl_3}} \tag{1}$$

$$EDC = \frac{K_A}{K_B} = CRF\frac{[G_B]_{H_2O}}{[G_A]_{H_2O}} \tag{2}$$

With eq 2 and the concentrations of amine salts used and extracted, the EDC values can be calculated for the experiments of the last section. In the extraction of racemic salt at 25 °C using (*RR*)-**1**, EDC = 1.54. In that performed at 0 °C using (*SS*)-**1**, EDC = 1.77.

Under ideal conditions, $K_A/K_B = (Ka)_A/(Ka)_B$, where $(Ka)_A$ and $(Ka)_B$ are defined by eq 3 and 4, in which $H{\cdot}G_A$ and $H{\cdot}G_B$ are the diastereomeric complexes.

$$H + G_A \underset{CHCl_3}{\overset{(Ka)_A}{\rightleftarrows}} H\cdot G_A \quad (Ka)_A = \frac{[H\cdot G_A]}{[H][G_A]} \tag{3}$$

$$H + G_B \underset{CHCl_3}{\overset{(Ka)_B}{\rightleftarrows}} H\cdot G_B \quad (Ka)_B = \frac{[H\cdot G_B]}{[H][G_B]} \tag{4}$$

$$\Delta(\Delta G^\circ) = -RT \ln EDC \tag{5}$$

Equation 5 follows from eq 3 and 4, and it relates the difference in free energies of the diastereomeric complexes to the EDC values. The conditions that must be fulfilled for these equations to apply rigorously are as follows. (1) Host must be distributed solely in the $CHCl_3$ layer, so chiral recognition occurs only in that layer. (2) Only complexed guest can be distributed in the $CHCl_3$ layer. (3) To the extent that enantiomeric guests are associated in the aqueous layer, the free energies of diastereomeric aggregates must equal one another. (4) The diastereomeric complexes in the $CHCl_3$ layer must be 1:1. To the small extent that conditions (1)–(3) did not apply to the above experiments, the observed EDC values would be lower than the values of $(Ka)_A/(Ka)_B$ in $CHCl_3$. Evidence that 1:1 complexation occurs is developed in the next section.

Application of eq 5 to the EDC values obtained at 25 and 0 °C provides $\Delta(\Delta G^\circ)$ values of 256 and 310 cal/mol, respectively, for the free-energy differences for the diastereomeric complexes at the two temperatures. The temperature dependence of $\Delta(\Delta G^\circ)$ indicates that the more stable (*SS*)(*R*) complex depends heavily on the enthalpic term, whereas the less stable (*SS*)(*S*) complex is more dependent on the entropic term. Although these energy differences are small, the *direction of the configurational bias shown in complexation correlates with expectations based on general structure* **9**.

D. Survey of the Effect of Counterion and Competing Cation on Chiral Recognition. The above results indicated that when PF_6^- was the counterion, α-phenylethylammonium ion could be extracted from aqueous solution into chloroform by forming highly structured diastereomeric complexes with (*RR*)- or (*SS*)-**1**. When Br^- was the counterion, such complexes were not formed when the components were mixed in solution, nor could extractions be performed. The dependence of complexation on the character of the counterion was then studied with various α-phenylethylammonium salts (**10**·HX) in the presence of inorganic salts. The object of the study was to gain information applicable to many $*RNH_3$ systems with differing pK_as and hydrophilicity–lipophilicity balances. It was particularly important to find out which counterions gave the highest chiral recognition, and what inorganic salts could be used in the aqueous phase to "salt out" hydrophilic amine salts without them being extracted and occupying the binding sites of the host.

Accordingly, D_2O solutions of **10**·HX that were 1 M in various inorganic salts were shaken at 0 °C with solutions of (*SS*)-**1** in $CDCl_3$. The organic phase was analyzed as before. Table I records the ratios of G/H (guest to host in the organic phase) and EDC values of the runs and control experiments in which components in the standard experiments were omitted.

Runs 1–3 established that **10**·HF, **10**·HCl, and **10**·HBr are not detectably extracted by host into $CDCl_3$ from D_2O. The D_2O solutions of **10**·HPF_6 used in runs 4–8 were free of other salts, and were prepared from **10** and $HPF_6{\cdot}O(C_2H_5)_2$. Variations in the concentrations of this salt from 2 to 0.4 M changed guest to host ratios in $CDCl_3$ from 1.0 to 0.6, but the EDC values remained within experimental error of one another (1.8

to 2.1 with no trends). Run 9 demonstrated that 1 M NaBr does not salt out **10**·HPF_6 and D_2O into $CDCl_3$ at 0.4 M, nor change the chiral recognition or the G/H ratio. In contrast, run 10 showed that KPF_6 at 2.5 times the concentration of **10**·H^+ was extracted in preference to **10**·HPF_6. Run 11 showed that at equal concentrations, **10**·HPF_6 was extracted in preference to KPF_6.

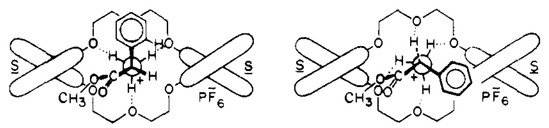
Runs 12–14 demonstrated that **10**·HI was extracted in preference to **10**·HPF_6, and that values of G/H in $CDCl_3$ exceeded 1.0 (as high as 1.5). As a result, the chiral recognition almost disappeared (EDC values approached unity). Runs 15–17 showed that **10**·HF mixed with $LiPF_6$ and $NaPF_6$ gave G/H values of 1.0, but with KPF_6, it dropped to 0.8 without affecting the EDC values much (1.7–2.2). Runs 18–20 showed that **10**·HBr mixed with $LiPF_6$, $NaPF_6$, and KPF_6 provided G/H values of 1.0, 0.9, and 0.5, respectively, without greatly affecting the EDC values (1.8–2.1). The results of runs 15–20 taken together indicate that KPF_6 competes somewhat with **10**·HPF_6 in extractability and that F^- ions salt out **10**·HPF_6 better than Br^-, and Li^+ better than Na^+ or K^+. The competition between KPF_6 and **10**·HPF_6 for complexation by host and the salting out effect do not interfere with the chiral recognition. Runs 21 and 22 demonstrated that **10**·HBr mixed with $NaAsF_6$ or $NaSbF_6$ provided G/H ratios of 1.0 and EDC values of 2.1 and 1.9, respectively.

The differences (Δ) in chemical shifts between the two CH_3 doublets in the ^1H NMR spectra of the diastereomeric complexes remained essentially constant at 24 ± 5 Hz for those runs (4–9, 11, 15–22) of Table I that gave similar EDC values. In the runs (12–14) that involved I^-, Δ decreased to 12–13 Hz while EDC values decreased to 1.0–1.2. Thus EDC and Δ values correlate roughly, and both indicate that in runs with I^- present the complexes are only partly structured. The fact that the three counterions PF_6^-, SbF_6^-, and AsF_6^- give essentially the same Δ values suggests the cationic complexes possess the same structures.

Similar exploratory extractions were also made with other **10**·HX and inorganic salts, and one other organic solvent. With (*RR*)-**1** in $CDCl_3$ and **10**·HBr–KSCN in D_2O at 0 °C, G/H = 1.5, complexation occurred, but EDC ~ 1. In the absence of **1**, **10**·HO_2CCCl_3 was extracted from D_2O into $CDCl_3$. In the presence of (*RR*)-**1**, this salt showed no evidence of complexation in $CDCl_3$. Neither in the absence nor presence of (*RR*)-**1** could more than small amounts of **10**·HO_2CCF_3 be extracted into $CDCl_3$. A saturated solution of **10**·H^+ picrate in D_2O was far less than 1 M, and extraction of the solution with (*RR*)-**1** in $CDCl_3$ gave no complexation. Substitution of *o*-dichlorobenzene for $CDCl_3$ under the conditions of run 8 (0.4 M **10**·HPF_6) gave G/H = 0.8, EDC = 2.0, and an ^1H NMR spectrum that showed highly structured complexation.

The important facts and interpretations derived from the experiments of this section are as follows. (1) Host (*RR*)-**1** or (*SS*)-**1** forms 1:1 complexes with α-phenylethylammonium hexafluorophosphate, hexafluoroarsenate, and hexafluorostibnate in $CDCl_3$ with the same degree of chiral recognition. These counterions appear to play no role in structuring the diastereomeric complexes. The large diameter of these anions and their symmetry make the charge highly delocalized. Thus in RNH_3^+·PF_6^- ion pairs, charge is already highly separated, hydrogen bonds are weak, and host can successfully compete with anion for hydrogen bonding all three hydrogens of RNH_3^+. These anions are relatively poorly solvated by water, which makes them more lipophilic than many of the other anions. (2) The extracted RNH_3PF_6 can be made by ion exchange in the presence of Li^+, Na^+, F^-, Cl^-, or Br^- ions without interfering with the extraction. However, K^+ competes somewhat with RNH_3^+ for host, and I^- with PF_6^- as a RNH_3^+ counterion in the extractions. At 1 M concentrations

Chart II



^1H NMR δ	(SS) (L)-13	(SS) (D)-13	(SS)-1
CH_3	3.60	3.52	–
NCH	4.59	4.97	–
aromatic H	6.56	6.9–7.4	–
CH_2OCH_2	2.9 (broad)	3.22	3.09
$ArOCH_2$	3.50; 3.98	3.54; 3.98	3.74

in water, only Li^+ and F^- showed evidence of salting out RNH_3PF_6. (3) Complexes between 1 and RNH_3X when formed at all are destructured when X = Br^- or $CCl_3CO_2^-$, probably because these ions hydrogen bond RNH_3^+ enough to inhibit host from hydrogen bonding more than one RNH_3^+ hydrogen. When X is I^- or SCN^-, there was ^1H NMR evidence of structuring of the complexes, but it was of a sufficiently low order to almost destroy chiral recognition. Therefore, these ions, too, were unsatisfactory. The $CF_3CO_2^-$ and picrate$^-$ and picrate salts of **10** proved to be difficult to extract. (4) Either $CDCl_3$ or *o*-$C_6H_4Cl_2$ is a satisfactory solvent for chiral recognition experiments, the former being preferred because of its volatility and the availability of deuterated material.

E. Compatibility of X-Ray and NMR Spectral Evidence for the Structures of Diastereomeric Complexes between (*RR*)-1 or (*SS*)-1 and D- or L-Methyl Ester Hexafluorophosphate Salts of Phenylglycine. Diastereomeric complexes of phenylglycine methyl ester hexafluorophosphate salts (**12**·HPF_6) were formed, and information regarding their structures in $CDCl_3$ solution was obtained from their ^1H NMR spectra. The diastereomeric complexes (*RR*)-**1**·D-**12**·HPF_6 and (*SS*)-**1**·D-**12**·HPF_6 were prepared by extracting at −3 °C 1.25 M solutions (6 equiv) of D-**12**·HPF_6[9d] in D_2O (1.25 M in $NaPF_6$) with 0.16 M solutions (1 equiv) of (*RR*)-**1** or (*SS*)-**1** in $CDCl_3$, respectively. The layers were separated carefully and the ^1H NMR spectra of the $CDCl_3$ layers were taken. Integrations of appropriate peaks indicated G/H ratios of ~0.8. Chart II summarizes the chemical shifts for the various protons of the two diastereomeric complexes, and contains hypothetical structures that provide explanations of the difference in chemical shifts for the diastereomers. Among the hypothetical structures of Chart II, the (*SS*)(*L*)-**13** diastereomer is drawn instead of the (*RR*)(*D*)-**13** diastereomer actually examined. The structural differences between diastereomers that possess a common host and different enantiomeric guests are easier to visualize than the reverse. Since (*SS*)(*L*)-**13** and (*RR*)-(*D*)-**13** complexes are enantiomers, they possess the same energies, structures that are mirror images of one another, and identical ^1H NMR spectra.

The (*SS*)(*L*)-**13** structure of Chart II was predicted in advance of the experiment as the more stable complex by examination of CPK molecular models. It conforms to **9** in which C_6H_5 is the large group (L), CO_2CH_3 is the medium (M), and H the small group (S), and resembles (*SS*)(*R*)-**11** of Chart I. Molecular models provide less help in predicting the structures of the less stable diastereomer, since steric compromises are involved. Fortunately, the (*SS*)-**1**·D-**12**·HPF_6·$CDCl_3$ complex was prepared in a separate experiment in a crystalline state, characterized,[4i] and its complete x-ray structure elucidated (photographs taken at −160 °C).[10a] Structure (*SS*)-

D-**13** is a crude representation of the observed x-ray structure of the *crystalline* complex. The complex in *solution* is probably an equilibrium mixture of conformers, none of which are sterically as compatible as the most stable conformer of the stabler diastereomer. The interesting question arises as to whether the ^{1}H NMR spectrum of (*SS*)-**1**·D-**12**·HPF_6 in $CDCl_3$ is as consistent with the presumed structure, (*SS*)-D-**13**, as it is with another conformation suggested earlier.[2b]

Drawings A and B are different views of the crystalline complex. As anticipated,[2b] the host's oxygens turn inward and hydrogen bond the NH_3^+ hydrogens. The C–N bond is nearly perpendicular to a plane defined by the three oxygen atoms that act as hydrogen acceptors. The ester group is distributed in one cavity, and the hydrogen and phenyl groups are distributed in the other. Unexpectedly, the plane of the CO_2CH_3 group, rather than that of the aryl, lies parallel to the plane of the naphthalene ring, and appears to stabilize the complex through a π-acid to π-base interaction. The C_6H_5 rises above the naphthalene wall, and the NCH hydrogen moves to a contact interaction distance with one of the host's oxygens. The NCH proton is relatively acidic, since it is attached to a carbon carrying three electron-attracting groups (NH_3^+, CO_2CH_3, and C_6H_5). Probably the thermodynamic acidity of this proton is great enough to weakly hydrogen bond ether oxygens when not overwhelmed by stronger, opposing structure–energy effects. Importantly for ^{1}H NMR spectral interpretations, the NCH proton is distant from the shielding region of the naphthalene wall, as are the protons of the C_6H_5 group. Furthermore, the host's CH_2OCH_2 protons lie far from the shielding region of the C_6H_5 group.

Our interpretations depend heavily on the assumption that host and guest are mainly held together and structured by three hydrogen bonds between RNH_3^+ and organized host oxygens or nitrogens. All five x-ray structures of complexes thus far completed support this assumption.[10]

The chemical shifts in the ^{1}H NMR spectra listed in Chart II of the actual complexes are compatible with structures (*SS*)-L-**13** and (*SS*)-D-**13**. Thus in both diastereomeric complexes, the CH_3O groups occupy about the same somewhat shielded positions, and this group in the (*SS*)-L and (*SS*)-D complexes gave signals at Δ 3.60 and 3.52, respectively. In (*SS*)-L-**13**, the NCH proton is well in the shielding region of the naphthalene wall, but not in (*SS*)-D-**13**. If hydrogen bonded as in (*SS*)-D-**13**, this proton should be deshielded. Thus both effects should place the NCH proton of the (*SS*)-L complex upfield of that of the (*SS*)-D complex. The (*SS*)-L complex gave a NCH signal 0.38 ppm upfield of that observed for the (*SS*)-D complex. In (*SS*)-L-**13**, one ortho proton of C_6H_5 lies in the shielding region of a naphthalene wall, but in (*SS*)-D-**13**, none of the C_6H_5 protons are near the region. The (*SS*)-L complex gave an averaged ortho proton signal at least 0.34 ppm higher field than that of the (*SS*)-D complex. In (*SS*)-L-**13**, the C_6H_5 group overlies two protons of the CH_2OCH_2 group of the host, but in (*SS*)-D-**13** it does not. The (*SS*)-L complex gave an averaged CH_2OCH_2 signal (eight in all), 0.19 ppm upfield of uncomplexed host (*SS*)-**1**, and 0.32 ppm upfield of the (*SS*)-D complex. Thus the structures of Chart II are consistent with the chemical shifts of four different kinds of protons in the diastereomeric complexes. The spectrum of the (*SS*)-D complex is also consistent with the alternative structure initially formulated.[2b]

In both (*SS*)-D-**13** and (*SS*)-L-**13**, the multiplet of the $ArOCH_2$ protons centered at δ 3.74 in (*SS*)-**1** is split into two distinct multiplets centered at δ 3.52 and 3.98 ($\pm$0.02). These are close to the δ 3.50 and 3.90 chemical shifts for the same protons observed for complexes (*SS*)(*R*)-**11** and (SS)(S)-**11**, respectively. This effect is explained as follows. The two $ArOCH_2$ protons in uncomplexed **1** time average across the plane of the naphthalene ring current from a shielding to a

H^2 shielded
H^1 deshielded

H^2 deshielded
H^1 shielded

deshielding region as formulated. Molecular model examination of the complexes indicates that this movement is prevented by the oxygens binding to and by the space occupation of the NH_3^+ group. Thus the averaged signal in uncomplexed **1** splits into two resonances of equal intensity, one moving upfield and the other downfield.

F. Results of Survey of Chiral Recognition by (*RR*)-1 or (*SS*)-1 of Enantiomers of Esters of α-Amino Acid Hexafluorophosphate Salts. The information gathered with α-phenylethylamine salts as guests in complexation of the bisdinaphthyl system (**1**) was applied to the methyl ester hexafluorophosphate salts of various α-amino acids. Attempts to prepare these salts as solids failed, so they were produced in D_2O–4 M in $LiPF_6$ solution by ion exchange with the easily handled hydrochloride salts of the amino esters. Thus host (*RR*)-**1** in $CDCl_3$ (0.20 M) was used to extract 1.2 M solutions of 3 equiv of racemic RNH_3·Cl salts in D_2O–4 M in $LiPF_6$ at pH 4. The $LiPF_6$ not only served as the source of the extractable PF_6^- ion, but Li^+, Cl^-, and excess PF_6^- ions "salted out" the organic guest from the D_2O layer and depressed the melting point of D_2O so temperatures as low as -18 °C could be reached.

Extraction experiments between (*RR*)-**1** and the methyl ester salts of racemic phenylglycine, *p*-hydroxyphenylglycine, valine, phenylalanine, methionine, tyrosine, serine, and alanine were examined. The results reported in Table II were obtained by a combination of ^{1}H NMR spectral and isolation techniques. The equilibrated layers were separated (the meniscus was discarded). By ^{1}H NMR integrations of appropriate signals of G and H in the $CDCl_3$ layer, the G/H ratios were determined. In all cases in which guest was extracted (runs 1–12), the amino esters were isolated from *each layer*, without enantiomer fractionation, and their rotations taken. The configurations of the more complexed enantiomers and EDC values were determined from the signs and magnitudes of rotation of the amino esters isolated from the $CDCl_3$ layers, and the correlations of the signs of rotation with absolute configurations of the amino esters.[9] The optical rotation of methionine ester (run 12) is so low that the EDC value was determined by the ^{1}H NMR integrations of the diastereomeric CH_3S protons of the complexes in the $CDCl_3$ layer. The more stable (*RR*)-L diastereomer gave a sharp singlet at δ 1.70, and the less stable (*RR*)-D diastereomer a sharp singlet at δ 1.74. The differences in free energies for the diastereomeric complexes ($\Delta(\Delta G°)$) were calculated assuming that eq 5 applied. The recovery of guest was determined by weighing the amount isolated from each layer.

The study was extended with (*SS*)-**1** as host to the isopropyl and *tert*-butyl esters of phenylglycine and the isopropyl ester of valine. Table III reports the results. Extraction ^{1}H NMR spectral-isolation techniques similar to those of the runs of Table II were used. These esters were more lipophilic than the methyl esters, so the concentrations of $LiPF_6$ in the D_2O layer were decreased from 1.0 to 0.5 M to adjust the G/H ratios in the $CDCl_3$ layer to 0.7–0.8. The ^{1}H NMR singlets of the $(CH_3)_3C$ protons of the diastereomeric *tert*-butyl phenylglycine ester-salt complexes in runs 2 and 3 occurred at δ 1.33 for the more stable (*SS*)-L complex and at δ 1.27 for the less stable (*SS*)-D complex. The (*SS*)-L complex gave δ 4.45 for its NCH proton as compared to δ 4.82 for the (*SS*)-D complex. Integrations of these signals provided the EDC values for these

Table II. Enantiomer Distribution Constants for the Extraction of Racemic Guest, $RC^*H(CO_2CH_3)NH_3PF_6$[a] (1.2 M in D_2O, 4 M $LiPF_6$), by Host (*RR*)-**1**[b] (0.20 M in $CDCl_3$)

Run no.	Temp, °C	R of amino ester salt	In $CDCl_3$ at equil G/H	Configuration dominant G	EDC (K_A/K_B)	$\Delta(\Delta G°)$, cal/mol	Recovery of G, %
1	26	C_6H_5	0.80	D	2.5	−540	96
2	15	C_6H_5	0.90	D	2.5	−525	97
3	2	C_6H_5	0.92	D	2.8	−555	91
4[c]	−10	C_6H_5	0.94	D	2.8	−535	87
5	−18	C_6H_5	0.98	D	3.1	−570	94
6	−6	*p*-HOC_6H_4	0.50	D	3.4	−680	80
7	−16	*p*-HOC_6H_4	0.66	D	5.0	−820	81
8	26	$(CH_3)_2CH$	~0.0				
9	−10	$(CH_3)_2CH$	0.58	L	1.5	−210	74
10[d]	−10	$(CH_3)_2CH$	0.63	L	1.5	−210	80
11	−1	$C_6H_5CH_2$	0.73	L	1.8	−320	92
12	−5	$CH_3SCH_2CH_2$	1.0	L	1.7	−280	50
13	−11	*p*-$HOC_6H_4CH_2$	0.0				
14	−3	$HOCH_2$	0.0				
15	0	CH_3	0.0				

[a] Equiv of RNH_3Cl per equiv of H in 11 mL of D_2O-4 M in $LiPF_6$ at pH 4. [b] 3.1 g in 21 mL of $CDCl_3$. [c] Duplicate run gave identical results. [d] Identical with run 9 except concentrations of guest in D_2O were doubled, and the volume of D_2O was halved.

Table III. Enantiomer Distribution Constants (EDC) for Extractions of Racemic Guest $RC^*H(NH_3PF_6)CO_2R'$ from D_2O-$LiPF_6$ Solutions by $CDCl_3$ Solutions of Host (*SS*)-**1**

Run no.	Temp, °C	$RC^*H(NH_3PF_6)CO_2R'$ Concn, M	R	R'	$LiPF_6$ concn, M	In $CDCl_3$ at equil G/H	Confign dom G	EDC (K_A/K_B)	$\Delta(\Delta G°)$, cal/mol
1	25	0.40	C_6H_5	$CH(CH_3)_2$	0.5	0.77	L	4.0	820
2	25	0.20	C_6H_5	$C(CH_3)_3$	0.5	0.75	L	4.0	820
3	0	0.20	C_6H_5	$C(CH_3)_3$	0.2	0.70	L	4.4	810
4	25	0.40	$(CH_3)_2CH$	$CH(CH_3)_2$	1.0	0.7		1.0	0
5	0	0.40	$(CH_3)_2CH$	$CH(CH_3)_2$	1.0	0.8		1.0	0

runs. The ortho protons of the C_6H_5 group appeared as a broad doublet at δ 6.56 and 6.64 in the (*SS*)-L complex, but was somewhere between δ 6.9 and 7.4 in the (*SS*)-D complex. Thus the ^1H NMR patterns of signals for these diastereomeric complexes resembled those observed for the diastereomeric complexes of the phenylglycine methyl ester salts (Chart II).

G. Models for Chiral Recognition in the Parent Dilocular System (*RR*)-1. The results of Table II indicate that (*RR*)-**1** lipophilizes, through complexation, the ester salts of phenylglycine, *p*-hydroxyphenylglycine, valine, phenylalanine, and methionine (runs 1–12). The methyl ester salts of tyrosine, serine, and alanine were too hydrophilic to be extractable (runs 13–15). With the methyl ester salts of phenylglycine, *p*-hydroxyphenylglycine, and valine (only ones studied), the lower the temperature, the more amino ester salt was extracted. For the ester–salt of phenylglycine (run 1) at 26 °C G/H = 0.80, and at −18 °C (run 5), G/H = 0.98. For the ester–salt of *p*-hydroxyphenylglycine G/H increased from 0.50 to 0.66 when the temperature was lowered from −6 to −16 °C (runs 6 and 7). For the ester–salt of valine, G/H increased from ~0 to ~0.6 when the temperature was lowered from 26 to −10 °C (runs 8–10). The above results indicate that for the complexation of these salts $\Delta S°$ of complexation is negative and differs substantially from zero.

In the complexation of the methyl ester salts, (*RR*)-**1** exhibited chiral recognition with EDC factors that ranged from a high of 5.0 ($\Delta(\Delta G°)$ ~−820 cal/mol) for *p*-hydroxyphenylglycine (run 7) to a low of 1.5 ($\Delta(\Delta G°)$ ~−210 cal/mol) for valine (runs 9, 10). The methyl ester salt of phenylglycine was the most studied. Its EDC value increased from 2.5 to 3.1 as the temperature decreased from 26 to −18 °C, but this change produced only a modest −30 cal/mol change in $\Delta(\Delta G°)$ for complexation (runs 1 and 5). A bigger change was observed for *p*-hydroxyphenylglycine, whose EDC of 3.4 at −6 °C increased to 5.0 at −16 °C, which represents a −140 cal/mol change in $\Delta(\Delta G°)$ for the two diastereoisomers. For both the phenylglycine and the *p*-hydroxyphenylglycine ester salts, the expected (*RR*)-D complexes were the more stable. The prediction was based on the general steric model **9**, and on the fact that Ar > CO_2CH_3 > H in bulk. The results are also compatible with the ester group behaving as a π acid toward a naphthalene ring as a π base, and thus providing a fourth binding site. In CPK molecular models of (*SS*)-L-**13**, the plane of the ester group is parallel to that of its adjacent naphthalene ring, and the two groups contact one another. This interaction, should it further organize the complexes, may enhance the observed chiral recognition between host and guest. Indeed the chiral recognition between **1** and these two methyl ester salts is higher than that between **1** and the α-phenylethylamine salts discussed in earlier sections.

The interesting question arises as to whether the rather acidic NCH hydrogen is involved in hydrogen bonding with the ether oxygens in the (*SS*)-L complex in solution as was shown in the x-ray structure for the (*SS*)-D complex. Although CPK molecular models of (*SS*)-L-**13** can accommodate such a contact interaction by many small conformational adjustments, the wide difference in chemical shifts for the NCH proton in the ^1H NMR spectra of the two diastereomers suggests that this interaction if it exists at all is less important for the more stable than for the less stable diastereomer.

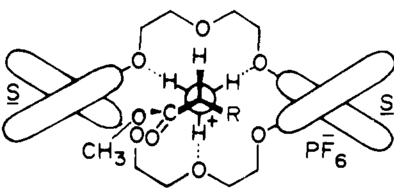
The patterns of differences in the ^1H NMR shifts for the diastereomeric complexes for the *p*-hydroxyphenylglycine methyl ester salt were similar to those for the nonhydroxylated parent. The shifts in $CDCl_3$ for the (*SS*)-L isomer were as follows: CH_3, δ 3.50; NCH, δ 4.40; C_6H_4, δ 6.26 and 6.52

(centers of two halves of an AA′BB′ system); CH_2OCH_2, δ 2.9. Those for the (*SS*)-D isomer follow: CH_3, δ 3.45; NCH, δ 4.84; C_6H_4, δ 6.9–7.4; CH_2OCH_2, δ 3.2. Thus the structures of the diastereomers for the *p*-hydroxyphenylglycine and those of phenylglycine ester salts resemble one another. However, **1** shows higher chiral recognition toward the guest with a *p*-hydroxyphenyl group than toward that with just a phenyl. Since the *p*-hydroxy group is too remote to exert a steric effect, it seems likely that the hydroxyl group electronically affects either or both of the other two contact sites, the CO_2CH_3, and the NCH groups. The delocalization of the electrons of the hydroxyl group into the benzene ring probably slightly reduces the π acidity and proton acidities of these two groups, respectively. The latter effect should destabilize the (*RR*)-L more than the (*RR*)-D complex, the net result being higher chiral recognition for the *p*-hydroxyphenylglycine ester salts, as is observed.

For the valine, phenylalanine, and methionine methyl ester salts, (*RR*)-**1** complexed the L better than the D enantiomers. The EDC values dropped to 1.5–1.8, and the $\Delta(\Delta G°)$ values dropped to −210 to −320 cal/mol. Particularly with valine, model **9** for the more stable diastereomeric complex fails because $(CH_3)_2CH \sim CO_2CH_3 > H$ in size. Model **9** is based on the existence of only the three $NH^+ \cdots O$ binding sites and on steric effects. The question arises as to why valine differs from phenylglycine. Unfortunately, the complexes of the valine, phenylalanine, and methionine ester salts gave ^1H NMR spectra whose overlapping signals provide structural information only with regard to the location of the CH_3O protons. The values for the respective (*RR*)-D and (*RR*)-L ester complexes were as follows: phenylglycine, δ 3.60 and 3.52; *p*-hydroxyphenylglycine, δ 3.50 and ~3.45; valine, δ 3.55 and 3.54; phenylalanine, δ 3.57 and 3.50; methionine, δ 3.55 for both diastereomers. Unfortunately, the ^1H NMR of neither $C_6H_5CH(CO_2CH_3)NH_3Br$ nor $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ could be recorded owing to their lack of solubility. Furthermore, spectra of mixtures of (*RR*)-**1** and $C_6H_5CH(CO_2CH_3)NH_3Br$ could not be taken owing to their lack of solubility. However, 18-crown-6, 0.2 M in $CDCl_3$, dissolved 0.75 equiv of $C_6H_5CH(CO_2CH_3)NH_3Cl$ to give a solution whose ^1H NMR spectrum gave δ 3.79 for the CH_3O protons. This signal was not altered by addition of 1 equiv of (*RR*)-**1.** The signals of all ten hexafluorophosphate complexes are upfield of this value by 0.26 ± 0.08 ppm. These similar upfield shifts suggest that the CO_2CH_3 group lies against the naphthalene wall in all ten complexes, much as it does in x-ray structure drawing A. This structure places the methyl in the shielding region of the naphthalene ring and points to the probable existence of a π-acid–π-base interaction as a fourth binding site for all ten complexes.

Fixation of this ester group in the complexes simplifies CPK molecular model examination. It also provides the following explanation for the differences in the directions of the configurational bias in complexation of the ester salts of phenylglycine and *p*-hydroxyphenylglycine on the one hand, and valine, phenylalanine, and methionine on the other.

In CPK molecular models of (*SS*)-D-**14,** when R is C_6H_5 or *p*-HOC_6H_4, the hydrogen or oxygen in the para position is distant from the asymmetric center C*, but lies on the axis of the C*–C bond. Thus in (*SS*)-D-**14,** an aryl group runs directly



(SS)(D)-14

into the naphthalene wall, or is forced to go above it (as in (*SS*)-D-**13**), tending to destabilize that diastereomeric complex relative to (*SS*)-L-**13.** When R is $(CH_3)_2CH$, $C_6H_5CH_2$, or $CH_3SCH_2CH_2$, by rotation about the *C–CH bond these groups can easily adopt conformations that allow them to fit into the cavity without serious steric repulsions. With these latter groups, CPK models offer little guidance as to which diastereomer should be the more stable, since any choice depends on the *C–CH rotamer chosen for comparison.

The results of Table III support this interpretation. When the methyl ester of the phenylglycine salt was converted to the isopropyl or *tert*-butyl esters, the direction of the configurational bias remained the same, and the chiral recognition increased by about −240 cal/mol. In contrast, conversion of the methyl ester of the valine salt to the isopropyl ester salt *decreased* the chiral recognition by 210 cal/mol, shifting its bias *away* from the (*RR*)-L salt and toward the (*RR*)-D salt. In other words, the more bulky isopropyl ester favored the (*RR*)-D salt more than the methyl ester salt by roughly −225 cal/mol, both for phenylglycine and valine. The most stable conformation within the $C{-}CO_2CH_3$ group is one in which the C–C and $O{-}CH_3$ bonds are coplanar and anti to one another (e.g., in the x-ray structure, A).[10a] Replacement of the relatively small CH_3 with the more bulky $(CH_3)_2CH$ or $(CH_3)_3C$ groups probably decreases the π attraction between the ester and naphthalene. The stabilities of the (*RR*)-L ester salts probably depend more on that interaction than do the stabilities of the (*RR*)-D ester salts. Thus the more bulky esters drive the chiral recognition toward the (*RR*)-D ester complexes.

The question of whether the results of runs 11 and 12 conform to the predictions of general model **9** as to the more stable diastereomeric complex is dependent upon the correct assignment of the relative sizes of CO_2CH_3 and the $CH_2C_6H_5$ or $CH_2CH_2SCH_3$ groups. Although the $CH_2C_6H_5$ and $CH_2CH_2SCH_3$ groups occupy more overall space than the CO_2CH_3 group, the latter branches closer to the asymmetric center. The CO_2CH_3 group is also more conformationally rigid and less adaptable than the other two groups. If the CO_2CH_3 group, for the above reasons, is presumed to be effectively larger in the neighborhood of the chiral barrier than the $CH_2C_6H_5$ or $CH_2CH_2SCH_3$ groups, then model **9** is accommodated. At least it can be said that the results are not inconsistent with model **9.**

H. Chiral Recognition of Hosts (*SS*)-2–(*SS*)-7 toward the Methyl Ester Hexafluorophosphate Salts of Phenylglycine and Valine. Table IV records the results of a survey of the chiral recognition properties of hosts (*SS*)-**2**–(*SS*)-**7** as 0.2 M solutions in $CDCl_3$ toward 1.2 M solutions of methyl ester hexafluorophosphate salts of phenylglycine and valine in D_2O–4 M in $LiPF_6$. These hosts are shaped very similarly to (*SS*)-**1** with respect to the positions of the naphthalene walls, heteroatom binding sites, and general shapes of the chiral cavities. They differ only by the substitution of CH_2OCH_2 groups of (*SS*)-**1** by $CH_2CH_2CH_2$, *m*-C_6H_4, or 2,6-pyridyl groups. Phenylglycine and valine methyl ester hexafluorophosphate salts were selected as standard guests since (*SS*)-**1** shows toward them configurational biases that are opposite to one another.

When a CH_2 group was substituted for a central oxygen of (*SS*)-**1** to give host (*SS*)-**2** as in runs 1 and 2, the amounts of guest extracted were too low to be measured. The same was true when a *m*-C_6H_4 group was substituted for one CH_2OCH_2 of (*SS*)-**1** to give host (*SS*)-**3.** In a study of simpler systems,[4b] 18-crown-6 was found to bind *t*-$BuNH_3SCN$ in $CDCl_3$ ~4 kcal/mol better than 18-crown-5, and ~3.5 kcal/mol better than 1,3-xylyl 18-crown-5. As before, the loss of even one binding site greatly reduces its ability to act as a host. When a 2,6-pyridyl group was substituted for a CH_2OCH_2 group of (*SS*)-**1,** as in (*SS*)-**4,** the binding ability toward phenylglycine

Table IV. Chiral Recognition between Dilocular Hosts (*SS*)-2–(*SS*)-7 (0.20 M $CDCl_3$) and $RC^*H(CO_2CH_3)NH_3PF_6$ (1.2 M in D_2O, Which Was 4 M in $LiPF_6$)[a]

Run no.	T, °C	Host No.	Host X	Host Y	Guest R	In $CDCl_3$ at equil.: G/H[b]	In $CDCl_3$ at equil.: Config. dom. G[c]	EDC[c]	Δ(ΔG°) (cal/mol)
1	-15	(*SS*)-2	CH_2OCH_2	$CH_2CH_2CH_2$	C_6H_5	~0	-	-	-
2	-6	(*SS*)-2	CH_2OCH_2	$CH_2CH_2CH_2$	$(CH_3)_2CH$	0	-	-	-
3	-10	(*SS*)-3	CH_2OCH_2	m-C_6H_4	C_6H_5	0	-	-	-
4	-10	(*SS*)-3	CH_2OCH_2	m-C_6H_4	$(CH_3)_2CH$	~0	-	-	-
5	-14	(*SS*)-4	CH_2OCH_2	2,6-pyridyl	C_6H_5	1.2	L	1.7	-270
6	-16	(*SS*)-4	CH_2OCH_2	2,6-pyridyl	$(CH_3)_2CH$	0.8	L	1.24	-110
7	-16	(*SS*)-5	2,6-pyridyl	2,6-pyridyl	C_6H_5	0.7	L	2.0	-355
8	-16	(*SS*)-5	2,6-pyridyl	2,6-pyridyl	$(CH_3)_2CH$	0.3	L	1.3	-135
9	-17	(*SS*)-6	2,6-pyridyl	m-C_6H_4	C_6H_5	0.3	-	1.0	~0
10	-16	(*SS*)-6	2,6-pyridyl	m-C_6H_4	$(CH_3)_2CH$	~0	-	-	-
11	-13	(*SS*)-7	2,6-pyridyl	$CH_2CH_2CH_2$	C_6H_5	0.4	L	1.35	-155
12	-16	(*SS*)-7	2,6-pyridyl	$CH_2CH_2CH_2$	$(CH_3)_2CH$	~0	-	-	-

[a] Molar ratio of G to H used in all runs was 3, as in those of Table 2. [b] Determined by appropriate ^1H NMR integrations. [c] Determined by isolation of amino ester from each layer, and determination of its rotation.

ester salt increased, and G/H went from 1.0 for (*SS*)-**1** (run 5, Table II) to 1.2 (run 4, Table IV). When two were introduced as in (*SS*)-**5**, G/H decreased to 0.7. These trends match what was observed when analogous changes were made in the simple 18-crown-6 system.[4c] Substitution of one 2,6-pyridyl and one m-C_6H_4 group for the CH_2OCH_2 groups, as in (*SS*)-**6**, gave G/H = 0.3 for phenylglycine ester salt (run 6). Thus the pyridyl group increases the binding enough to partially cancel the effect of the m-C_6H_4 group, and the system is barely on scale. Similarly, substitution of one 2,6-pyridyl and one $CH_2CH_2CH_2$ for the CH_2OCH_2 groups as in **7** (run 11) gave the reduced, but measurable, value of G/H = 0.4.

The chiral recognition toward the two guests in all runs where it could be measured (5–9 and 11) was below that observed for (*SS*)-**1**. Had the extraction conditions of run 5 been adjusted to give G/H < 1, the chiral recognition of (*SS*)-**4** toward phenylglycine ester salt would probably have increased considerably, and might even have exceeded that of (*SS*)-**1**. The two hosts that were the better binders, (*SS*)-**4** and (*SS*)-**5**, exhibited the highest chiral recognition toward the two guests, with $\Delta(\Delta G°)$ values ranging from −135 to −355 cal/mol. Only with (*SS*)-**4** and (*SS*)-**5** were comparisons between the chiral recognition of valine and phenylglycine ester salts possible (runs 5–8). As with (*SS*)-**1**, both hosts exhibited higher chiral recognition toward phenylglycine than toward valine ester salt (compare run 5 with 6, and run 7 with 8). The less effective hosts, (*SS*)-**6** and (*SS*)-**7**, gave poor chiral recognition toward phenylglycine ester salt, $\Delta(\Delta G°)$ being ~0 for the former and −155 cal/mol for the latter.

The most interesting aspect of these data is the *direction of the configuration bias* in chiral recognition. As with (*SS*)-**1**, the hosts (*SS*)-**4**, (*SS*)-**5**, and (*SS*)-**7** favor binding phenylglycine ester salt of the L configuration, as predicted by both the general model **9** and the more detailed model (*SS*)-L-**13** of Chart II. This correlation suggests that the general shapes of the cavities and steric barriers govern the direction of the chiral bias toward phenylglycine ester salt, rather than a change in the rigidity or nature of the electron-pair hydrogen bonding sites in the bridges. Thus, the phenomena of chiral recognition and the direction of the configurational bias are not uniquely associated with having a "crown ether" set of hydrogen bonding sites.

Unlike (*SS*)-**1**, hosts (*SS*)-**4** and (*SS*)-**5** favor binding the valine methyl ester salt of the L configuration. This switch is attributed to the lowered adaptability of the bridges when the planar 2,6-pyridyl group is substituted for a flexible CH_2OCH_2 group in one or two of the bridges linking the dinaphthyl units. Not only are the floors of the cavities and locations of the naphthalene walls more rigidly defined with the pyridyl group present, but the single electron pair on nitrogen is more rigidly oriented inward. Thus the pyridyl group forces the valine ester guest to conform to general model **9**, which takes into account only three hydrogen bonding sites and steric effects. One other effect may contribute to this switch. Introduction of the strongly electron-withdrawing pyridyl groups separated by the OCH_2 links from the naphthalene rings should reduce the naphthalene's π-basicity. Thus the importance of the ester to naphthalene binding should be reduced, and a host–guest relationship should be produced which is more like that observed between α-phenylethylamine salt and **1** (Chart I). Such an effect would explain why (*SS*)-**5** gave chiral recognition toward phenylglycine ester salt of −355 cal/mol (run 7, Table IV), a value similar to that of (*SS*)-**1** toward α-phenylethylamine salt (~−355 cal/mol, Table I) but of a lower order than that of (*RR*)-**1** toward phenylglycine ester salt (−555 cal/mol, run 3, Table II).

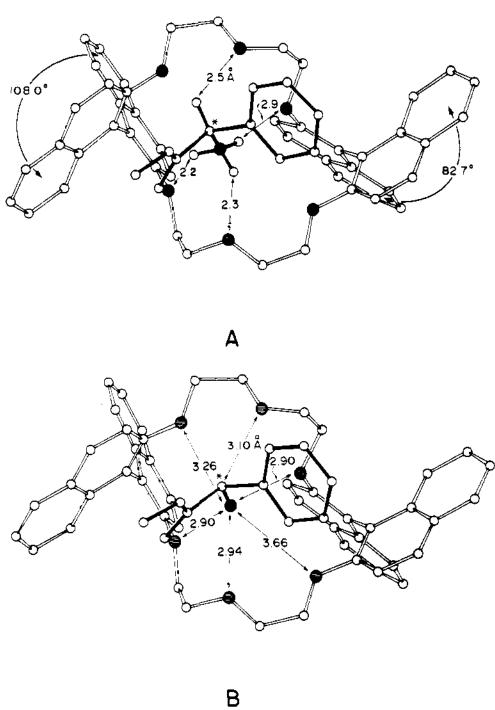
I. Chiral Recognition Properties of the Less Symmetrical Host, (*SS*)-8. Host (*SS*)-**8**[2d,4h] is an isomer of (*SS*)-**1** in which the two 1,1′-dinaphthyl units are separated by one ethylene glycol unit on one side, and by a triethylene glycol unit on the other, instead of by a diethylene glycol unit on both sides, as in (*SS*)-**1**. This structural change of (*SS*)-**1** to (SS)-**8** reduces the symmetry of the system from three mutually perpendicular C_2 axes in (*SS*)-**1** to one C_2 axis in (*SS*)-**8**. Thus while (*SS*)-**8** is "nonsided", its two chiral cavities on each face of the macroring are not identical as in (*SS*)-**1**, but one is much larger than the other.

In an extraction experiment, 0.80 mL of D_2O, 0.94 M in $NaPF_6$ and 0.94 M in racemic α-phenylethylammonium bromide, was shaken at 0 °C with 0.80 mL of (*SS*)-**8** in $CDCl_3$ (0.16 M). The ^1H NMR spectrum of the $CDCl_3$ layer indicated a G/H ratio of 1.0, and the two diastereomeric CH_3 signals appeared as doublets which integrated equally to provide an EDC value of 1.0 and $\Delta(\Delta G°) = 0$ cal/mol. One of the doublets appeared at δ 1.20 ppm ((*SS*)(*S*) diastereomer) and the other at δ 1.23 ppm ((*SS*)(*R*) diastereomer), each with a splitting of 6 Hz. The assignments were based on control experiments with the enantiomeric salts and (*SS*)-**8**. The difference in chemical shifts for the two diastereomeric methyl groups is only 0.03 ppm, much less than the 0.29 ppm observed for the difference in the complexes of (*SS*)-**1** and the enantiomers of $C_6H_5CH(CH_3)NH_3PF_6$ (Chart I). These results correlate with the presence of chiral recognition in the complexes of (*SS*)-**1**, and the absence of it in those of (*SS*)-**8**. Interestingly, the average of the chemical shifts for the diastereomers formed from (*SS*)-**1** is δ 1.23, and the averaged chemical shift for its isomer (*SS*)-**8** is δ 1.22. Thus the averaged environment for all four methyl groups in the four complexes is about the same. Host (*SS*)-**8** appears to be a stronger binder than (*SS*)-**1** (based on G/H ratios), and offers less steric constraints to binding than (*SS*)-**1**. Molecular model (CPK) examination suggests that dividing the space around the central hole into a large and a small cavity is less confining to guests than is dividing the space into two equal medium-sized cavities.

The results of chiral recognition experiments between phenylglycine methyl ester hexafluorophosphate and (*SS*)-**8** proved more interesting. Extraction experiments were performed identically with those of runs 4 and 5 of Table II except that (*SS*)-**8** was substituted for (*SS*)-**1**. In each run, G/H = 0.9, based on recovered guest from each layer. From the

rotations of guest isolated (both layers), the EDC values for the two runs made at −10 and −17 °C were each 2.2. Unlike the results observed with host **1**, the configurational bias favored the (*SS*)-D complex over the (*SS*)-L complex by −405 cal/mol. This result is rationalized in terms of model (*SS*)-D-**15**, in which the CO_2CH_3 and C_6H_5 groups are distributed in the large cavity with the ester group bound to the naphthalene wall.

(SS)-8 + (D)-ester salt ⟶ (SS)(D)-15



J. Conclusions Concerning Highly Structured Molecular Complexation between Dilocular Hosts and Primary Amine Salts. The results of the previous sections have shown how chiral recognition combined with ^1H NMR spectral and x-ray structural probes have been combined to gain information about the structures of complexes between organic hosts and guests. The beautiful feature of comparing diastereomeric complexes is that any differences in their physical characteristics or free energies must be ultimately derived from differences in steric effects. The structures of both host and guest have been varied, and the patterns of results that emerge provide conclusions useful in further design of host–guest complementary relationships. These conclusions are summarized as follows.

Compared to large energies and rigid geometric requirements for covalent bonds, the electrostatic forces binding and organizing these complexes are very small, amounting collectively to only a few kcal/mol. The individual contact interactions are worth at most only about −2 kcal/mol of free energy[4b,c] each, and are probably much less in the complexes studied here, whose dilocular hosts are much poorer complexers than those without dinaphthyl units.[11] If the binding energy of the more stable diastereomeric complex happened to be −4 kcal/mol and the $\Delta(\Delta G°)$ for the two diastereomers was −1 kcal/mol, 25% of the total binding would reflect chiral recognition. In a sense, this 25% would be the "chiral yield". When considered in these terms, the $\Delta(\Delta G)$ values of −200 to −800 cal/mol are more impressive than when considered out of context. Clearly, more highly structured complexes and higher chiral recognition will be encountered when binding free energies are increased.

The x-ray structure of the less stable diastereomeric complex (*SS*)-**1**·D-**12**·HPF_6·$CDCl_3$ (drawings A and B) illustrates several important principles. This complex which was "designed not to form" owes its stability to an accommodation to the unfavorable steric interactions by a large number of small conformational adjustments and to a partial reorganization of its binding sites. Thus a free-energy minimum is attained by several adjustments: splaying the chiral cavities through rotation of the dinaphthyl units away from the guest; forming one large (108°) and one small (83°) dihedral angle for the dinaphthyl units; utilizing unanticipated NCH···O and CO_2CH_3 to naphthalene binding; employing far-from-linear $^+N–H···O$ bonds; using essentially no direct $^+N···O$ interactions.[4b] To maximize differences in free energies between diastereomeric complexes, one must design to inhibit such adjustments. One way is to minimize the number of conformational degrees of freedom in both host and guest. Another is to use all potential binding sites as part of the design for complementary vs. noncomplementary placement of binding sites in host and guest.

The fact that the guest salts in water are lipophilized by complexation and drawn into the chloroform layer indicates that the host's binding sites have taken the place of the water molecules solvating RNH_3^+. Equally important, to produce highly structured complexes, the $RNH_3^+···X^-$ hydrogen bond must be broken. In this study the hosts are such poor binders that the $RNH_3^+···X^-$ bond had to be made very weak to start with by maximizing the diameter and dispersing the charge of X^-. Of the ions examined, only the PF_6^-, AsF_6^-, and SbF_6^- ions allowed highly structured complexation to occur. Other studies suggest that ClO_4^- [4d,12] might have been used.

Just as in crystal lattices, host–guest complexes are expected to be more stable, the more thoroughly filled are the cavities. In other words, other things being equal, the more contact sites between host and guest and the fewer the oriented solvent molecules, the more stable the complex is expected to be. Possibly the greater binding and higher chiral recognition observed when (*SS*)-**1** complexed the *tert*-butyl compared to the methyl ester of phenylglycine salt reflects an accumulation of many small van der Waals attractive forces associated with the filling of the cavity with the larger ester group. Such an effect may also explain why model **9** based on specific binding sites and steric repulsions failed to predict the configuration of the more stable diastereomeric complex between (*RR*)-**1** and the methyl ester of valine hexafluorophosphate. The cavities may be more completely and compatibly filled in the "wrong" (*RR*)-L complex than in the "right" (*RR*)-D complex. The low chiral recognition in the "wrong" direction

(~200 cal/mol) may provide an indication of the free-energy magnitude associated with such a "filling up" effect.

The important phenomenon of organic to organic highly structured complexation is obviously very complicated. Chiral recognition as a finely honed probe of structure to energy relationships is expected to further reveal the character of complexation in studies to be reported in future papers of this series.

Experimental Section

General. All ^{1}H NMR spectra were taken on a Varian HA-100 spectrometer operated at ambient probe temperature with Me_4Si as internal standard. Rotations were taken in a 1-dm thermostated cell on a Perkin-Elmer polarimeter 141. Reagent grade CH_2Cl_2, *o*-$Cl_2C_6H_4$, and ethyl acetate were fractionally distilled before use. Chloroform was washed five times with equal volumes of water, dried over Na_2SO_4, distilled, and deoxygenated with nitrogen before use. Salts $LiPF_6$, $NaPF_6$, KPF_6, $NaAsF_6$, and $NaSbF_6$ were purchased from Ventron (98+% pure) and were used directly. Hexafluorophosphoric acid diethyl etherate (Aldrich) was used to prepare aqueous HPF_6 solutions, or amine salts in solution.

Host Compounds. Host compounds **1–8** of maximum rotation were employed throughout this study. Their syntheses and characterizations were reported in part 7 of this series.[4g]

Amine Salts. The hydrochloride and hydrobromide salts of racemic (*R*)- and (*S*)-α-phenylethylamine[8] were prepared by bubbling HCl or HBr gas (respectively) into solutions of the amine in dry ether. The precipitated salts were recrystallized from ethanol-ether.[13a,b] The HF salt of racemic α-phenylethylamine was made by neutralizing the amine in water with 48% HF in water. The water was evaporated under reduced pressure, and the solid residue was washed with 1:2 (v/v) acetone-ether. This salt sublimed at 80 °C at 0.1 mm pressure, and gave mp 130-140 °C when hydrated, mp 253-255 °C when dry.[13a] The trifluoroacetate, trichloroacetate, and picrate[13c] salts of α-phenylethylamine were similarly prepared. Attempts to obtain the anhydrous α-phenylethylammonium PF_6^-, AsF_6^-, and SbF_6^- salts always led to hygroscopic and unstable materials which eventually gave the F^- salt.

Amino Acid and Ester Starting Materials. The following amino acid methyl ester hydrochloride salts were purchased from Sigma: racemic methyl alaninate; racemic and L-methyl methionate; racemic methyl serinate; racemic methyl tyrosinate; racemic and L-methyl phenylalaninate; and racemic methyl tryptophanate. Racemic phenylglycine and D-phenylglycine were purchased from Aldrich, $[\alpha]^{25}_{589}$ −154.5° (*c* 1, 1 N HCl), 98% optically pure. The authors thank the Upjohn Co. for generous samples of L-phenylglycine, $[\alpha]^{25}_{589}$ +155°C (*c* 1, 1 N HCl), 98% optically pure; for D-phenylglycine, $[\alpha]^{25}_{589}$ −158° (*c*, 1 1 N HCl); for racemic *p*-hydroxyphenylglycine; for D-*p*-hydroxyphenylglycine, $[\alpha]^{25}_{589}$ −106.2° (*c* 1.03, H_2O), lit.[9g] $[\alpha]^{25}_{589}$ −108° (*c* 1.0, H_2O), $[\alpha]^{25}_{546}$ −189.3° (*c* 1.0, 1 N HCl); and for D-*p*-hydroxyphenylglycine methyl ester hydrochloride, $[\alpha]^{25}_{546}$ −172.8° (*c* 1.0, CH_3OH).

Racemic Methyl Phenylglycinate Hydrochloride. Procedure A. Racemic phenylglycine (30.2 g, 0.2 mol) was suspended in 500 mL of methanol (stored over 3 Å sieves) and dry HCl gas bubbled into the suspension until dissolution occurred. The solution was then refluxed for 5 h, cooled, and evaporated to dryness. The residue was dissolved in 200 mL of water, 500 mL of CH_2Cl_2 was added, and enough aqueous ammonium hydroxide was added to give pH 10. Unreacted amino acid, which precipitated from solution at this point, was filtered and later recycled. The organic phase containing the free amino ester was withdrawn and the aqueous solution extracted with another 500 mL of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and dry HCl gas was bubbled in to form the salt. The solvent was evaporated and the solid dried (24 °C, 0.1 mm, 24 h) to give methyl phenylglycinate hydrochloride as a white solid (32 g, 80%), mp 223-224 °C (lit. mp 222 °C)[9e].

D-Methyl Phenylglycinate Hydrochloride. To a suspension of D-phenylglycine (30.2 g, 0.2 mol) in 500 mL of dry methanol was added HCl gas in order to effect dissolution. Since optically pure (*R*)-phenylglycine racemized slowly upon refluxing this solution, the solution was evaporated to dryness to remove all excess acid, then the crude hydrochloride salt was redissolved in 500 mL of *dry* methanol and the solution was refluxed for 5 h. Extractive isolation, as for the racemic salt above, gave 31 g (77%) of the methyl ester salt, mp 200-203 °C (lit. mp 199-200 °C),[9f] $[\alpha]^{25}_{589}$ −131°, $[\alpha]^{25}_{578}$ −136°, $[\alpha]^{25}_{546}$ −157°, $[\alpha]^{25}_{436}$ −282° (*c* 1.0, CH_3OH), lit. $[\alpha]^{25}_{589}$ −133.1° (*c* 1.0, CH_3OH).[9f]

Racemic Methyl Valinate Hydrochloride. Racemic valine (30.0 g, 0.256 mol) was treated as in procedure A to give 32 g (75%) of the racemic product, mp 110-115 °C (the following melting points have been reported: 90-97, 112-113, 120-122 °C).[9d]

L-Methyl Valinate Hydrochloride. L-Valine (30.0 g, 0.256 mol) was treated as in procedure A to give 31.2 g (73%) of the desired product, mp 155-160 °C (the following melting points have been reported: 146-149, 161-162, 167-168, 170, 175 °C),[9d] $[\alpha]^{25}_{589}$ +15.7°, $[\alpha]^{25}_{578}$ +16.4°, $[\alpha]^{25}_{546}$ +18.0°, $[\alpha]^{25}_{436}$ +35.8° (*c* 2, H_2O), lit. $[\alpha]^{25}_{589}$ +15.5° (*c* 2, H_2O).[9d]

Racemic Methyl Phenylalaninate Hydrochloride. Racemic phenylalanine (40 g, 0.24 mol) was treated as in procedure A to give 38.6 g (75%) of product, mp 157-160 °C (lit. mp 156-158 °C).[9d]

L-Methyl Phenylalaninate Hydrochloride. L-Phenylalanine (40 g, 0.24 mol) was treated according to procedure A to give 39.5 g (77%) of product, mp 157-160 °C (lit. mp 159-161 °C),[9d] $[\alpha]^{25}_{589}$ +18.6° (*c* 4.5, CH_3OH), lit. $[\alpha]^{25}_{589}$ +18.9° (*c* 4, CH_3OH).[9d]

L-Methyl Methionate Methyl Ester Hydrochloride. Application of procedure A to L-methionine gave an 80% yield of its methyl ester hydrochloride salt, $[\alpha]^{25}_{589}$ +26.6°, $[\alpha]^{25}_{578}$ +28.0°, $[\alpha]^{25}_{578}$ +31.4°, $[\alpha]^{25}_{436}$ +56° (*c* 1, H_2O), lit.[9d] $[\alpha]^{25}_{589}$ +26.8° (*c* 1, H_2O).

D-*p*-Hydroxyphenylglycine Methyl Ester Hydrochloride. A 2.00-g sample of D-*p*-hydroxyphenylglycine was suspended in 35 mL of dry methanol and 1.0 g of dry HCl gas was added. The solution was allowed to stand for 48 h in the sealed flask at 25 °C, after which time the solvent was evaporated under vacuum below 30 °C. The solid residue was ground in a mortar with 10 mL of acetone and filtered. The trituration was repeated, and the collected solid was washed with 10 mL of ether and dried to give 21.3 g (82%) of product, $[\alpha]^{25}_{589}$ −121.1°, $[\alpha]^{25}_{578}$ −125.9°, $[\alpha]^{25}_{546}$ −145.5°, and $[\alpha]^{25}_{436}$ −267.3° (*c* 1, 1 N HCl), or $[\alpha]^{25}_{546}$ −171.1° (*c* 1.0, CH_3OH); $[\alpha]^{25}_{546}$ −172.8° (*c* 1, CH_3OH), private communication from Dr. H. Jaeger, The Upjohn Co. The ^{1}H NMR spectrum of this material gave proton integrations that suggested that $\lesssim$5% of the starting amino acid was present. Attempts to remove it failed.

D-Methyl Esters of Amino Acids. Procedure B. A sample of D-methyl phenylglycinate hydrochloride salt (0.50 g, 2.5 mmol) was shaken with 50 mL of water and 50 mL of CH_2Cl_2, and the solution was adjusted to pH 10 with aqueous NH_4OH. The organic phase was dried ($MgSO_4$) and evaporated to give 0.40 g (97%) of D-methyl phenylglycinate as an oil, $[\alpha]^{25}_{578}$ −161°, $[\alpha]^{25}_{546}$ −185°, $[\alpha]^{25}_{436}$ −340° (*c* 2, CH_2Cl_2). The amine ester was then redissolved in dichloromethane (50 mL) and dry HCl gas bubbled into the solution to form the hydrochloride. The solvent was evaporated and the solid dried (24 °C, 0.1 mm, 24 h) to give the hydrochloride salt (0.45 g, 90% overall). The specific rotations of this salt were within 1% of the values for those of the starting material. Thus no racemization occurred in the conversion of the salt to the free ester and back to the salt.

Treatment of L-methyl valinate hydrochloride according to procedure B gave L-methyl valinate as an oil, $[\alpha]^{25}_{578}$ +43.3°, $[\alpha]^{25}_{546}$ +50.0°, $[\alpha]^{25}_{436}$ +93° (*c* 2, CH_2Cl_2), which, when reconverted to its hydrochloride salt, gave material whose specific rotations were within 1% of those of the original starting material.

Treatment of L-methyl phenylalaninate hydrochloride according to procedure B gave L-methyl phenylalaninate as an oil, $[\alpha]^{25}_{578}$ +16.9°, $[\alpha]^{25}_{546}$ +19.9°, $[\alpha]^{25}_{436}$ +39.7° (*c* 2, CH_2Cl_2), which, when reconverted to its hydrochloride salt, gave the original rotation within 1%.

Treatment of L-methyl methionate hydrochloride according to procedure B gave L-methyl methionate as an oil, $[\alpha]^{25}_{589}$ +26.6°, $[\alpha]^{25}_{578}$ +28.0°, $[\alpha]^{25}_{546}$ +31.4°, and $[\alpha]^{25}_{436}$ +56° (*c* 1, H_2O) (lit. $[\alpha]^{25}_{589}$ +26.8°),[9b] which, when reconverted to its hydrochloride salt, gave the original rotation within 1%.

Isopropyl Phenylglycinate Hydrochloride. For preparation of racemic material, anhydrous HCl gas was bubbled slowly through a refluxing suspension of 12.0 g (80 mmol) of phenylglycine in 250 mL of dry 2-propanol for 4.5 h. The solvent was evaporated in vacuo, and the remaining powder was recrystallized from acetone-water to give 8.8 g (48%) of ester salt as white crystals: mp 225-228 °C; ^{1}H NMR spectra in D_2O δ 1.3 (d, J = 7 Hz, 6 H, $(CH_3)_2CH$) (s, 1 H, ArCH), 5.0–5.4 (m, 1 H, $(CH_3)_2CH$), 7.6 (s, 5 H, ArH). Anal. Calcd for $C_{11}H_{16}NO_2Cl$: C, 57.51; H, 7.02. Found: C, 57.44; H, 7.02.

The same procedure was applied to D-phenylglycine except that HCl gas was bubbled through the solution for only 2.0 h. The un-

reacted phenylglycine hydrochloride salt was collected and dried under high vacuum to give $[\alpha]^{25}{}_D$ −151° (*c* 1.21, 1 N HCl) compared to $[\alpha]^{20}{}_D$ −154.5° (*c* 1, 1 N HCl) for the starting material. The crude ester salt was recrystallized four times to constant rotation from acetone-water to give 52% of ester salt as white needles: mp 216-221 °C; ^{1}H NMR in D_2O superimposable on that of racemic material; $[\alpha]^{25}_{578}$ −69.4°, $[\alpha]^{25}_{546}$ −80.6°, $[\alpha]^{25}_{436}$ −146.9° (*c* 1, H_2O). Anal. Calcd for $C_{11}H_{16}NO_2Cl$: C, 57.51; H, 7.02. Found: C, 57.50; H, 7.02.

***tert*-Butyl Phenylglycinate Hydrochloride.** In a pressure bottle were placed 5.0 g (33.3 mmol) of racemic phenylglycine suspended in 50 mL of dioxane (purified) and 5 mL of concentrated H_2SO_4. The reaction mixture turned yellow and became homogeneous. To the solution was added 50 mL of liquid isobutylene, and the bottle was then sealed and shaken for 20 h. The precipitate that formed was collected and the filtrate was extracted with several portions of ether. The solid precipitate was combined with the extracts, and anhydrous HCl gas was bubbled through the solution. The precipitate that separated was recrystallized from acetone-water to give 1.85 g (23%) of pure *tert*-butyl phenylglycinate hydrochloride: mp 219-225 °C dec; ^{1}H NMR in D_2O δ 1.2 (s, 9 H, CH_3), 5.2 (s, 1 H, ArCH), 7.6 (s, 5 H, ArH). Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.14; H, 7.44. Found: C, 59.35; H, 7.35.

Isopropyl Valinate Hydrochloride. Anhydrous HCl gas was bubbled slowly through a suspension of 20.0 g (0.17 mol) of racemic valine in 500 mL of dry 2-propanol for 6 h. The solvent was evaporated under vacuum, and the residual powder was recrystallized from acetone to give 17.4 g (52%) of ester salt as needles: mp 114-116 °C; ^{1}H NMR (D_2O) 1.1 (d, J = 7 Hz, 6 H, $CHCH(CH_3)_2$), 1.3 (d, J = 7 Hz, 6 H, $OCH(CH_3)_2$), 2.0-2.5 (m, 1 H, $CHCH(CH_3)_2$), 3.9 (d, 1 H, $(CH_3)_2CHCH$)), 4.8-5.4 (m, 1 H, OCH). Anal. Calcd for $C_8H_{18}NO_2Cl$: C, 49.10; H, 9.27. Found: C, 48.95; H, 9.10.

Similarly, L-isopropyl valinate hydrochloride was prepared and recrystallized from acetone-water (55%): mp 112-114 °C; ^{1}H NMR (D_2O) was superimposable on that of racemate; $[\alpha]^{25}_{578}$ 5.41°, $[\alpha]^{25}_{546}$ 6.29°, $[\alpha]^{25}_{436}$ 13.82° (*c* 3.4, H_2O). Anal. Calcd for $C_8H_{18}ClNO_2$: C, 49.10; H, 9.27. Found: C, 49.35; H, 9.17.

Extraction, Isolation, and Rotation Experiment of α-Phenylethylammonium Salt and Host 1. A solution of 3.9 g of racemic α-phenylethylammonium chloride and 4.2 g of $NaPF_6$ in 30 mL of water (0.83 M in each component) was shaken at 0 °C for 15 min with a 25-mL $CHCl_3$ solution containing 3.00 g of (*SS*)-**1** (0.17 M). The layers were carefully separated, the meniscus was discarded, and the $CHCl_3$ solution was diluted to 50 mL and extracted with two 50-mL portions of water. Evaporation of the $CHCl_3$ solution gave 2.7 g (90%) of (*SS*)-**1**, $[\alpha]^{25}_{578}$ −216°, $[\alpha]^{25}_{546}$ −260°, and $[\alpha]^{25}_{436}$ −596° (*c* 0.93, CH_2Cl_2), whose ^{1}H NMR spectrum demonstrated the absence of amine salt. The rotations of this material are 99% the magnitude of the original (*SS*)-**1**. The 100 mL of aqueous extract was concentrated to 85 mL under vacuum to remove traces of $CHCl_3$, and 20 g of KOH was added with cooling. The resulting mixture was extracted with two 100-mL portions of ether, and the combined extracts were dried ($MgSO_4$) and concentrated. The residual oil was submitted to three freeze-pump-thaw cycles and flash distilled at 30 °C (25 μ) to give 345 mg of α-phenylethylamine contaminated with 3.7% (w/w) of $(C_2H_5)_2O$, as shown by ^{1}H NMR. The yield was 65%, based on (*SS*)-**1** and corrected for the ether contaminant. Rotations of this material were corrected for the 3.7% ether impurity, $[\alpha]^{25}_{578}$ +9.41°, $[\alpha]^{25}_{546}$ +10.8°, $[\alpha]^{25}_{436}$ +18.8° (*c* 7.56, $CHCl_3$). The degree of optical purity of this material was measured by comparing these rotations with those of a 94.5% optically pure sample of (*R*)-α-phenylethylamine, $[\alpha]^{25}{}_D$ +38.1° (neat) (lit.[8] $[\alpha]^{22}{}_D$ 40.3° (neat) for optically pure material) taken under the same conditions: $[\alpha]^{25}_{578}$ +37.3°, $[\alpha]^{25}_{546}$ +42.6°, $[\alpha]^{25}_{436}$ +74.2° (*c* 7.38, $CHCl_3$). The enantiomeric excess at the three wavelengths gives 23.9, 24.0, and 24.0%, respectively. These values agree well with those obtained by ^{1}H NMR measurements described in the Results and Discussion section.

In a similar but small-scale extraction, $CDCl_3$ and D_2O were used. No host could be detected in the ^{1}H NMR spectrum of the D_2O layer.

Experiments Reported in Table I. The standard extraction procedure was as follows. A D_2O solution (0.80 mL) of an α-phenylethylammonium salt (from 0.40 to 1.0 M, see Table I) that was 1 M in various inorganic salts was shaken at 0 °C for 15 min with 0.8 mL of a 0.14 M solution of (*SS*)-**1** in $CDCl_3$. The phases were carefully separated, the meniscus was discarded, and the $CDCl_3$ layer was analyzed by ^{1}H NMR. The ratio of G/H (**10**/**1**) was determined from integrals of the CH_3 doublets vs. the combined signals of the OCH_2CH_2O and NCH protons. The CRF value in $CDCl_3$ was calculated from the ratios of the integrals of the well-defined CH_3 doublets of the (*R*)- and (*S*)-α-phenylethylammonium complexes.

In runs 4-8, the aqueous solutions of α-phenylethylammonium hexafluorophosphate were prepared by titrating the amine in D_2O with a 65% H_2O solution of HPF_6. This HPF_6 solution was prepared at −80 °C from $HPF_6 \cdot O(C_2H_5)_2$, followed by evaporation of the ether by three freeze-pump-thaw cycles. In a typical titration 1.82 g of α-phenylethylamine (15 mmol) in 10 mL of D_2O was neutralized with 1.87 g of 65% HPF_6 in H_2O. An additional 0.5 g of amine was added as well as enough additional D_2O to create a volume of 15 mL. This solution was washed free of excess amine by two extractions with CH_2Cl_2. The aqueous solution was freed of CH_2Cl_2 by three freeze-pump-thaw cycles.

Preparation of Aqueous Lithium and Sodium Hexafluorophosphate Solutions. These solutions had to be prepared carefully since the dry salts react exothermically with water to generate NaF and LiF. The following procedure was used to avoid this difficulty. In a drybox, 21.27 g of $LiPF_6$ was weighed and dissolved in very small portions in a stirred D_2O slurry cooled using a −5 °C bath, the reaction temperature being maintained at 10 °C or lower at all times. The pH was then adjusted to 2.1 by adding 2.7 mL of a 5 M solution of LiOD in D_2O. The solution was filtered from 0.5 g of insoluble material. The filtrate was diluted to 35 mL with D_2O, weighed, and calculated to be 4 M $LiPF_6$. This solution was stored at −20 °C, and over a period of months slowly precipitated LiF. Solutions of $NaPF_6$ were similarly prepared, and diluted where necessary, as were the $NaSbF_6$ and $NaAsF_6$ solutions. The $LiPF_6$ salt concentrations reported in the tables are maximal and approximate because of the reaction of $LiPF_6$ with H_2O.

Amino Ester Salt Extraction Runs Reported in Tables II and IV. The extractions of runs 1-15 of Tables II and IV were all conducted at the same molar concentration of all components, and the products were isolated and similarly analyzed except where noted otherwise in the footnotes of Tables II or IV, or in the following examples. Run 1 of Table II illustrates the standard procedure. Host (*RR*)-**1** (3.1 g, 4.35 mmol) was dissolved in 22 mL of $CDCl_3$ to give a 0.20 M solution. This solution was used to extract 3 equiv of racemic methyl phenylglycinate hydrochloride (13 mmol, 2.62 g) dissolved in 10.8 mL of an aqueous D_2O solution (1.2 M in guest) which was 4 M in $LiPF_6$ (pH 4.0). After equilibration at 26 °C (about 1 h), the phases were carefully separated, and the meniscus was discarded. The organic phase was diluted with 40 mL of CH_2Cl_2 and extracted with three 30-mL portions of 0.1 N HCl. The combined aqueous extracts were added to 100 mL of CH_2Cl_2 and aqueous ammonium hydroxide was added to adjust the pH to 10. The organic phase (containing the free amino ester) was withdrawn, the aqueous phase was reextracted with another 50 mL of CH_2Cl_2, and the combined organic extracts were dried with $MgSO_4$. The solvent was evaporated to give 550 mg of the amino ester, as an oil (3.34 mmol), $[\alpha]^{25}_{578}$ −52.5°, $[\alpha]^{25}_{546}$ −60.4°, $[\alpha]^{25}_{436}$ −110.6° (*c* 2, CH_2Cl_2), indicating an optical purity of 32.6%, enriched in the D enantiomer. The CRF value was therefore 1.97.

The aqueous phase was diluted with 40 mL of water and extracted with three 30-mL portions of CH_2Cl_2. It was then added to 100 mL of CH_2Cl_2, aqueous ammonium hydroxide was added to give pH 10, and the organic phase was withdrawn. The aqueous phase was extracted with another 50 mL of CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$). The solvent was evaporated to give 1.5 g of the free amino ester, as an oil (9.1 mmol, 96% total recovery of guest), $[\alpha]^{25}_{578}$ +20.8°, $[\alpha]^{25}_{546}$ +23.8°, $[\alpha]^{25}_{436}$ +43.9° (*c* 2, CH_2Cl_2). This material is 12.7% optically pure, enriched in the L enantiomer. The value of $([G_B]_{D_2O}/[G_A]_{D_2O})$ was therefore 1.29, and the EDC value was 2.50. The guest to host ratio in the organic phase (G/H) (corrected to 100% recovery of the guest) was 0.80.

Since methyl *p*-hydroxyphenylglycinate is a solid and optical fractionation had to be avoided during isolation, the following isolation procedure was devised for runs 6 and 7. Run 7 is illustrated. Host (*RR*)-**1** (2.6 g, 3.66 mmol) was used, and the other amounts and volumes used in the procedure outlined for methyl phenylglycinate were scaled to this amount of host. After the equilibration of the layers and phase separation, the organic phase was diluted with 40 mL of CH_2Cl_2 and extracted with three 100-mL portions of 1 N HCl. The combined aqueous extracts were brought to pH 9 with Na_2CO_3, with the formation of a solid. The aqueous-solid mixture was extracted with seven 100-mL portions of ethyl acetate. The remaining solid was fil-

tered and dried (24 °C, 0.1 mm, 24 h). The combined organic extracts were back-extracted with three 100-mL portions of 1 N HCl, and the combined aqueous extracts were adjusted to pH 9 with Na_2CO_3 (no solid formation) and extracted with seven 100-mL portions of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to give 300 mg of an orange solid, which was dried (24 °C, 0.1 mm, 24 h).

The original white solid precipitate (100 mg) was shown by its zero rotation to be the racemic amino ester of *p*-hydroxyphenylglycine. The orange solid gave $[\alpha]^{25}_{578}$ −90°, $[\alpha]^{25}_{546}$ −105° (*c* 1.75, 1 N HCl).

When optically pure D-methyl *p*-hydroxyphenylglycinate was cycled through the above extractive workup, optical rotations of $[\alpha]^{25}_{578}$ −129° and $[\alpha]^{25}_{546}$ −149° (*c* 1.6, 1 N HCl) were obtained. The optical purity of the orange solid above was therefore 70%. When the orange solid was redissolved in acidic water and the entire extraction procedure listed above was repeated, optical rotations gave a purity of 80%, enriched in the D enantiomer. Recycling the solid a third time gave material (250 mg) which still had an optical purity of 80%. When combined with the white solid that originally precipitated from solution, a total of 350 mg of the amino ester was obtained, with an optical purity of 57.1%, which gave a CRF of 3.66. From these observations, it appears that the racemic amino ester is only very slightly soluble in both ethyl acetate and basic water, whereas the enantiomers are more soluble. Extensive ethyl acetate extraction also results in the solubilization of inorganic salts, which lowers the observed rotations.

The aqueous phase from the initial extraction was treated similarly to that given above for the organic phase. A white precipitate was collected (1.215 g) which was again the racemic methyl *p*-hydroxyphenylglycinate. The orange solid recovered from the ethyl acetate extraction had to be recycled through the above extraction procedure five times before a constant rotation was obtained (520 mg that was 51% optically pure, enriched in the L enantiomer). Combination of this material with the racemic material isolated above gave material that was about 15% optically pure, resulting in a ($[G_B]_{D_2O}/[G_A]_{D_2O}$) value of 1.36 and an EDC value of 5.0. The amino ester recovered represents 81% of the total initially used. Use of ^{1}H NMR spectral integration of the diastereomeric complexes of the original $CDCl_3$ layer provided a EDC = 4.5 ± 0.5 for the same run.

In run 12, the enantiomers of methionine methyl ester gave such low rotations that ^{1}H NMR spectral integrations of the well-defined diastereomeric CH_3S singlets were used to determine the CRF in the $CDCl_3$ layer. These singlets occurred at 1.70 for the more stable (*RR*)-L diastereomer and at 1.74 for the less stable (*RR*)-D diastereomer. The G/H ratio was also calculated from integrations of appropriate peaks. The $(G_B)/(G_A)$ in the D_2O layer was calculated by difference. The signs of rotations of material isolated from each layer identified the more stable diastereomer in the $CDCl_3$ layer.

Although the absolute amounts of materials varied somewhat from run to run of the two tables, the molar proportions, concentrations, and volumes were kept the same. The amounts of material used in runs 1-12 of Table III were in general lower than those of Table II, and more accurate G/H values in the $CDCl_3$ layers could be obtained by appropriate ^{1}H NMR spectral integrations. However, the EDC values were always calculated from the rotations of materials isolated from both layers.

Amino Ester Salt Extraction Runs Reported in Table III. Replacement of the methyl ester group of methyl phenylglycinate and methyl valinate salts by either isopropyl or *tert*-butyl ester groups increases their lipophilicity. Accordingly, lower $LiPF_6$ concentrations in the D_2O layer were needed for salting out purposes. The initial molar ratio of host to guest was 2 in the runs of Table III, rather than the ratio of 3, for the runs of Tables II and IV. In the runs of Table III, the initial concentration of (*SS*)-**1** in $CDCl_3$ was 0.20 M and the intial concentrations of guest were either 0.40 or 0.20 M. The volumes of the two solutions were as follows: run 1, 5 mL of D_2O, 5 mL of $CDCl_3$; run 2, 1.4 mL of D_2O, 0.70 mL of $CDCl_3$; run 3, 1.4 mL of D_2O, 0.70 mL of $CDCl_3$; run 4, 4 mL of D_2O, 4 mL of $CDCl_3$; run 5, 4 mL of D_2O, 4 mL of $CDCl_3$. The G/H ratios in the $CDCl_3$ layer at equilibrium were determined in all runs by integrations of appropriate ^{1}H NMR signals. In runs 1, 4, and 5, the EDC values were calculated from the rotations of ester samples isolated from each of the two layers, and the configurations of the more stable diastereomers from the signs of rotation of the isolated amino esters. In runs 2 and 3, the CRF was calculated from the ratio of integrals of the NCH proton signals in the ^{1}H NMR spectra of the two diastereomers at equilibrium in the $CDCl_3$ layer. These were well separated, and occurred at δ 4.45 for the more stable (*SS*)-L complex and at δ 4.82 for the less stable (*SS*)-D complex. The values of ($[G_B]_{D_2O}/[G_A]_{D_2O}$ were calculated by difference using the G/H ratio in the $CDCl_3$ layer at equilibrium and the CRF value. The identity of the configuration of the more stable diastereomer in the $CDCl_3$ layer was determined from the signs of rotations of the guests recovered from each of the two layers. The EDC values were calculated from these data. The $\Delta(\Delta G°)$ values were calculated presuming that eq 5 applied.

References and Notes

(1) This work was supported by the U.S. Public Health Service Research Grant GM 12690 from the Department of Health, Education and Welfare, and by a grant from the National Science Foundation, GP 33533.
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