# Host–Guest Complexation. 13. High Chiral Recognition of Amino Esters by Dilocular Hosts Containing Extended Steric Barriers[†,1,2]

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**Abstract:** The direction of configurational bias and extent of chiral recognition have been determined for complexation between 8 different guests and 13 different hosts. Racemic guest in $D_2O$ was extracted by optically pure host in $CDCl_3$. From the signs and magnitudes of rotations of the guests recovered from each layer, the directions of configurational bias and differences in free energies between the diastereomeric complexes ($\Delta(\Delta G°)$ values) were obtained. The R groups of the ester guests, $RCH(CO_2CH_3)NH_3PF_6$ or $ClO_4$ salts, were varied as follows: $C_6H_5$, $p$-$HOC_6H_4$, $p$-$CH_3O_2CC_6H_4$, $p$-$ClC_6H_4$, $(CH_3)_2CH$, $C_6H_5CH_2$, and $CH_3SCH_2CH_2$. Guest salts $C_6H_5CH(CH_3)NH_3PF_6$ and $ClO_4$ were also examined. The hosts were 22-membered ring systems containing six roughly coplanar ether oxygens regularly spaced by attachment to one another through ethylene units (E units, four per host), two chiral units of identical configurations, and similarly shaped steric barriers. The chiral units were 1,1′-dinaphthyl (D units) or 1,1′-ditetralyl (T units) attached at their 2,2′ positions to O's, and with substituents H, $CH_3$, $(CH_3)_2CH$, or Br at their 3,3′ positions. The hosts examined had structures whose shapes fell into five classes, I–V, as follows: $D(OEOEO)_2D$ and $T(OEOEO)_2T$, shape I; $(CH_3)_2D(OEOEO)_2D$, $(i$-$Pr)_2D(OEOEO)_2D$, $(CH_3)_2T(OEOEO)_2T$, $(CH_3)_2D(OEOEO)_2T$, $(CH_3)_2T(OEOEO)_2D$, $Br_2T(OEOEO)_2D$, shape II; $(CH_3)_2D(OEOEO)_2D(CH_3)_2$ and $Br_2T(OEOEO)_2TBr_2$, shape III; $D(OEO)(OEOEOEO)D$ and $T(OEO)(OEOEOEO)T$, shape IV; and $Br_2T(OEO)$-$(OEOEOEO)TBr_2$, shape V. Useful information about the structures of the diastereomeric complexes in $CHCl_3$ was obtained by correlating their $^1H$ NMR spectra with conclusions drawn from examinations of CPK molecular models and from X-ray structures. Three NH⋯O hydrogen bonds and one π to π ($CO_2CH_3$ to aryl) attractive interaction structured most of the complexes. The shapes of the hosts and stereoelectronic properties of the R groups of the guests correlated with the direction of configurational bias and degree of chiral recognition as follows. Shape I hosts gave $\Delta(\Delta G°)$ values that ranged from $-1.02$ to $-0.18$ kcal/mol when R = $p$-$ZC_6H_4$. Host variation gave about a 0.32 kcal/mol change in $\Delta(\Delta G°)$, whereas Z variation gave about a 0.55 kcal/mol change. The $(RR)(D)$ or $(SS)(L)$ complexes were always more stable than their $(RR)(L)$ or $(SS)(D)$ counterparts. In contrast with R = $(CH_3)_2CH$, $C_6H_5CH_2$, or $CH_3SCH_2CH_2$, shape I hosts gave $\Delta(\Delta G°)$ values of $-0.32$ to $-0.05$ kcal/mol, usually favoring $(RR)(L)$ configurations. Shape II hosts (the most studied) gave the highest chiral recognition observed, favoring the $(RR)(D)$ or $(SS)(L)$ configurations. For example, with $(CH_3)_2D(OEOEO)D$, $\Delta(\Delta G°)$ values in kcal/mol varied with R-group-changes as follows: $C_6H_5$, $-1.9$; $p$-$HOC_6H_4$, $-1.4$; $(CH_3)_2CH$, $-0.87$; $C_6H_5CH_2$, $-0.87$; $CH_3SCH_2CH_2$, $-0.21$. Hosts possessing IV and V shapes gave $\Delta(\Delta G°)$ values of $-0.32$ to $-0.05$ kcal/mol, which favored the $(SS)(D)$ configuration with R = $C_6H_5$ or $(CH_3)_2CH$. The 1,1′-dinaphthyl and 1,1′-ditetralyl units imparted to hosts similar chiral recognition properties. Temperature-dependence studies indicated that the more stable diastereomeric complexes were held together by forces relatively more enthalpic, and the less stable by forces that were relatively more entropic in nature. Higher chiral recognition was observed with $PF_6$ than with $ClO_4$ salts. The results are rationalized in terms of structures in which binding and steric interactions between host and guest are geometrically complementary for the more stable and noncomplementary for the less stable diastereomeric complexes.

The syntheses, optical stabilities, absolute configurations, and maximum rotations of a large number of host compounds (**1–22**) containing *two* chiral elements (*dilocular* systems) have been described in parts 7[3a] and 8[3b] of this series. Part 11 reported the chiral recognition properties of hosts **1** and **14–20** containing two 1,1′-dinaphthyl units, 4- to 6-oxygen binding sites, and, in some cases, $(CH_2)_5$, 1,3-$C_6H_4$, and 2,6-$C_5H_3N$ (pyrido) units as parts of their 22-membered ring systems.[4] Hosts of the $(RR)$ or $(SS)$ configurations in $CDCl_3$ solutions were used to extract aqueous solutions of racemic α-phenylethylammonium and amino ester salts. The greatest chiral recognition observed involved only about $-0.82$ kcal/mol difference in stability between the diastereomeric complexes.

This paper reports a similar study extended to dilocular hosts **2, 3, 6–13, 21,** and **22**. These compounds possess two chiral barriers, *both* of the $(RR)$ or $(SS)$ configurations. These barriers are either 1,1′-dinaphthyl or 1,1′-ditetralyl units incorporated into 22-membered macrocycles by attachment at their 2,2′ positions to oxygens. These oxygens in turn are linked through ethylene units to other oxygens to give cycles containing six evenly spaced binding sites. Some of the chiral barriers carry substituents in their 3,3′ positions, such as $CH_3$, $(CH_3)_2CH$, or Br groups. Examination of Corey–Pauling–Koltun (CPK) molecular models of complexes of these hosts with chiral alkylammonium ions suggested that certain of the host–guest combinations might produce higher chiral recognition than was observed previously.

Since the systematic names of the hosts are useless for visualization, and the structural formulas are too large for frequent duplication, abbreviated formulas have been adopted to lower the dependence on compound numbers for structural identification. In this system, D refers to 1,1′-dinaphthyl and T to 1,1′-ditetralyl units attached at their 2,2′ positions to ring oxygens, and sometimes carrying other substituents at their 3,3′ positions. In all hosts, the two chiral units always possessed the same configurations. In the abbreviated formulas, the $CH_2CH_2$ units are denoted E, the 1,3-benzo units B, the 2,6-pyrido units P, and the oxygen and methylene units are indicated by their usual formulas. The structures of the hosts studied are formulated and numbered and, in representative cases, the abbreviated formulas are listed.

The capacity for chiral recognition in complexation by a series of similarly shaped hosts is expected to increase with their binding abilities toward a common nonchiral guest. Although association constants ($K_a$) in $CDCl_3$ between a large number of hosts and $t$-$BuNH_3X$ guests have been reported.[5]
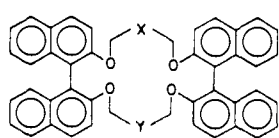
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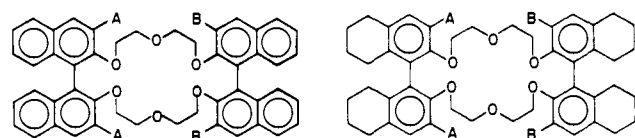
1, A=B=H, or D(OEOEO)₂D
2, A=CH₃, B=H, or (CH₃)₂D(OEOEO)₂O
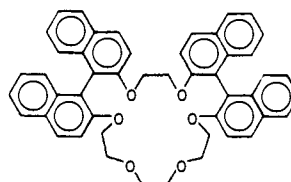3, A=i-Pr, B=H
4, A=CH₂Cl, B=H
5, A=CH₂Br, B=H
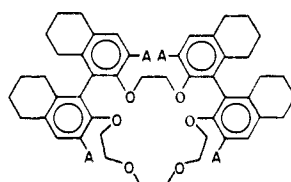6, A=B=CH₃

7, A=B=H, or T(OEOEO)₂T
8, A=CH₃, B=H
9, A=B=Br
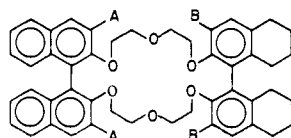
10, A=B=H
11, A=CH₃, B=H or (CH₃)₂D(OEOEO)T
12, A=H, B=CH₃ or (CH₃)₂T(OEOEO)D
13, A=H, B=Br

14, X=CH₂OCH₂, Y=(CH₂)₃
15, X=CH₂OCH₂, Y=1,3-benzo or D(OEO)(OCH₂BCH₂O)D
16, X=CH₂OCH₂, Y=2,6-pyrido
17, Y=Y=2,6-pyrido or D(OCH₂PCH₂O)₂D
18, X=2,6-pyrido, Y=1,3-benzo
19, X=2,6-pyrido, Y=(CH₂)₃ or O(OCH₂PCH₂O)(OECH₂EO)O
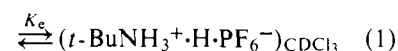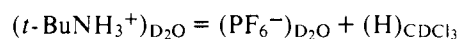
20, or D(OEO)(OEOEOEO)D

21, A=H
22, A=Br, or Br₂T(OEO)(OEOFOEO)TBr₂

the dilocular systems were poor enough complexing agents to be off scale when X = SCN. Accordingly, the *relative binding abilities* of dilocular hosts **1–22** toward *t*-BuNH₃PF₆ were determined in CHCl₃, and these results are also reported in this paper.

## Results

**Relative Complexing Power of Hosts toward *t*-BuNH₃PF₆.** Aliquots of a standard solution of *t*-BuNH₃PF₆ in D₂O containing LiPF₆ at pH 4 were extracted at −10 °C with CDCl₃ solutions of hosts **1–10** and **12–22**. The relative concentrations of guest to host (G/H) in the CDCl₃ layers were determined by $^1$H NMR integrations. No host was distributed in the D₂O layer. In the absence of host, the amount of salt extractable into the organic layer was too low to be detected and measured. The results are expressed in Table I in terms of $K_e$ (extraction constant) values,[5a] which are defined by eq 1. Ideally, the association constant ($K_a$) in CDCl₃ for each host and *t*-BuNH₃PF₆ is proportional to $K_e$, since $K_a = K_e/k_d$.[5b] The distribution constant ($K_d$) of *t*-BuNH₃PF₆ between CDCl₃

and D₂O in the absence of host is the same for different hosts. Thus, the differences in thermodynamic stabilities of the *t*-BuNH₃PF₆ complexes in CDCl₃ can be estimated from the $K_e$ values themselves.

$$(t\text{-}BuNH_3^+)_{D_2O} = (PF_6^-)_{D_2O} + (H)_{CDCl_3}$$

$$\overset{K_e}{\rightleftharpoons} (t\text{-}BuNH_3^+\cdot H\cdot PF_6^-)_{CDCl_3} \quad (1)$$

**Differential Extraction of Enantiomers of Racemic Amino Ester Salts from D₂O Solutions by CDCl₃ Solutions of (*RR*) or (*SS*) Host Compounds.** Solutions of NMR-grade CDCl₃, (0.2 M in host of maximum rotation (either (*RR*) or (*SS*) configurations), were shaken with D₂O solutions of racemic amine–salt guests, whose concentrations ranged from 0.3 to 1.2 M (usually the latter). In all experiments, 3 mol of racemic guest per mol of optically active host was used. In no case was there any detectable amount ($^1$H NMR) of host in the D₂O layer. Since solid HPF₆ salts of the amines were hygroscopic and unstable, they were formed by ion exchange by addition of the amine hydrochlorides or hydrobromides to aqueous LiPF₆ solutions whose pH had been adjusted to about 4 with LiOD. Control experiments established that with the relatively lipophilic α-phenylethylammonium ion in D₂O and the parent host **1** in CDCl₃, only the PF₆⁻ salt was extractable, and that the F⁻, Cl⁻, and Br⁻ salts could not be extracted in detectable quantities.[4] For convenience, the ClO₄⁻ salts also were formed in D₂O (pH 4) solution by ion exchange between added LiClO₄ and RNH₃Cl. The D₂O solutions of LiClO₄ were much easier to prepare and store without decomposition than the LiPF₆ solutions, which always contained LiF and hydrolysis products of LiPF₆. Thus, the concentrations of the LiPF₆ solutions in D₂O recorded are approximate and maximal. The PF₆⁻ salts possessed the advantage of giving slightly higher chiral recognition and the ClO₄⁻ of being more handleable and stable.

The degree of chiral recognition was in most runs determined by isolation and examination of the configuration and optical purity of the amino ester in each layer of an equilibrated mixture (see below). The hosts exhibited a wide range of binding and lipophilizing abilities, and the guests an equally wide range of binding and hydrophilic characters. Isolation of the desired 30–80 mg of guest from the CDCl₃ phases required a G/H ratio of between 0.2 and 1.0 in the organic phase at equilibrium. These ratios could be obtained by adjusting the concentration of the salting-out agent (LiPF₆ or LiClO₄) in the aqueous layer, or by varying the temperature or the nature of the solvent. It was found that at lower temperatures, in extreme cases as low as −16 °C (added salt depressed the freezing point of water), a higher G/H ratio could be obtained. Addition of CD₃CN to CDCl₃ (1:9 v:v) also greatly increased the extractability (by complexation of the guest) into the organic layer. Table II records the conditions used and the results

**Table I.** Extraction Constants ($K_e$) of Hosts in CDCl₃ for *t*-BuNH₃PF₆ Guests in D₂O at −10 °C

| no. | host structure | $K_e$, M⁻² | no. | host structure | $K_e$, M⁻² |
|-----|------|------|-----|------|------|
| 8 | (CH₃)₂T(OEOEO)₂T | 0.54 | 22 | Br₂T(OEO)(OEOEOEO)TBr₂ | 0.020 |
| 21 | T(OEO)(OEOEOEO)T | 0.22 | 6 | (CH₃)₂D(OEOEO)₂D(CH₃)₂ | 0.018 |
| 20 | D(OEO)(OEOEOEO)D | 0.2 | 5 | (BrCH₂)₂D(OEOEO)₂D | 0.016 |
| 12 | (CH₃)₂T(OEOEO)D | 0.18 | 4 | (ClCH₂)₂D(OEOEO)₂D | 0.011 |
| 2 | (CH₃)₂D(OEOEO)₂D | 0.14 | 17 | D(OCH₂PCH₂O)₂D | 0.011 |
| 16 | D(OEOEO)(OCH₂PCH₂O)D | 0.11 | 3 | (i-Pr)₂D(OEOEO)₂D | 0.011 |
| 7 | T(OEOEO)₂T | 0.061 | 18 | D(OCH₂PCH₂O)(OCH₂BCH₂O)D | 0.0090 |
| 10 | D(OEOEO)₂T | 0.054 | 15 | D(OEOEO)(OCH₂BCH₂O)D | 0.0054 |
| 1 | D(OEOEO)₂D | 0.047 | 19 | D(OCH₂PCH₂O(OECH₂EO)D | <0.0045 |
| 13 | Br₂T(OEOEO)₂D | 0.036 | 14 | D(OEOEO)(OECH₂EO)D | <0.0045 |
| 9 | Br₂T(OEOEO)₂TBr₂ | 0.031 | | | |

**Table II.** Enantiomer Distribution Constants (EDC) and $\Delta(\Delta G°)$ Values for Extractions of Racemic Guests (G) from $D_2O$ into $CDCl_3$ Solutions of Optically Pure Hosts (H)

| run no. | T, °C | host in CDCl3 no. | host in CDCl3 structure | guest in D2O R of RCH(CO2CH3)NH3+ | concn, M | LiX X- | concn, M | CDCl3 solution G/H | CDCl3 solution domin compl | EDC | Δ(ΔG°) of complex, kcal/mol |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 1 | D(OEOEO)2D | C6H5 | 1.2 | PF6 | 3.5 | 0.8 | (RR)(D) | 2.8 | −0.56 |
| 2 | 0 | 1 | D(OEOEO)2D | C6H5 | 0.6 | ClO4 | 2 | 0.5 | (SS)(L) | 2.4 | −0.48 |
| 3 | 0 | 7 | T(OEOEO)2T | C6H5 | 0.6 | ClO4 | 2 | 0.5 | (RR)(D) | 3.1 | −0.62 |
| 4 | 0 | 9 | Br2T(OEOEO)2TBr2 | C6H5 | 0.6 | ClO4 | 4 | <0.1 | (SS)(L) | 1.5 | −0.22 |
| 5 | 0 | 1 | D(OEOEO)2D | (CH3)2CH | 0.6 | ClO4 | 4 | <0.1 | | 1.0 | 0.0 |
| 6 | 0 | 7 | T(OEOEO)2T | (CH3)2CH | 0.6 | ClO4 | 4 | <0.1 | (RR)(D) | 1.2 | −0.1 |
| 7 | 0 | 1 | D(OEOEO)2D | (CH3)2CH | 0.6 | ClO4 | 2 | <0.1 | (SS)(D) | 1.1 | −0.05 |
| 8 | 0 | 7 | T(OEOEO)2T | (CH3)2CH | 0.6 | ClO4 | 2 | <0.1 | (RR)(D) | 1.2 | −0.10 |
| 9 | −10 | 20 | D(OEO)(OEOEOEO)D | C6H5 | 1.2 | PF6 | 3.5 | 0.9 | (SS)(D) | 2.2 | −0.45 |
| 10 | 0 | 20 | D(OEO)(OEOEOEO)D | C6H5 | 0.6 | ClO4 | 2 | 0.4 | (SS)(D) | 1.8 | −0.32 |
| 11 | 0 | 21 | T(OEO)(OEOEOEO)T | C6H5 | 0.6 | ClO4 | 2 | 0.6 | (SS)(D) | 1.1 | −0.05 |
| 12 | 0 | 22 | Br2T(OEO)(OEOEOEO)TBr2 | C6H5 | 0.6 | ClO4 | 2 | 0.2 | (SS)(D) | 1.8 | −0.32 |
| 13 | 0 | 20 | D(OEO)(OEOEOEO)D | (CH3)2CH | 0.6 | ClO4 | 4 | <0.1 | (SS)(D) | 1.3 | −0.14 |
| 14 | 0 | 21 | T(OEO)(OEOEOEO)T | (CH3)2CH | 0.6 | ClO4 | 4 | <0.1 | | | |
| 15 | 0 | 1 | **D(OEOEO)2D** | p-HOC6H4 | 0.6 | ClO4 | 4 | 0.1 | (SS)(L) | 3.5 | −0.68 |
| 16 | 0 | 1 | D(OEOEO)2D | p-CH3O2CC6H4 | 0.3 | ClO4 | 0.5 | 0.3 | (SS)(L) | 2.3 | −0.46 |
| 17 | 0 | 1 | D(OEOEO)2D | p-HC6H4 | 0.3 | ClO4 | 0.5 | 0.2 | (SS)(L) | 2.4 | −0.48 |
| 18 | 0 | 1 | D(OEOEO)2D | p-ClC6H4 | 0.3 | ClO4 | 0.5 | 0.2 | (SS)(L) | 1.3 | −0.15 |
| 19 | 0 | 7 | T(OEOEO)2T | p-HOC6H4 | 0.6 | ClO4 | 4 | 0.2 | (RR)(D) | 6.6 | −1.0 |
| 20 | 0 | 7 | T(OEOEO)2T | p-CH3O2CC6H4 | 0.3 | ClO4 | 0.5 | 0.3 | (RR)(D) | 3.6 | −0.69 |
| 21 | 0 | 7 | T(OEOEO)2T | p-HC6H4 | 0.3 | ClO4 | 0.5 | 0.15 | (RR)(D) | 3.2 | −0.63 |
| 22 | 0 | 7 | T(OEOEO)2T | p-ClC6H4 | 0.3 | ClO4 | 0.5 | 0.8 | (RR)(D) | 2.1 | −0.40 |
| 23 | 24 | 2 | (CH3)2D(OEOEO)2D | C6H5 | 1.2 | PF6 | 2.9 | 1.0 | (RR)(D) | 12.4 | −1.5 |
| 24 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5 | 1.2 | PF6 | 1.4 | 0.8 | (RR)(D) | 31 | −1.9 |
| 25 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5 | 1.2 | PF6 | 3.5 | 1.1 | (SS)(L) | 19 | −1.6 |
| 26 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5 | 1.2 | PF6 | 1.4 | 1.07 | (SS)(L) | 22 | −1.7 |
| 27 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5 | 1.2 | PF6 | 0.75 | 0.8 | (SS)(L) | 31 | −1.9 |
| 28 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5 | 1.2 | PF6 | 0.50 | 0.5 | (SS)(L) | 26 | −1.8 |
| 29 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5 | 1.2 | ClO4 | 3.5 | 0.9 | (RR)(D) | 21 | −1.65 |
| 30 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5 | 1.2 | ClO4 | 1.0 | 0.95 | (SS)(L) | 22 | −1.68 |
| 31 | 24 | 2 | (CH3)2D(OEOEO)2D | p-HOC6H4 | 1.2 | PF6 | 3.5 | 1.0 | (RR)(D) | 8.9 | −1.3 |
| 32 | 0 | 2 | (CH3)2D(OEOEO)2D | p-HOC6H4 | 1.2 | PF6 | 1.4 | 0.75 | (RR)(D) | 12.4 | −1.4 |
| 33 | 11 | 2 | (CH3)2D(OEOEO)2D | (CH3)2CH | 1.2 | PF6 | 3.5 | 0.75 | (RR)(D) | 5.3 | −0.87 |
| 34 | 5 | 2 | (CH3)2D(OEOEO)2D | CH3SCH2CH2 | 1.2 | PF6 | 3.5 | 0.95 | (RR)(D) | 2.2 | −0.42 |
| 35 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5CH2 | 1.2 | PF6 | 0.75 | 0.85 | (RR)(D) | 5.3 | −0.87 |
| 36 | 0 | 2 | (CH3)2D(OEOEO)2D | C6H5CH2 | 1.2 | PF6 | 1.0 | 1.3 | (SS)(L) | 3.8 | −0.73 |
| 37 | 24 | 3 | (CH3)2D(OEOEO)2D(CH3)2 | C6H5 | 1.2 | PF6 | 3.5 | ~0 | | | |
| 38 | −10 | 6 | (CH3)2D(OEOEO)2D(CH3)2 | CH3SCH2CH2 | 1.2 | PF6 | 3.5 | 0.4 | (RR)(D) | 1.5 | −0.21 |
| 39 | −16 | 3 | (i-Pr)2D(OEOEO)2D | C6H5 | 1.2 | PF6 | 3.5 | 1.0 | (RR)(D) | 5.0 | −0.82 |
| 40 | 0 | 8 | (CH3)2T(OEOEO)2T | C6H5 | 1.0 | PF6 | 0.75 | .54 | (SS)(L) | 13.6 | −1.4 |
| 41 | 0 | 8 | (CH3)2T(OEOEO)2T | C6H5 | 1.2 | PF6 | 3.5 | 1.3 | (RR)(D) | 8 | −1.12 |
| 42 | 0 | 8 | (CH3)2T(OEOEO)2T | C6H5 | 1.0 | ClO4 | 2 | .81 | (SS)(L) | 10.2 | −1.3 |
| 43 | 0 | 8 | (CH3)2T(OEOEO)2T | C6H5CH2 | 1.0 | PF6 | 0.75 | .34 | (SS)(L) | 2.38 | −0.47 |
| 44 | 27 | 13 | Br2T(OEOEO)2D | C6H5 | 1.2 | PF6 | 3.5 | 0.85 | (RR)(D) | 7.4 | −1.20 |
| 45 | −17 | 13 | Br2T(OEOEO)2D | C6H5 | 1.2 | PF6 | 3.5 | 0.95 | (RR)(D) | 11.5 | −1.25 |
| 46 | −10 | 13 | Br2T(OEOEO)2D | (CH3)2CH | 1.2 | PF6 | 3.5 | 0.7 | (RR)(D) | 4.8 | −0.82 |
| 47 | 0 | 11 | (CH3)2D(OEOEO)2T | C6H5 | 1.2 | PF6 | 1.4 | 0.8 | (RR)(D) | 31 | −1.9 |
| 48 | 0 | 12 | (CH3)2T(OEOEO)2D | C6H5 | 1.2 | PF6 | 1.4 | 0.95 | (RR)(D) | 20 | −1.6 |

obtained in the extractions involving the various hosts and guests.

The enantiomer distribution constant (EDC) was used to measure the degree of chiral recognition in each run, and was calculated with eq 2 and 3, where the following definitions apply: $G_A$ is the more and $G_B$ the less soluble guest enantiomer in the CDCl$_3$ layer (the D$_2$O layer is enriched in $G_B$); $[G_A]_{CDCl_3}$, $[G_A]_{H_2O}$, $[G_B]_{CDCl_3}$, and $[G_B]_{D_2O}$ are the concentrations of the enantiomeric guests in the two phases; $K_A$ and $K_B$ are the distribution constants of the enantiomers A and B between the two phases; CRF is the chiral recognition factor in the CHCl$_3$ phase; and CSF is the chiral storage factor in the D$_2$O phase. Equation 3 indicates that if a small amount of guest was extracted from an infinitely large reservoir of racemic guest, EDC and CRF values would become identical.

$$K_A = \frac{[G_A]_{CDCl_3}}{[G_A]_{D_2O}} \qquad K_B = \frac{[G_B]_{CDCl_3}}{[G_B]_{D_2O}}$$

$$\mathrm{CRF} = \frac{[G_A]_{CDCl_3}}{[G_B]_{CDCl_3}} \qquad \mathrm{CSF} = \frac{[G_B]_{D_2O}}{[G_A]_{D_2O}} \qquad (2)$$
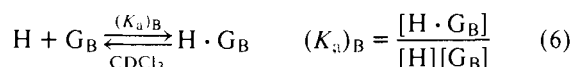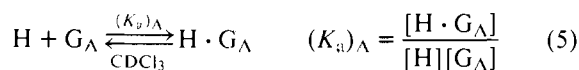
$$\mathrm{EDC} = K_A/K_B = \mathrm{CRF} \cdot \mathrm{CSF} \qquad (3)$$

The independent determinations of the optical purities of the guests recovered from the organic and aqueous phases allowed CRF and CSF values to be calculated independently. These values not only provided EDCs, but also allowed G/H values (guest to host ratios in CDCl$_3$ phases) to be estimated through the use of eq 4. In eq 4, $G_i$ and $H_i$ are the initially used

$$\mathrm{G/H} = \frac{G_i(\mathrm{CRF} + 1)(\mathrm{CSF} - 1)}{2H_i(\mathrm{EDC} - 1)} \qquad (4)$$

moles of guest and host, respectively. In some runs, the G/H values were also determined directly by comparisons of appropriate integrations of $^1$H NMR signals of guest and host in the CDCl$_3$ layers. The agreement between the two methods was 0.1 or better. Table II records the EDC and G/H values determined in most cases from the optical rotations of guest isolated from each layer.

Under ideal conditions, $K_A/K_B = (K_a)_A/(K_a)_B$, where $(K_a)_A$ and $(K_a)_B$ are defined by eq 5 and 6, in which H·G$_A$ and H·G$_B$ are the diastereomeric complexes. Equation 7 follows from eq 5 and 6, and relates the difference in free energies of the diastereomeric complexes to the EDC values. These $\Delta(\Delta G°)$ estimates are recorded in Table II.

$$\mathrm{H} + \mathrm{G_A} \underset{\mathrm{CDCl_3}}{\overset{(K_a)_A}{\rightleftharpoons}} \mathrm{H \cdot G_A} \qquad (K_a)_A = \frac{[\mathrm{H \cdot G_A}]}{[\mathrm{H}][\mathrm{G_A}]} \qquad (5)$$

$$\mathrm{H} + \mathrm{G_B} \underset{\mathrm{CDCl_3}}{\overset{(K_a)_B}{\rightleftharpoons}} \mathrm{H \cdot G_B} \qquad (K_a)_B = \frac{[\mathrm{H \cdot G_B}]}{[\mathrm{H}][\mathrm{G_B}]} \qquad (6)$$

$$\Delta(\Delta G°) = -RT \ln \mathrm{EDC} \qquad (7)$$

Several conditions must be fulfilled for eq 5-7 to apply rigorously. (1) Host must be distributed solely in the CDCl$_3$ layer, so chiral recognition occurs only there. (2) Only *complexed* guest must be distributed in the CDCl$_3$ layer. Some uncomplexed guest is undoubtedly present in the CDCl$_3$ layers, particularly in those runs in which the CDCl$_3$ is diluted with CD$_3$CN, and the more lipophilic esters were used. (3) To the extent that enantiomeric guests are associated in the aqueous layers, the free energies of the diastereomeric aggregates must equal one another. (4) The diastereomeric complexes in the CDCl$_3$ layer must be one to one. To the small extent that conditions 1, 2, and 4 above do not apply to our experiments, the true free energy differences between the diastereomeric complexes would be of higher magnitude. Thus the EDC and $\Delta(\Delta G°)$ values of Table II are approximate and minimal.

Table II deals exclusively with the methyl esters of amino acids as guests. For purposes of comparison, racemic α-phenylethylammonium perchlorate was distributed at 0 °C between (*RR*)-2 in CDCl$_3$ and 2 M LiClO$_4$ in D$_2$O to provide an EDC of 1.9 and $\Delta(\Delta G°) = -0.35$ kcal/mol, the (*RR*)(*S*) complex being the more stable. A similar experiment that involved LiPF$_6$ gave EDC = 1.8 and $\Delta(\Delta G°) = -0.32$ kcal/mol, the (*RR*)(*S*) complex being the more stable.

## Discussion

The effects of changes in structure of the host and guest on the complexing parameters are the main theme of this paper. The complexing abilities, the extent of chiral recognition, and the direction of the configurational bias were surveyed for a wide range of complexing partners. We prospected for structure-selectivity correlations that might guide more refined investigations of those systems that possessed the most interesting properties. Within certain series of host-guest combinations, experimental conditions could be kept constant. However, since the intrinsic complexing abilities of the partners varied over such a wide range, some of the runs required adjustments in experimental conditions to provide enough extracted material for examination.

Five X-ray structures of one to one complexes between macrocyclic hosts and alkylammonium salts have been determined.[7] Common to these structures are three hydrogen bonds between host and guest of the $^+$NH···O or $^+$NH···N varieties arranged like a tripod, the base of which is the best plane of the host's heteroatoms, and the apex of which is N$^+$. This type of binding places the C–N bond roughly normal to the best plane of the binding heteroatoms. Molecular model examination (CPK) of all of the hosts, coupled with the X-ray structures of the two complexes containing dinaphthyl units that have been determined,[7a,d] indicate that the planes of the naphthalene rings cannot be far from normal and are tangent to the macroring. Each dinaphthyl unit contains one naphthalene ring which protrudes from one face and a second from the opposite face of the best plane of the macrocycle. Thus the naphthalene rings form walls that divide the space available to the L, M, and S substituents of LMSCN$^+$H$_3$ guests into two chiral cavities.

The dinaphthyl and ditetralyl units possess very similar shapes. Substituents in their 3 positions extend their walls, and somewhat encroach on the space available for L and M substituents. The simple, idealized drawings I–V in Chart 1 indicate the five general types of shapes anticipated for the hosts of this investigation. In I–V, the cross sections of only the two naphthalene or tetralin rings rising above the planes of the macroring (that of the page) are drawn. Beneath drawings I–V are identified the hosts that generally conform to the shapes drawn. Drawing VI depicts the idealized structure of a complex without chiral barriers in its host.

**Ranking of Complexing Abilities of Hosts with *t*-BuNH$_3$PF$_6$.** Table I ranks 21 hosts in order of decreasing ability to extract (by complexation) *t*-BuNH$_3$PF$_6$ from D$_2$O-LiPF$_6$ into CDCl$_3$ at −10 °C. The complexes differ in stability at the extremes by an estimated >2.4 kcal/mol in free energy.

The ditetralyl-containing hosts complex better than their dinaphthyl counterparts; e.g., **8** > **12** > **2**, **21** > **20**, and **7** > **10** > **1**. This effect is attributed to an expected greater basicity and hence hydrogen-bonding ability of the oxygens attached to a ditetralyl unit as compared to those attached to a dinaphthyl unit.

Two methyl groups substituted for hydrogens at the 3,3' positions of *one of the two* chiral units arranged as in structure II enhance the complexing ability of that host. This generalization holds whether a dinaphthyl or a ditetralyl unit is so substituted. For example, **8**, **12**, or **2** > **7**, **1**, or **10** in complexing ability. This effect is attributed mainly to the enforcement of a conformation by the methyls in which the electron pairs of

**Chart I**



I: 1, 7, 10, 14-19          II: 2-5, 8, 11-13

III: 6, 9          IV: 20, 21

V: 22          VI (complexes)
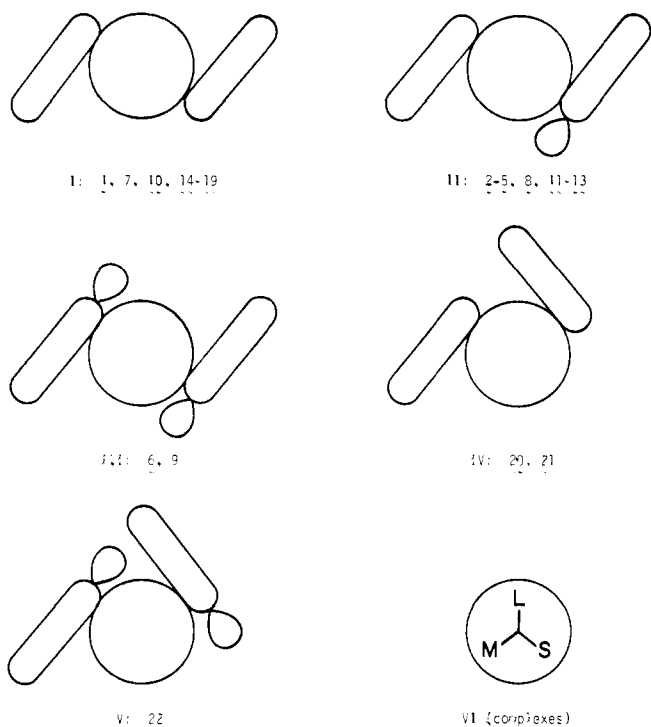
the aryl oxygens converge on the center of the macrocycle. Only such a conformation provides the methylenes attached to those oxygens with adequate space. This enforced conformation is best for ArO⋯HN⁺ and ArO⋯N⁺ binding, both from a geometric and an electronic point of view. The orbitals containing the electron pairs of these oxygens are held in conformations that overlap minimally with the molecular orbitals of the attached aryl groups. Thus the electron pairs tend to be more localized on the oxygens, which in turn makes them more basic and better at hydrogen bonding. The electron-releasing inductive effect of the two methyl groups attached to the aryls also tends to make the aryl groups inductively less electron withdrawing toward their attached oxygens. Substitution of two bromines for hydrogens in the 3,3' positions as in **13** decreases its binding ability as compared with **10**. Since methyl and bromine occupy about the same amount of space, it appears that the electron-withdrawing inductive effect of the bromine more than cancels the favorable steric effect on complexation, but not by a large amount.

Substitution of two larger groups (e.g., $(CH_3)_2CH_2$, $CH_2Cl$, or $CH_2Br$) in the 3,3' positions of one chiral unit of systems of the II type greatly reduces the complexing abilities of the hosts. Thus **5**, **4**, and **3** are much poorer complexing agents than unsubstituted hosts **7**, **10**, or **1**, or **8**, **12**, **2**, or **13**, which are substituted with two methyls or two bromines. Apparently as the steric requirements of substituents in the 3,3' positions increase, they encroach more and more on the space occupied by the three methyl groups of the $t$-$BuNH_3^+$ in the complex. Two methyls or two bromines do not seriously inhibit complexation, but the larger groups do.

The presence of four methyls or four bromines at the 3,3' positions of both chiral units, as in systems of type III (i.e., **6** or **9**), greatly reduces their complexing abilities. Again complexation appears to be sterically inhibited. The same effect is evident for systems of the IV and V types, since **21** (unsubstituted) is a vastly better binder than **22** (tetrabrominated derivative).

Systems of the IV variety appear to complex better than those of the isomeric I variety. In molecular models, gathering of the two chiral barriers on one side of the macroring as in IV

**Table III.** Effect of Host Structure on Chiral Recognition at 0 °C of $C_6H_5CH(CO_2CH_3)NH_3PF_6$

| host | EDC | $\Delta(\Delta G°)$, kcal/mol | more stable complex | run no. |
|------|-----|---------------------------|---------------------|---------|
| $(CH_3)_2D(OEOEO)_2D$ | 31 | −1.9 | $(RR)(D)$ | 24 |
| $(CH_3)_2D(OEOEO)_2D$ | 31 | −1.9 | $(SS)(L)$ | 27 |
| $CH_3)_2D(OEOEO)_2T$ | 31 | −1.9 | $(RR)(D)$ | 47 |
| $(CH_3)_2T(OEOEO)_2D$ | 20 | −1.6 | $(RR)(D)$ | 48 |
| $(CH_3)_2T(OEOEO)_2T$ | 13.6 | −1.4 | $(RR)(D)$ | 40 |
| $Br_2T(OEOEO)_2D^a$ | 11.5 | −1.25 | $(RR)(D)$ | 45 |
| $(i\text{-}Pr)_2D(OEOEO)_2D^b$ | 5 | −0.82 | $(RR)(D)$ | 39 |
| $D(OEOEO)_2D$ | 2.8 | −0.56 | $(RR)(D)$ | 1 |

$^a$ Run at −17 °C. $^b$ Run at −16 °C.

and V provides a sterically more flexible host than distributing them on opposite sides as in I–III. The naphthalene or tetralin walls of the host can move away from the methyl groups of the $t$-$BuNH_3^+$ guest in the complexes. However, this splaying movement brings the naphthalene or tetralin rings toward one another on the unbound face. The cavities in complexes of IV and V can be expanded by this movement much more than those in complexes of I, II, or III varieties, since in those of the latter types, this movement is ultimately limited by the two rigid units running into one another on the unbound face.

As previously observed in simple 18-membered ring systems,[5b,c] substitution of $(CH_2)_5$, $m$-$CH_2C_6H_4CH_2$ or 2,6-$CH_2C_5H_3NCH_2$ (pyridodimethylyl) for $CH_2CH_2OCH_2CH_2$ units of these more elaborate hosts substantially reduces their complexing abilities. Thus **1** > **17** > **18** > **15** in $K_c$ values. An exception is observed when *one* 2,6-$CH_2C_5H_3NCH_2$ is substituted for one $CH_2CH_2OCH_2CH_2$ unit (**16** > **1**), as was observed for the simple 18-membered ring systems.[5c]

The correlations of Table I between host structure and complexing ability toward $t$-$BuNH_3PF_6$ were generally useful in finding conditions that would provide G/H ratios in the measurable range for the same hosts complexing the various amino ester salts of Table II. To the extent that comparisons are possible, the hosts ranked similarly in their binding abilities toward $t$-$BuNH_3PF_6$ and the $RCH(CO_2CH_3)NH_3PF_6$ salts.

**Effect of Host Structure on Chiral Recognition of Enantiomers of Phenylglycine Methyl Ester Salts.** In Table III, hosts are arranged in decreasing order of their abilities to distinguish by complexation the enantiomers of $C_6H_5CH(CO_2CH_3)$-$NH_3PF_6$ in $CDCl_3$ at 0 °C. The EDC values range from a high of 31 ($\Delta(\Delta G°)$ = −1.9 kcal/mol) for $(CH_3)_2D(OEOEO)_2D$ to a low of 2.8 ($\Delta(\Delta G°)$ = −0.56 kcal/mol) for D(OEOEO)$_2$D. All of these runs involved complexes of hosts of the I and II varieties (Chart I), and the configurational bias favored the $(RR)(D)$ or $(SS)(L)$ over the $(RR)(L)$ or $(SS)(D)$ complexes. Hosts of the II variety with one of their sets of chiral barriers extended exhibited dramatically higher chiral recognition than those of the I variety containing only hydrogen at their 3,3' positions. For example, $(CH_3)_2D(OEOEO)_2D$ and $(CH_3)_2D(OEOEO)_2T$ provided −1.3 kcal/mol higher chiral recognition than D(OEOEO)$_2$D. Similarly, $(CH_3)_2$-$T(OEOEO)_2D$ and $(CH_3)_2T(OEOEO)_2T$ gave respectively −1.0 and −0.84 kcal/mol higher chiral recognition than D(OEOEO)$_2$D. Thus incorporation of two methyl groups in the hosts had a much more important effect than substitution of a ditetralyl for a dinaphthyl unit. Even substitution of two hydrogens by two bromines as in $Br_2T(OEOEO)_2D$ provided about −0.7 kcal/mol increase in chiral recognition over that of D(OEOEO)D. However, the two isopropyl groups in ($i$-Pr)$_2$D(OEOEO)$_2$D provide an increase of only −0.26 kcal/mol over that of the parent cycle, D(OEOEO)$_2$D. Attempts to use $(CH_3)_2D(OEOEO)_2D(CH_3)_2$ as host with this salt led to formation of an amorphous precipitate.

**Chart II**
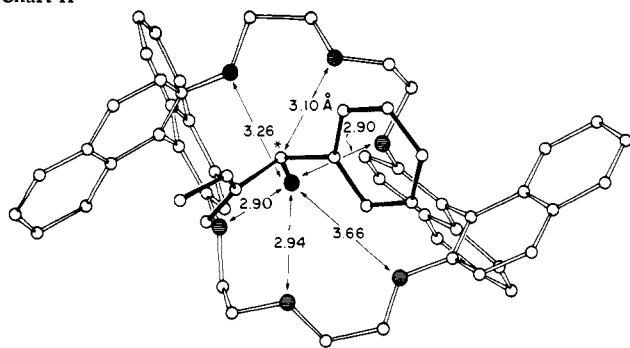


**VII**
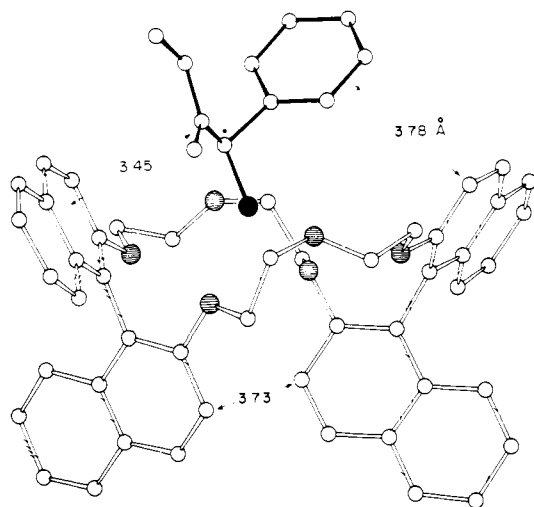


**VIII**

The dramatic increase in chiral recognition provided by the two methyl groups of $(CH_3)_2D(OEOEO)_2D$, $(CH_3)_2$-$D(OEOEO)_2T$, $(CH_3)_2T(OEOEO)_2D$, and $(CH_3)_2$-$T(OEOEO)_2T$ is interpreted as follows. The X-ray structure of the less stable $(SS)(D)$ diastereomeric complex between $D(OEOEO)_2D$ and $C_6H_5CH(CO_2CH_3)NH_3PF_6$ (which will

be referred to as $(SS)(D)$-**23**) is illustrated in drawings VII and VIII[7a] of Chart II. Besides the three NH⋯O hydrogen bonds in VII, the complex appears stabilized and structured by a π-acid to π-base interaction between the $CO_2CH_3$ group and one naphthalene ring. These two groups occupy nearly parallel planes that are close to one another. To accommodate unfavorable naphthalene to phenyl interactions, the naphthalene walls protruding from the upper face of the macroring rotate away from one another. This "splaying" motion requires those naphthalenes protruding from the lower face to approach one another (see VIII). Substitution of methyls for hydrogens in the 3,3′ positions reduces the total space available for the H, $CO_2CH_3$, and $C_6H_5$ groups of the guest on the upper face of the complex for two reasons. The methyl group on the upper face crowds the phenyl, and the methyl group on the lower face inhibits the splaying motion. Molecular model (CPK) examinations indicate that these steric effects should inhibit binding leading to the complexes of the $(SS)(D)$ or $(RR)(L)$ configurations, but less to those of the $(SS)(L)$ or $(RR)(D)$ configurations.

The $^1H$ NMR spectra were determined for the diastereomeric complexes formed in $CDCl_3$ by equilibrating at 0 °C 1.2 M solutions (3 equiv) in $D_2O$ (2 M in $LiClO_4$) of either (D)- or (L)-$C_6H_5CH(CO_2CH_3)NH_3Cl$ with 0.20 M solutions of $(SS)$-$(CH_3)_2D(OEOEO)_2D$ (1 equiv). Integrations of appropriate signals indicated G/H > 0.8. Chart III lists the chemical shifts relative to $Me_4Si$ of the identifiable protons of the complexes $(SS)(L)$-**24** and $(SS)(D)$-**24** and of the host $(SS)$-$(CH_3)_2D(OEOEO)_2D$. The chemical shifts of the corresponding complexes, $(SS)(L)$- and $(SS)(D)$-**23**, and of host $(SS)$-$D(OEOEO)_2D$ are listed in parentheses.[4] Chart III also assigns as working hypotheses those structures $(SS)(L)$-**24** and $(SS)(D)$-**24** which are the most compatible with the experimental results, and with what molecular model examination indicates to be sterically feasible.

The patterns of proton chemical shift differences in the diastereomeric complexes with and without the methyl groups at the 3,3 positions of the hosts parallel one another. Thus the guest's $CH_3O$ protons in $(SS)(L)$-**24** are 0.11 ppm downfield from those in $(SS)(D)$-**24**, whereas those in $(SS)(L)$-**23** are 0.08 ppm downfield from those in $(SS)(D)$-**23**. Molecular models of all four complexes suggest that all four methoxyl protons are somewhat shielded by their adjacent naphthalene rings. The NCH proton of $(SS)(L)$-**24** is 0.55 ppm upfield from that in $(SS)(D)$-**24**, whereas the same proton of $(SS)$-$(L)$-**23** is 0.38 ppm upfield from that in $(SS)(L)$-**23**. In molecular models of the $(SS)(L)$ complexes, this NCH proton is

**Chart III**



| $^1H$ NMR δ | $(SS)(L)$-**24** | $(SS)(D)$-**24** | $(SS)$-$(CH_3)_2D(OEOEO)_2D$ |
|---|---|---|---|
| $CH_3O$ | 3.69 (3.60)* | 3.58 (3.52)* | — |
| NCH | 4.42 (4.59)* | 4.97 (4.97)* | — |
| phenyl H | 6.31 (6.56)* | 6.9–7.4 (6.9–7.4)* | — |
| $CH_3Ar$ | 2.26 | 2.34 | 2.40 |
| $OCH_2CH_2O$ | 3.44, as 4 mult. (3.32, as 3 mult.)* | 3.56, as 4 mult. (3.49, as 3 mult.)* | 3.51, as 3 mult. (3.42, as 2 mult.)* |

*Corresponding chemical shifts of systems without 3,3′-dimethyl groups in the host.

in the shielding region of the naphthalene ring, but not in the $(SS)$(D)-complexes. If the NCH···O hydrogen bond exists in $(SS)$(D)-**24** as is probable for $(SS)$(D)-**23** (see VII), this proton would be deshielded by the interaction. Interestingly, the NCH protons in the $(SS)$(D) isomers of **23** and **24** both occur at δ 4.97, which suggests that both protons possess similar environments. The averaged ortho-proton signal of $C_6H_5$ in $(SS)$(L)-**24** is at least 0.59 ppm upfield of that signal in $(SS)$(D)-**24**, whereas that in $(SS)$(L)-**23** is at least 0.34 ppm upfield of that signal in $(SS)$(D)-**23**. In what appears in molecular models to be sterically the most stable conformation for the $(SS)$(L) complexes, one ortho proton of $C_6H_5$ lies in the shielding region of a naphthalene wall as in structure $(SS)$(L)-**24**. In molecular models of the structure indicated in Chart III for $(SS)$(D)-**24**, none of the $C_6H_5$ protons are near that region. The fact that the ortho protons have the same chemical shift in both complexes of the $(SS)$(D) configuration again suggests that $(SS)$(D)-**23** and $(SS)$(D)-**24** are similarly structured. These protons in complex $(SS)$(L)-**24** are 0.25 ppm upfield of the same protons in complex $(SS)$(L)-**23**. Molecular models indicate that the inhibition of the splaying motion by the methyl groups in structure $(SS)$(L)-**24** pushes the ortho protons closer to the naphthalene ring than in structure $(SS)$(L)-**23**, which, by greater splaying, can enlarge its cavities on the top face.

Host $(SS)$-D(OEOEO)$_2$D possesses $D_2$ symmetry, which not only makes the compound nonsided, but also makes the four chiral cavities between the naphthalene walls equivalent. Host $(SS)$-(CH$_3$)$_2$D(OEOEO)$_2$D possesses only $C_2$ symmetry, which makes it nonsided, but provides two sets of slightly different chiral cavities. As a result, the Ar$OCH_2$ and $CH_2OCH_2$ proton signals in the former host and its complexes can be identified, but these protons cannot be assigned in the $^1$H NMR spectra of the latter host and its complexes. Therefore, only the "centers of gravity" of the multiplets associated with the 16 $OCH_2CH_2O$ protons in the four complexes and two hosts are listed in Chart III. In complex $(SS)$(L)-**24**, these protons are 0.12 ppm upfield of where they are in complex $(SS)$(D)-**24**, and 0.07 ppm upfield of those of $(SS)$-(CH$_3$)$_2$D(OEOEO)$_2$D. In $(SS)$(L)-**23**, they are 0.17 ppm upfield of where they are in $(SS)$(D)-**23**, and 0.10 ppm upfield of where they are in host $(SS)$-D(OEOEO)$_2$D. In molecular models of both structure $(SS)$(L)-**24** and $(SS)$-(L)-**23**, the $C_6H_5$ group faces two of the protons in the $CH_2OCH_2$ part of one of the bridges, whereas in $(SS)$(D)-**24** and $(SS)$(D)-**23**, the aryl group is distant from the protons of the bridge. Thus in the $(SS)$(L) complexes, two of the 16 protons of the bridges are in the shielding region of the $C_6H_5$ group of the guest, and if multiplied by the factor of 8, the observed upfield chemical shifts are substantial.

In the $(SS)$(L)- and $(SS)$(D)-**24** complexes, the host's $ArCH_3$ protons are moved respectively upfield by 0.14 and 0.06 ppm relative to those of host $(SS)$-(CH$_3$)$_2$D(OEOEO)$_2$D. In molecular models of the complexes, the splaying motion brings the $CH_3$ group on the noncomplexed face slightly into the shielding region of the transannular naphthalene ring.

Although other structures can be written for complexes $(SS)$(L)- and $(SS)$(D)-**24**, those of Chart III best reconcile four different types of observations. They correlate the differences in $^1$H NMR spectra between the two diastereomeric complexes with what molecular models indicate to be the most sterically feasible. They explain why $(SS)$(L)-**24** is more stable than $(SS)$(D)-**24**. They also explain why the two methyl groups of $(SS)$-(CH$_3$)$_2$D(OEOEO)$_2$D potentiate chiral recognition over that of $(SS)$-D(OEOEO)$_2$D. They correlate X-ray structure VII of $(SS)$(D)-**23** with the similarities of $^1$H NMR spectra of $(SS)$(D)-**23** and $(SS)$(D)-**24**.

The $\Delta(\Delta G°)$ values of Table III for the four hosts (CH$_3$)$_2$D(OEOEO)$_2$D, (CH$_3$)$_2$D(OEOEO)$_2$T, (CH$_3$)$_2$-

**Table IV.** Effect of Host Structure on Chiral Recognition at 0 °C of $C_6H_5CH(CO_2CH_3)NH_3ClO_4$

| host | EDC | $\Delta(\Delta G°)$, kcal/mol | more stable complex | run no. |
|---|---|---|---|---|
| (CH$_3$)$_2$D(OEOEO)$_2$D | 21 | −1.65 | $(RR)$(D) | 29 |
| (CH$_3$)$_2$D(OEOEO)$_2$D | 22 | −1.68 | $(SS)$(L) | 30 |
| (CH$_3$)$_2$T(EOEOE)$_2$T | 10.2 | −1.3 | $(SS)$(L) | 42 |
| T(OEOEO)$_2$T | 3.1 | −0.62 | $(RR)$(D) | 3 |
| D(OEOEO)$_2$D | 2.4 | −0.48 | $(SS)$(L) | 2 |
| D(OEO)(OEOEOEO)D | 1.8 | −0.32 | $(SS)$(D) | 10 |
| Br$_2$T(OEO)(OEOEOEO)TBr$_2$ | 1.8 | −0.32 | $(SS)$(D) | 12 |
| Br$_2$T(OEOEO)$_2$TBr$_2$ | 1.5 | −0.22 | $(SS)$(L) | 4 |
| T(OEO)(OEOEOEO)T | 1.1 | −0.05 | $(SS)$(D) | 11 |

T(OEOEO)$_2$D, and (CH$_3$)$_2$T(OEOEO)$_2$T complexing $C_6H_5CH(CO_2CH_3)NH_3PF_6$ differ by only −0.5 kcal/mol, and show the same configurational bias. Molecular models of complexes of the four hosts similar to $(SS)$(L)-**24** and $(SS)$-(D)-**24** greatly resemble one another in shape. Thus the steric effects associated with shape contribute dominantly to both the chiral recognition and to the direction of configurational bias. If differences exist between the binding due to $\pi$-$\pi$ $CO_2CH_3$-naphthalene vs. $CO_2 CH_3$-tetralin interactions, they appear not to dominate the patterns of results. Even the electron-withdrawing effects of the two bromines of Br$_2$T(OEOEO)$_2$D decreased $\Delta(\Delta G°)$ by only −0.35 kcal/mol compared to (CH$_3$)$_2$T(OEOEO)$_2$D. However, the greater steric bulk of the *i*-Pr groups of (*i*-Pr)$_2$D(OEOEO)$_2$D reduced the chiral recognition by over −1 kcal/mol compared to (CH$_3$)$_2$D(OEOEO)$_2$D. Apparently the *i*-Pr group is large enough to both inhibit complexation generally (see Table I) and also to partially destructure the complexes that do form. Possibly fewer binding sites are available for steric reasons, and as a result, the less structured diastereomeric complexes are closer together in free energy.

Table IV summarizes the effects of a wider range of host-structural changes on chiral recognition in complexation of the enantiomers of $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ in CDCl$_3$. As expected, (CH$_3$)$_2$D(OEOEO)$_2$D provided about −1 kcal/mol higher chiral recognition than D(OEOEO)$_2$D, and (CH$_3$)$_2$-T(OEOEO)$_2$T, −0.7 kcal/mol higher than T(OEOEO)$_2$T. Interestingly, T(OEOEO)$_2$T showed higher chiral recognition than D(OEOEO)$_2$D by about −0.14 kcal/mol. Substitution of four bromines for hydrogens in the 3,3' positions of T(OEOEO)$_2$T to give Br$_2$T(OEOEO)$_2$TBr$_2$ diminished the chiral recognition by +0.40 kcal/mol. As with (*i*-Pr)$_2$-D(OEOEO)$_2$D, steric effects appear to be great enough in Br$_2$T(OEOEO)$_2$TBr$_2$ to partially destructure the complexes that are formed, probably by reducing the number of binding sites.

The comparisons made thus far indicate that of the complexes formed from I-, II-, and III-type hosts, those from type II show the highest chiral recognition. In the complexes of II, steric effects and binding power appear to maximize their opposition to one another in the least stable diastereomeric complexes. In the complexes from type I hosts, steric effects are too low, and in the complexes from III, they are too high.

Location of the chiral barriers close to one another, as in D(OEO)(OEOEOEO)D, which possesses the shape of IV, has two effects. The direction of the configurational bias inverts (the $(SS)$(D) diastereomer becomes the more stable), and the chiral recognition decreases. The reasons for the direction of the configurational bias are discussed in a future section. Interestingly, D(OEO)(OEOEOEO)D shows −0.27 kcal/mol higher chiral recognition than T(OEO)(OEOEOEO)T, but Br$_2$T(OEO)(OEOEOEO)TBr$_2$ of the V variety gives the same chiral recognition as D(OEO)(OEOEOEO)D ($\Delta(\Delta G°)$ = −0.32 kcal/mol). Furthermore, chiral recognition by host

$Br_2T(OEO(OEOEOEO)TBr_2$ of the V type shows $-0.10$ kcal/mol higher chiral recognition than $Br_2T(OEOEO)_2TBr_2$ which is of the III type. In molecular models, the effect of substituting four 3,3' hydrogens by bromines in hosts containing two OEOEO bridges reduces the cavity sizes more than in hosts containing one OEO and one OEOEOEO bridge. However, such substitution severely inhibits splaying of the chiral barriers in complexes away from the chiral centers of the guests. This rigidity in the guest is probably responsible for the $-0.27$ kcal/mol greater chiral recognition exhibited by $Br_2T(OEO)(OEOEOEO)TBr_2$ as compared to $T(OEO)$-$(OEOEOEO)T$.

Since $(CH_3)_2D(OEOEO)_2D(CH_3)_2$ could not be used as a host for $C_6H_5CH(CO_2CH_3)NH_3PF_6$, in run 38 of Table II it was tested as a host for $CH_3SCH_2CH_2CH(CO_2CH_3)$-$NH_3PF_6$, which has a lower steric requirement for complexation. At $-10$ °C, the $(RR)(D)$ diastereomeric complex was the more stable, the EDC was 1.5, and $\Delta(\Delta G°) = -0.21$ kcal/mol. With $(CH_3)_2D(OEOEO)_2D$ as host in a run made at $-5$ °C (run 34, Table II), again the $(RR)(D)$ diastereomeric complex was the more stable, the EDC was 2.2, and $\Delta(\Delta G°)$ $= -0.42$ kcal/mol. Thus the cavities of $(CH_3)_2D(OEOEO)_2$-$D(CH_3)_2$ appear to be too sterically restricted to bind well even with that enantiomer of $CH_3SCH_2CH_2CH(CO_2CH_3)$-$NH_3PF_6$ which has the more complementary structure.

**Effects of Para Substituents Z in $p$-$ZC_6H_4CH(CO_2CH_3)$-$NH_3ClO_4$ on Chiral Recognition in Complexation. Structures** $(SS)(L)$-**24** for the more stable and $(SS)(D)$-**24** for the less stable diastereomeric complexes between $(CH_3)_2$-$D(OEOEO)_2D$ and $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ take account of steric effects, of $NH^+···O$ and $NCH···O$ hydrogen bonds, and of $CO_2CH_3$ to naphthalene $\pi$ binding. Molecular models of these structures indicate that substituents in the para positions of these guests are too remote from the chiral center of the guest and the chiral barrier of the host to greatly influence steric interactions. However, by transmission of electronic effects through the benzene ring, they might affect the degree of chiral recognition by differentially contributing to these three types of binding. Hosts $D(OEOEO)_2D$ and $T(OEOEO)_2T$ were used to examine this possibility.

The data of Table V indicate that, although remote substituents do not affect the direction of the configurational bias, they do affect the extent of chiral recognition. Thus $(SS)$-$T(OEOEO)_2T$ formed the more stable complexes with $(L)$-$p$-$ZC_6H_4CH(CO_2CH_3)NH_3ClO_4$, and the $\Delta(\Delta G°)$ values decreased as the Z substituents were changed in the order HO, $CH_3O_2C$, H, and Cl. Similarly, $(RR)$-$D(OEOEO)_2D$ better complexed (D) guests, and $\Delta(\Delta G°)$ values decreased as the Z substituents were changed in the same order.

The responses of the ditetralyl and dinaphthyl types of hosts to changes in substituents in the four guests are very similar. For each substituent, $T(OEOEO)_2T$ exhibited an average of $-0.24$ kcal/mol higher chiral recognition for each guest than did $D(OEOEO)_2D$. The maximum spread in $\Delta(\Delta G°)$ values as substituents were changed was about 0.55 kcal/mol for each guest.

The $\Delta(\Delta G°)$ values show no correlation with any of the usual $\sigma$ substituent constants. This is not surprising, since at least three and probably more types of binding contribute to the stability of at least one of the diastereomeric complexes. Each type of binding is expected to have a different response to each substituent. In the X-ray structure of the less stable diastereomeric complex between $D(OEOEO)_2D$ and $C_6H_5CH(CO_2CH_3)NH_3PF_6$ (Chart II), the three identified types of binding were not ideally complementary to one another. The structure reflects a minimization of the free energy associated with binding between $D(OEOEO)_2D$ and $C_6H_5CH(CO_2CH_3)NH_3PF_6$. Each type of binding site responds somewhat differently to changes in the nature of the

**Table V.** Effect of Para Substituent Z in $p$-$ZC_6H_4CH(CO_2CH_3)$-$NH_3ClO_4$ on Chiral Recognition at 0 °C in $CDCl_3$-$CD_3CN$ (9:1 v:v)

| host | Z of guest | EDC | $\Delta(\Delta G°)$, kcal/mol | run no. |
|---|---|---|---|---|
| $T(OEOEO)_2T$ | HO | 6.6 | $-1.0$ | 19 |
| $T(OEOEO)_2T$ | $CH_3O_2C$ | 3.6 | $-0.69$ | 20 |
| $T(OEOEO)_2T$ | H | 3.2 | $-0.63$ | 21 |
| $T(OEOEO)_2T$ | Cl | 2.1 | $-0.40$ | 22 |
| $D(OEOEO)_2D$ | HO | 3.5 | $-0.68$ | 15 |
| $D(OEOEO)_2D$ | $CH_3O_2C$ | 2.3 | $-0.46$ | 16 |
| $D(OEOEO)_2D$ | H | 2.4 | $-0.48$ | 17 |
| $D(OEOEO)_2D$ | Cl | 1.3 | $-0.15$ | 18 |

**Table VI.** Effect of Structure of R Group of Guest $RCH(CO_2CH_3)NH_3PF_6$ on Chiral Recognition at 0 °C by Host $(CH_3)_2D(OEOEO)_2D$

| R | EDC | $\Delta(\Delta G°)$, kcal/mol | more stable complex | run no. |
|---|---|---|---|---|
| $C_6H_5$ | 31 | $-1.9$ | $(RR)(D)$ | 24 |
| $p$-$HOC_6H_4$ | 8.9 | $-1.4$ | $(RR)(D)$ | 32 |
| $(CH_3)_2CH$[a] | 5.3 | $-0.87$ | $(RR)(D)$ | 33 |
| $C_6H_5CH_2$[b] | 5.3 | $-0.87$ | $(RR)(D)$ | 35 |
| $CH_3SCH_2CH_2$[c] | 2.2 | $-0.42$ | $(RR)(D)$ | 34 |

[a] Run made at $-11$ °C. [b] Run made at $-10$ °C. [c] Run made at $-5$ °C.

remote substituents, and therefore may alter the structures of the diastereomeric complexes, as well as their relative stabilities.

**Effect of Structure of R Group of Guest $RCH(CO_2CH_3)$-$NH_3PF_6$ on Chiral Recognition by Host $(CH_3)_2D(OEOEO)_2D$.** Table VI ranks guest $RCH(CO_2CH_3)NH_3PF_6$ in decreasing order of chiral recognition by host $(CH_3)_2D(OEOEO)_2D$. The chiral recognition decreases as R groups are changed in the order $C_6H_5 > p$-$HOC_6H_4 > (CH_3)_2CH \sim C_6H_5CH_2 > CH_3SCH_2CH_2$. The EDC of 31 with a $\Delta(\Delta G°) = -1.9$ kcal/mol difference in free energy for the two diastereomeric complexes is the highest reported to date for amino ester salts. This value drops to $-1.4$ kcal/mol with R = $p$-$HOC_6H_4$. For the rest of the series, a similar substituent effect was observed with complexes of hosts of the I type. As the size of R decreases from $C_6H_5$ to $(CH_3)_2CH$, the EDC value drops from 31 to 5.3, and $\Delta(\Delta G°)$ from $-1.9$ to $-0.87$ kcal/mol. With R = $(CH_3)_2CH$ or $C_6H_5CH_2$, the EDC and $\Delta(\Delta G°)$ values are about the same. With the unbranched $CH_3SCH_2CH_2$ group as R, the EDC value drops further to 2.2, and $\Delta(\Delta G°)$ goes to $-0.42$ kcal/mol. For all five of these amino esters, the configurational bias favors the $(RR)(D)$ complex as the more stable of the two diastereomers.

The $^1H$ NMR spectra in $CDCl_3$ of the diastereomeric complexes with R = $C_6H_5$ have already been discussed (see last section). Similarly prepared solutions of the separate diastereomeric complexes with the other R groups also provided information about their structures. When R = $p$-$HOC_6H_4$, the chemical shifts for the respective $(RR)(D)$ and $(RR)(L)$ diastereomers were as follows: $CO_2CH_3$, $\delta$ 3.50 and 3.44; NCH, $\delta$ 4.38 and 4.83; $C_6H_4$, protons ortho to amino ester side chain, $\delta$ 6.26 and 6.52 (centers of two AB patterns) and 6.9–7.4. These trends in chemical shifts are similar to those when R = $C_6H_5$ (Chart I), and indicate that the $p$-HO group affects the structures very little. The complexes with R = $(CH_3)_2CH$, $CH_3SCH_2CH_2$, and $C_6H_5CH_2$ afforded spectra whose overlapping signals provided structural information mainly with regard to the locations of the $CH_3O$ protons. The respective values for the $CH_3O$ signals of the $(RR)(D)$ and

$(RR)(\text{L})$ complexes were as follows: R = $(CH_3)_2CH$, $\delta$ 3.57 and 3.54; R = $CH_3SCH_2CH_2$, $\delta$ 3.55 and 3.55; R = $C_6H_5CH_2$, $\delta$ 3.59 and 3.49. The complex of $C_6H_5CH(CO_2CH_3)NH_3Cl$ with 18-crown-6 in CDCl$_3$ gave $\delta$ 3.79 for the CH$_3$O protons.[4] Thus the CH$_3$O protons of all ten complexes of Table IV are upfield of this value by an average of 0.24 ppm, and gave chemical shifts very similar to those reported for similar complexes in which the two methyls were absent from the 3,3' positions of one dinaphthyl unit.[4] These data, coupled with the X-ray structure of Chart II, suggest that in all ten complexes the CO$_2$CH$_3$ groups occupy roughly similar positions lying against the naphthalene wall. In such structures, the methyl protons are somewhat shielded by the naphthalene ring current. Thus $\pi$-acid to $\pi$-base attractions probably provide a fourth binding site for all ten complexes.

Another comparison supports the hypothesis that CO$_2$CH$_3$ to aryl $\pi$ binding partially structures the complexes of amino ester salt hosts. Guests $C_6H_5CH(CO_2CH_3)NH_3X$ and $C_6H_5CH(CH_3)NH_3X$ differ only by the CO$_2$CH$_3$ group in the former being substituted by a CH$_3$ group in the latter. With $D(OEOEO)_2D$ as host, $C_6H_5CH(CO_2CH_3)NH_3PF_6$ at 0 °C in CDCl$_3$ gave $\Delta(\Delta G°) = -0.56$ kcal/mol (run 1, Table II), whereas $C_6H_5CH(CH_3)NH_3PF_6$ gave only $\Delta(\Delta G°) = -0.31$ kcal/mol.[4] The direction of the configurational bias was similar for the two guests, as were many of the $^1$H NMR chemical shifts.[4] With $(CH_3)_2D(OEOEO)_2D$ as host, $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ in CDCl$_3$ at 0 °C gave $\Delta(\Delta G°) = -1.65$ kcal/mol (run 29, Table II), whereas $C_6H_5CH(CH_3)NH_3ClO_4$ gave $\Delta(\Delta G°) = -0.35$ kcal/mol (see Experimental Section). The respective $\Delta(\Delta G°)$ values for the PF$_6$ salts were $-1.9$ and $-0.32$ kcal/mol (run 27 and Experimental Section). Again, the configurational bias was in the same direction for the two guests. Thus the CO$_2$CH$_3$ potentiates chiral recognition over the CH$_3$ group by $-0.25$ kcal/mol for $D(OEOEO)_2D$ and by $-1.3$ to $-1.6$ kcal/mol for $(CH_3)_2D(OEOEO)_2D$. This large difference strongly supports the conclusion that the electronic effect associated with the CO$_2$CH$_3$, but absent in the CH$_3$ group, structures the complexes and thus increases the free energy differences between the diastereomers.

Fixation of this ester group in the complexes reduces the number of conformations that need to be considered in CPK molecular model examination. Structure $(RR)(\text{D})$-**35** on steric
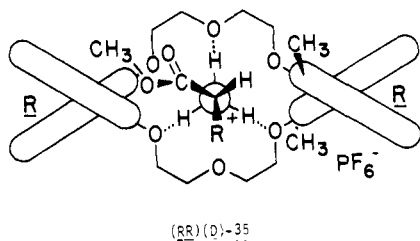


(RR)(D)-35

grounds appears to be the most stable in models. In $(RR)$-(D)-**35**, the R group lies in the most spacious cavity, and the NCH hydrogen rests against the chiral barrier of the host. An alternative conformation involves binding the CO$_2$CH$_3$ to the methyl-bearing naphthalene ring. In such a conformation, the space available for the R group is somewhat reduced. Irrespective of which conformation applies, models such as $(RR)(\text{D})$-**35** explain the configuration–stability relationships for all five sets of complexes of Table VI.

Interestingly, substitution of two methyl groups for the 3,3' hydrogens in $D(OEOEO)_2D$ greatly accentuated the chiral recognition toward the enantiomers of the ester salts whose R groups were $C_6H_5$ and $p$-HOC$_6$H$_4$. The presence of the CH$_3$ groups in the host did not change the direction of the configurational bias. However, with R = $(CH_3)_2CH$, $C_6H_5CH_2$, and

**Table VII.** Effects of Two Methyl Groups in $D(OEOEO)_2D$-Type Hosts on Free Energy Differences between Diastereomeric Complexes in CDCl$_3$ at 0 to $-11$ °C

| R group of guest RCH(CO$_2$CH$_3$)-NH$_3$PF$_6$ | $\Delta(\Delta G°)(CH_3) - \Delta(\Delta G°)(H)$, kcal/mol[a] | runs involved |
|---|---|---|
| $C_6H_5$ | $-1.3$ | 27 and 1 |
| $p$-HOC$_6$H$_4$ | $-0.7$ | 32 and (6)[b] |
| $(CH_3)_2CH$ | $-1.1$ | 33 and (9)[b] |
| $C_6H_5CH_2$ | $-1.2$ | 35 and (11)[b] |
| $CH_3SCH_2CH_2$ | $-0.7$ | 34 and (12)[b] |

[a] See text for definitions. [b] Run numbers of Table II, ref 4.

$CH_3SCH_2CH_2$, the methyl groups both increased the chiral recognition *and changed the direction of the chiral bias.*

The magnitudes of these effects are measured by the values of Table VII for $\Delta(\Delta G°)(CH_3) = \Delta G°(RR)(\text{D}) - \Delta G°(RR)(\text{L})$ for $(CH_3)_2D(OEOEO)_2D$ as host, and $\Delta(\Delta G°)(H) = \Delta G°(RR)(\text{D}) - \Delta G(RR)(\text{L})$ for $D(OEOEO)_2D$ as host. The $\Delta(\Delta G°)(CH_3) - \Delta(\Delta G°)(H)$ values for guests with R = $C_6H_5$, $p$-HOC$_6$H$_4$, $(CH_3)_2CH$, $C_6H_5CH_2$, and $CH_3SCH_2CH_2$ are listed.

The interesting thing about these $\Delta(\Delta G°)(CH_3) - \Delta(\Delta G°)(H)$ values is how similar they are ($-1.2 \pm 0.1$ kcal/mol) for guests with R groups $C_6H_5$, $(CH_3)_2CH$, and $C_6H_5CH_2$. These groups are totally hydrocarbon, are all branched, and in CPK molecular models they fully occupy one of the cavities of the hosts. However, the CH$_3$SCH$_2$CH$_2$ group does not completely fill one cavity, and the $\Delta(\Delta G°)(CH_3) - \Delta(\Delta G°)(H)$ value drops to $-0.7$. Thus the response of the chiral recognition to the substitution of the 3,3' hydrogens of the host by methyl groups probably represents mainly steric effects.

**Effects of Host Structure on Chiral Recognition of $(CH_3)_2CHCH(CO_2CH_3)NH_3X$.** Table VIII ranks several hosts in order of their decreasing abilities to stabilize the $(RR)(\text{D})$ relative to the $(SS)(\text{L})$ complex with $(CH_3)_2$-$CHCH(CO_2CH_3)NH_3X$ as guest. As noted with $C_6H_5CH(CO_2CH_3)NH_3X$ guests, the 3,3'-disubstituted hosts show significantly greater chiral recognition than the nonsubstituted. Thus $(CH_3)_2D(OEOEO)_2D$ and $Br_2T(OEOEO)_2D$ give $\Delta(\Delta G°)$ values of $-0.87$ and $-0.82$ kcal/mol, respectively, the $(RR)(\text{D})$ diastereomer being the more stable. These values represent between $-0.6$ and $-0.8$ kcal/mol greater chiral recognition than any of the nonsubstituted hosts. The very similar shapes of $(RR)$-$(CH_3)_2$-$D(OEOEO)_2D$ and $(RR)$-$Br_2T(OEOEO)_2D$ molecular models correlate with their similar behavior. A model for the more stable diastereomeric complex with $(RR)$-$Br_2T(OEOEO)_2D$ would resemble structure $(RR)(R)$-**35** of the last section.

The EDC values of $T(OEOEO)_2T$ and $D(OEOEO)_2D$ for the enantiomers of $(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$ are within experimental error of being unity in runs 8 and 7, respectively.

Interestingly, the direction of the configurational bias of $D(OEO)(OEOEOEO)D$ favors the stability of the $(SS)(\text{D})$ diastereomer by $-0.14$ kcal/mol. All of the complexes examined of hosts of shapes IV and V (Chart I) whose guests are $RCH(CO_2CH_3)NH_3X$ favor the $(RR)(\text{L})$ or $(SS)(\text{D})$ diastereomers. Molecular models of complexes of $(SS)$-$D(OEO)(OEOEOEO)D$ with methyl ester amine salts indicate that if the CH$_3$O$_2$C group $\pi$ binds the less hindered naphthalene face, structure $(SS)(\text{D})$-**36** appears sterically more compatible than its diastereomer. Examination of molecular models of complexes of hosts such as $T(OEO)$-$(OEOEOEO)T$ and $Br_2T(OEO)(OEOEOEO)TBr_2$ provide

**Table VIII.** Effect of Host Structure on Chiral Recognition of $(CH_3)_2CHCH(CO_2CH_3)NH_3X$

| host | $T$, °C | $X^-$ | EDC | $\Delta(\Delta G°)$, kcal/mol | more stable complex | run no. |
|---|---|---|---|---|---|---|
| $(CH_3)_2D(OEOEO)_2D$ | −11 | $PF_6$ | 5.3 | −0.87 | $(RR)(D)$ | 33 |
| $Br_2T(OEOEO)_2D$ | −10 | $PF_6$ | 4.8 | −0.82 | $(RR)(D)$ | 46 |
| $T(OEOEO)_2T$ | 0 | $ClO_4$ | 1.2 | −0.10 | $(RR)(D)$ | $8^a$ |
| $D(OEOEO)_2D$ | 0 | $ClO_4$ | 1.1 | −0.05 | $(SS)(D)$ | $7^a$ |
| $D(OEO)(OEOEOEO)D$ | 0 | $ClO_4$ | 1.3 | −0.14 | $(SS)(D)$ | 13 |
| $D(OEOEO)_2D$ | −10 | $PF_6$ | 1.5 | −0.21 | $(RR)(L)$ | $9^b$ |

$^a$ Organic phase was $CDCl_3$-$CD_3CN$ (9:1 v:v) instead of $CDCl_3$ used in the other runs. $^b$ Table II, ref 4.

**Table IX.** Correlation of Structures of Diastereomeric Complexes with Estimated Enthalpic vs. Entropic Contributions to Free Energy of Complexation at 0 °C

| host | $RCH(R')NH_3PF_6$ | | parameters, kcal/mol | | | run no. |
|---|---|---|---|---|---|---|
| | $R$ | $R'$ | $\Delta(\Delta G°)$ | $\Delta(\Delta H°)$ | $-T\Delta(\Delta S°)$ | |
| $(CH_3)_2D(OEOEO)_2D$ | $C_6H_5$ | $CO_2CH_3$ | −1.9 | −6 | 4 | 23 + 24 |
| $(CH_3)_2D(OEOEO)_2D$ | $p$-$HOC_6H_4$ | $CO_2CH_3$ | −1.4 | −2.5 | 1 | 31 + 32 |
| $Br_2T(OEOEO)_2D$ | $C_6H_5$ | $CO_2CH_3$ | −1.25 | −1.6 | 0.3 | 44 + 45 |
| $D(OEOEO)_2D$ | $C_6H_5$ | $CO_2CH_3$ | −0.55 | −0.7 | 0.2 | $1^a + 5^a$ |
| $D(OEOEO)_2D$ | $C_6H_5$ | $CH_3$ | −0.31 | −0.9 | 0.6 | $a$ |

$^a$ Reference 4.
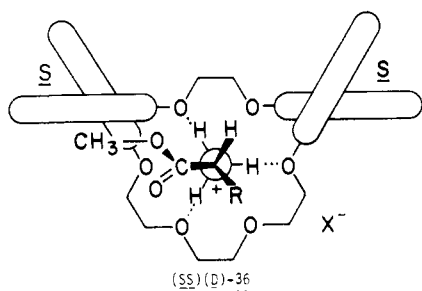


$(\underline{SS})(\underline{D})\text{-}36$

the same conclusion. In structure $(SS)(D)$-**36,** the H of $NC^*HR$ occupies the more and R the less congested cavity of the host.

Earlier, $D(OEO)(OEOEOEO)D$ in $CDCl_3$ at 0 °C was observed to bind $C_6H_5CH(CH_3)NH_3PF_6$ well, and the two diastereomeric complexes exhibited different $^1H$ NMR spectra. However, $\Delta(\Delta G°)$ was equal to zero.[4] This result contrasts with those obtained with $RCH(CO_2CH_3)NH_3X$ guests in which complexation favors the $(SS)(D)$ diastereomers by −0.14 to −0.45 kcal/mol (runs 9 and 13, Table II). These comparisons provide additional evidence that $CO_2CH_3$ to naphthalene $\pi$ binding helps to structure the complexes.

**Effects of Temperature and Counterion on Chiral Recognition.** The effect of temperature changes on chiral recognition was examined for three new sets of complexing partners. Data for two other sets were available from a previous study.[4] For all five combinations of hosts and guests, the lower temperatures gave higher EDC values and more negative $\Delta(\Delta G°)$ values. Although two temperatures are hardly enough to calculate accurately $\Delta(\Delta H°)$ and $-T\Delta(\Delta S°)$ contributions to $\Delta(\Delta G°)$, estimations point to trends that correlate with structure. Application of eq 8 to the data for the five sets of complexing partners provided the estimates of the thermodynamic parameters listed in Table IX.

$$\Delta(\Delta G°) = \Delta(\Delta H°) - T\Delta(\Delta S°) \qquad (8)$$

Particularly for the first two partner sets of Table IX, the more stable diastereomeric complexes are held together by forces that are more enthalpic than those of the less stable diastereomeric complexes. Conversely, the less stable diastereomeric complex is more stabilized (or less destabilized) by forces that are more entropic than those of the more stable diastereomeric complex. This result correlates with the ex-

pectation that complementary steric relationships of host and guest allow the complex to be fairly rigidly structured by enthalpic driving forces, such as pole–dipole and other attractions, associated with the "fit of guest in host." However, this "fitting" process has high entropic costs because of the numbers of degrees of freedom frozen out. Noncomplementary steric interactions reduce the enthalpic driving forces, and the less stable complexes are less rigidly structured and are more conformationally mobile. Thus the entropic cost of orientation in binding is less for the less stable diastereomer. This interpretation suggests that the higher the chiral recognition, the greater should be the opposition of enthalpic and entropic driving forces for complexation. The limited data available point in this direction.

The effect on chiral recognition of changing X of guest $C_6H_5CH(CO_2CH_3)NH_3X$ from $PF_6$ to $ClO_4$ was determined for three of the more studied hosts (see Table X). In an earlier study,[4] it was found that with host $D(OEOEO)_2D$ and $C_6H_5CH(CH_3)NH_3X$ as guest, the tendency for both complexation and chiral recognition to occur depended on X. With X as $PF_6$, $AsF_6$, $SbF_6$, roughly the same degree of complexation and chiral recognition was observed. With X = I or SCN, extensive complexation, but little chiral recognition, was found; and with X = Br, no complexation could be detected. It was concluded that the more the charges of the complexed ion pairs were separated by ion size and charge delocalization, the more structured were the complexes.

The results of Table X indicate that chiral recognition, as measured by $\Delta(\Delta G°)$ values, decreased about 7–15% with the three hosts when $X^-$ was changed from $PF_6^-$ to $ClO_4^-$. It appears that in $CDCl_3$ in the absence of a more polar cosolvent, $ClO_4^-$ plays a low order destructing role with hosts and guests with as little affinity for one another as those at hand. In complexation in a solvent as nonpolar as $CDCl_3$, host and $X^-$

**Table X.** Effect of Counterion on Chiral Recognition of $C_6H_5CH(CO_2CH_3)NH_3X$

| host | $X^-$ | $-\Delta(\Delta G°)$ | run no. |
|---|---|---|---|
| $D(OEOEO)_2D$ | $PF_6$ | −0.56 | 1 |
| $D(OEOEO)_2D$ | $ClO_4$ | −0.48 | 2 |
| $(CH_3)_2D(OEOEO)_2D$ | $PF_6$ | −1.9 | 24 |
| $(CH_3)_2D(OEOEO)_2D$ | $ClO_4$ | −1.7 | 29 |
| $(CH_3)_2T(OEOEO)_2T$ | $PF_6$ | −1.4 | 40 |
| $(CH_3)_2T(OEOEO)_2T$ | $ClO_4$ | −1.3 | 42 |

compete for $RNH_3^+$. The more charge is separated before complexation, the more thoroughly host displaces $X^-$, and the less the structure of the complex depends on the counterion. Charge is intrinsically more delocalized and the ion diameter is larger for $PF_6^-$ than for $ClO_4^-$. Thus for these particular host–guest relationships in this particular solvent, the complexes of the $PF_6$ salts are more structured and show somewhat higher chiral recognition than the $ClO_4^-$ salts.

**Relationships between Chiral Recognition, Host–Guest Structure, and Binding Affinities.** In this survey, an attempt was made to maximize chiral recognition in host–guest complexation, and in so doing to identify those parameters that control the structures of organic to organic complexes. Chiral recognition in complexation is measured by the differences in free energies of diastereomeric complexes. These values should be largest when the largest number of contact sites is maximally attractive in one diastereomer, and least attractive in the second. Mainly electronic effects have been used to generate the attractive forces, and steric effects to oppose them. In other words, chiral recognition is greatest when the relationships between contact sites in host and guest are the most complementary in one diastereomeric complex and the least complementary in the other.

Complexes of hosts of shape I (Chart I) exhibit low chiral recognition probably because they are held together by low binding energies opposed by small steric effects. Complexes of hosts of shape II show the highest chiral recognition, and then only when the groups used to extend the chiral barriers are not too large or electron withdrawing. Complexes formed from hosts of shape III appear held together by binding energies that are too small to accommodate the large steric forces that oppose binding. Hosts of shape IV form complexes with relatively high binding energies that are too little opposed by steric effects to give high chiral recognition. Complexes formed from hosts of shape V were too little studied to generalize, but what data are available suggest that appropriate structural manipulation might produce moderately high chiral recognition.

The highest chiral recognition was shown toward those guests that most completely occupied the chiral cavities in the more stable diastereomers without compromising the geometry of the binding sites. For complexes formed from $(CH_3)_2$-$D(OEOEO)_2D$, $C_6H_5$, $(CH_3)_2CH$, and $C_6H_5CH_2$ as side chains of the guests provided the highest chiral recognition, and in molecular models best satisfied the above conditions.

The observed direction of configurational bias in complexation correlated well with fits of guest to host in CPK molecular models, particularly when chiral recognition reached several hundred cal/mol. In molecular model construction, both X-ray crystal structures and $^1H$ NMR spectra provided guidance as to relative locations of parts of guests and hosts. In all interpretations, it was assumed that the $NH_3$ and $CO_2CH_3$ groups act as binding sites. Generalizations are as follows. (1) In complexes formed from host types I and II with Ar-$CH(CO_2CH_3)NH_3X$ as guests, complexes of the $(RR)(D)$ or $(SS)(L)$ configurations were always the more stable by substantial amounts. (2) In complexes formed from hosts of type II and $RCH(CO_2CH_3)NH_3X$ guests with $R = (CH_3)_2CH$, $C_6H_5CH_2$, or $CH_3SCH_2CH_2$, the $(RR)(D)$ or $(SS)(L)$ diastereomers were always the more stable. In complexes formed from these same guests and type I hosts, the $(RR)(L)$ or $(SS)(D)$ diastereomers were the more stable, but the chiral recognition was low. (3) In the two complexes examined from hosts of the III variety, the chiral recognition was low and the $(RR)(D)$ or $(SS)(L)$ diastereomers were the more stable. (4) In all complexes examined that involved IV- and V-type hosts, the $(RR)(L)$ or $(SS)(D)$ diastereomers were the more stable.

A necessary, but not sufficient, relationship exists between high chiral recognition and high binding ability. The hosts that exhibited the higher chiral recognition all ranked high in their binding powers toward $t$-$BuNH_3PF_6$ (Table I). None of those found in the lower ranks showed high chiral recognition. However, hosts of shape IV ranked high in binding power, but low in chiral recognition. More "fine-grained" correlations failed. For example, although $(CH_3)_2T(OEOEO)_2T$ is the most powerful complexer of $t$-$BuNH_3PF_6$, $(CH_3)_2$-$D(OEOEO)_2D$ exhibits higher chiral recognition. However, $T(OEOEO)_2T$ is a better complexer of $t$-$BuNH_3PF_6$ than $D(OEOEO)_2D$, and also exhibits higher chiral recognition. Obviously, factors of shape and fit destroy anything other than gross correlations between complexing potential and chiral recognition, since geometric and electronic factors can either act in concert or can oppose one another. Chiral recognition with $\Delta(\Delta G°)$ values as high as $-5$ kcal/mol obviously will require higher binding energies than are observed with these host–guest partners, as well as large differences in placements of binding sites and steric barriers in diastereomeric complexes.

## Experimental Section

**General.** All $^1H$ 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 $CH_2Cl_2$ was fractionally distilled before use. Chloroform was washed five times with equal volumes of water, dried over $Na_2SO_4$, distilled, and deoxygenated with $N_2$ before use. Salts $LiPF_6$ and $LiClO_4$ were purchased from Ventron.

**Host Compounds.** Host compounds **1** and **14–20** were reported in part 7[3a] and **2–13**, **21**, and **22** in part 8[3b] of this series. Hosts of maximum rotation were employed in the chiral recognition experiments.

**Determination of Extraction Constants** $(K_e)$ **between Hosts and** $t$-$BuNH_3PF_6$**.** A $D_2O$ solution, 3.5 M in $LiPF_6$ and 2.0 M in $t$-$BuNH_3Cl$, was carefully prepared at 0 °C. The resulting solution was adjusted to pH 4.0 by the addition of $LiOD$.[4] A 0.50-mL aliquot of this solution was shaken at $-10$ °C with 0.50 mL of $CDCl_3$. The two phases were carefully separated and the $^1H$ NMR spectrum of the $CDCl_3$ phase was recorded. No *tert*-butyl signal was detected. In the complexation experiments, 0.50 mL of a 2.0 M solution of host in $CDCl_3$ was shaken at $-10$ °C with 0.50 mL of the $D_2O$ solution described above. From the $^1H$ NMR spectrum of the $CDCl_3$ phase, the relative concentrations of guest and host (G/H) could be determined by a comparison between the integrations of the *tert*-butyl signal of the guests and the ArH or $OCH_2$ signals of the host. From the spectrum of the $D_2O$ phase, it was concluded that none of the host had distributed into that phase. The values of the extraction constants, $K_e$, which define the equilibrium described in eq 1, have been calculated using a procedure described previously.[5a] Table I reports the data.

**Amine Salts Used as Guests.** Preparations of most of the racemic amine salts used have been reported in part 11 of this series,[4] which also refers to their maximum rotations and absolute configurations.[4] The exceptions are as follows. Racemic phenylglycine methyl ester perchlorate salt was prepared as follows. A solution of 5 g of $C_6H_5CH(CO_2CH_3)NH_3Cl$ in 100 mL of water was shaken with enough 3% $NH_3$ in $H_2O$ solution to give pH 9, and the amino ester generated was extracted with $CH_2Cl_2$. The organic phase was washed with brine and dried with $MgSO_4$. The $CH_2Cl_2$ was evaporated at 20 mm to give amino ester which was dissolved in 30 mL of acetonitrile to which was added 1 equiv of 70% aqueous $HClO_4$. The acetonitrile–water was evaporated at 20 mm of pressure to give a wet solid, which was dried by azeotropic distillation with additional acetonitrile at 20 mm. The remaining white solid was recrystallized from $CHCl_3$–$CH_3CN$ solution to give 6.3 g (96%) of $C_6H_5CH$-$(CO_2CH_3)NH_3ClO_4$. This salt exhibited a strong infrared absorption at 1120 cm$^{-1}$.

Racemic $p$-carbomethoxyphenylglycine methyl ester was prepared as follows. A 25-g sample of $p$-carboxybenzaldehyde slurried in 200 mL of 95% ethanol was added to a stirred solution of 12.2 g of NaCN and 76 g of $(NH_4)_2CO_3$ in 350 mL of water, and the resulting solution was allowed to stand for 1 week. The solvent was two-thirds evaporated at 25 mm, and the resulting solution was acidified to pH 1 with con-

centrated hydrochloric acid. The precipitate that formed was collected and added to 250 mL of 10% NaOH in water, and the mixture was held at reflux for 12 h. The solution was decolorized with activated charcoal and filtered, and the filtrate was brought to pH 7 with hydrochloric acid. This solution was evaporated at 25 mm, and the residue was held at reflux for 15 h in a mixture of 600 mL of methanol and 150 mL of thionyl chloride. Most of the suspended solid dissolved. The mixture was filtered, the filtrate was evaporated at 25 mm, and the residue was dissolved in 500 mL of water. The solution was brought to pH 9 with concentrated $NH_4OH$ solution and extracted with four 150-mL portions of $CH_2Cl_2$. The combined organic layers were washed with water–$NH_4OH$ (pH 9) and evaporated at 25 mm to give an orange oil. This oil was dissolved in 400 mL of anhydrous ether, and dry, gaseous HCl was bubbled into the solution to produce a voluminous, white precipitate. This material was collected, ether washed, and dried for 12 h under vacuum to give 22.6 g (50%) of $p$-$CH_3O_2CC_6H_4CH(CO_2CH_3)NH_3Cl$, mp 211–212 °C. Anal. Calcd for $C_{11}H_{14}NO_4Cl$: C, 50.87; H, 5.43. Found: C, 50.62; H, 5.68. A sample was dissolved in water and brought to pH 9 with $NH_4OH$, and the solution was extracted with $CH_2Cl_2$. This solution was dried ($MgSO_4$) and evaporated at 25 mm, and the residual amino ester gave the following $^1H$ NMR spectrum (60 MHz, $CDCl_3$): δ 2.0 (s, 2, $NH_2$), 3.6 (s, 3, $CH_3$), 3.8 (s, 3, $CH_3$), 4.6 (s, 1, NCH), 7.6 (q, 4, ArH).

Racemic $p$-chlorophenylglycine methyl ester was prepared as follows. A 50-g sample of $p$-chlorobenzaldehyde in 25 mL of ether and 50 mL of tetrahydrofuran was cooled to 0 °C, and a chilled solution of 21.5 g of $NH_4Cl$ in 65 mL of water was added, followed by a chilled solution of 18.0 g of NaCN in 40 mL, which was added over 30 min. The entire solution was shaken in a stoppered bottle at 25 °C for 18 h. The solution was then treated with 60 mL of concentrated HCl solution (HCN evolution). The resulting mixture was refluxed for 4 h, the solvents were removed under reduced pressure, and the resulting yellow solid was digested with 600 mL of 95% ethanol and filtered to remove insoluble material. The solvent was evaporated from the filtrate at 25 mm, and the residue dissolved in 250 mL of 95% ethanol and 5 mL of 6 N HCl solution. A 100-mL portion of ether was added, the mixture was filtered, and the solvent was evaporated from the filtrate at 25 mm, and finally at 1 mm for 24 h. The residue was refluxed in 300 mL of $CH_3OH$ and 50 mL of $SOCl_2$ for 15 h, the solvent was evaporated at 25 mm, and the resulting sludge was dissolved in 450 mL of water and brought to pH 9 with concentrated $NH_4OH$. The solution was extracted with two 250-mL portions of $CH_2Cl_2$, and the combined layers were filtered through a pad of $Na_2SO_4$. Hydrogen chloride gas was bubbled through the filtrate to the saturation point. An equal volume of ether was added, and the precipitate that separated in several crops was collected and dried under high vacuum, wt 14.9 g (18%), mp 194–197 °C. Anal. Calcd for $C_9H_{11}Cl_2NO_2$: C, 45.78; H, 4.70. Found: C, 45.61; H, 4.73. A sample was converted by the usual method to the free ester: $^1H$ NMR (60 MHz, $CDCl_3$) δ 1.8 (s, 2, $NH_2$), 3.6 (s, 3, $CH_3$), 4.6 (s, 1, NCH), 7.3 (s, 4 H, ArH).

**Rotations and Absolute Configurations of Amino Esters.** The calculations of the EDC and $\Delta(\Delta G°)$ values depend on the maximum rotations of the amino esters. The direction of the chiral bias in complexation depends on the signs of rotations of enantiomers of known absolute configurations. The values of the maximum rotations used for the amino esters and their configurations were taken from part 11,[4] and are recorded here at 25 °C ($c$ 2, $CH_2Cl_2$): ($R$)-methyl phenylglycinate, $[\alpha]_{578}$ −161°, $[\alpha]_{546}$ −185°, $[\alpha]_{436}$ −340°; ($S$)-methyl valinate, $[\alpha]_{578}$ +43.3°, $[\alpha]_{546}$ +50°, $[\alpha]_{436}$ +93°; ($S$)-methyl phenylalaninate, $[\alpha]_{578}$ +16.9°, $[\alpha]_{546}$ +19.9°, $[\alpha]_{436}$ +39.7°; ($S$)-methyl methioninate, $[\alpha]_{578}$ +5.5°, $[\alpha]_{546}$ + 6.7°, $[\alpha]_{436}$ +16.3°. The above esters were prepared from their hydrochloride salts, whose rotations at 25 °C were as follows:[4] ($R$)-$C_6H_5CH(CO_2CH_3)NH_3Cl$ ($c$ 1, $CH_3OH$), $[\alpha]_{589}$ −131°, $[\alpha]_{578}$ −136°, $[\alpha]_{546}$ −156°, $[\alpha]_{436}$ −282° (lit.[8a] $[\alpha]_{589}$ −133° ($c$ 1, $CH_3OH$)); ($S$)-$(CH_3)_2$-$CHCH(CO_2CO_3)NH_3Cl$ ($c$ 2.0, $H_2O$), $[\alpha]_{589}$ +15.7°, $[\alpha]_{578}$ +16.4°, $[\alpha]_{546}$ +18.0°, $[\alpha]_{436}$ +35.8° (lit.[8b] $[\alpha]_{589}^{25}$ +15.5° ($c$ 2, $H_2O$)); ($S$)-$C_6H_5CH_2CH(CO_2CH_3)NH_3Cl$ ($c$ 4.5, $CH_3OH$), $[\alpha]_{589}$ +18.6° (lit.[8b] $[\alpha]_{589}$ +18.9° ($c$ 4.5, $CH_3OH$); ($S$)-$CH_3SCH_2CH_2CH(CO_2CH_3)NH_3Cl$ ($c$ 1.0, $H_2O$), $[\alpha]_{589}$ +26.6°, $[\alpha]_{578}$ +28.0°, $[\alpha]_{546}$ +31.4°, $[\alpha]_{436}$ +56° (lit.[8c] $[\alpha]_{589}$ +26.8° ($c$ 1.0, $H_2O$); ($R$)-$p$-$HOC_6H_4CH(CO_2CH_3)NH_3Cl$ ($c$ 1.0, 1 N HCl), $[\alpha]_{589}$ −121.1°, $[\alpha]_{578}$ −125.9°, $[\alpha]_{546}$ −145.5°, $[\alpha]_{436}$ −267.3°, and $[\alpha]_{546}$ −171.1° ($c$ 1.0, $CH_3OH$) ($[\alpha]_{546}$ −172.8°, $c$ 1.0, $CH_3OH$, private communication from Dr. H. Jaeger, The Upjohn Co.). Racemic methyl ester perchlorate salts of $p$-carbomethoxyphenylglycine and $p$-chlorophenylglycine were optically resolved by chromatogra-

phy, and their absolute configurations assigned by comparisons of their CD spectra with those of the corresponding ester salts of phenylglycine and $p$-hydroxyphenylglycine of known configurations.[8d] The rotations and configurations of these salts at 25 °C were as follows: ($S$)-$p$-$ClC_6H_4CH(CO_2CH_3)NH_3ClO_4$, $[\alpha]_{578}$ +73.7°, $[\alpha]_{546}$ +84.3° ($c$ 0.8, $CH_3OH$); ($R$)-$CH_3O_2CC_6H_4CH(CO_2CH_3)NH_3ClO_4$, $[\alpha]_{578}$ −76.0°. These rotations were employed as maximal in the calculations of EDC and $\Delta(\Delta G°)$ values of Table 11. The rotations observed in $c$ 1.0 $CH_3OH$ were actually taken on the hydrochloride rather than the perchlorate salts, but the concentrations were corrected to those of the perchlorate salts.

**General Extraction Procedure for EDC Determinations.** A solution of 5.0–5.6 mL of 0.17–0.20 M host of maximum rotation (1.00 mmol) in $CDCl_3$ was prepared in a 25-mL graduated centrifuge tube at 25 °C. To this at 25 °C was added a solution of racemic amino ester (3.00 mmol) as the hydrochloride or perchlorate salt in $D_2O$ (3.0 mL, 1.0 M in guest) which contained various concentrations of $LiPF_6$ or $LiClO_4$ (see Table 11). This two-phase system was placed in a cold room at 1 to −1 °C, and shaken for 15 s with a vortex mixer. The mixture was allowed to stand for 1 h, again shaken for 15 s with a vortex mixer, and centrifuged. The phases were very carefully separated with drawn Pasteur pipets in the order aqueous (1.5–2.0 mL), interphase (1.2–1.7 mL), and organic (3.0–4.0 mL). The interphase and residual organic solutions were saved for recovery of host. All remaining operations were carried out at 25 °C. The aqueous phase was diluted to 30 mL with $H_2O$, washed with two 25-mL portions of $CH_2Cl_2$ to remove traces of host, and neutralized to pH 9 with 3% $NH_3$ in $H_2O$. This solution was extracted with five 10-mL portions of $CH_2Cl_2$, and the combined organic layers were filtered through a small amount of $Na_2SO_4$. The solvent was evaporated under reduced pressure, the residue was transferred quantitatively to a smaller tared flask, and the last trace of solvent was removed at 0.1 mm to constant weight. The entire sample of free amino ester was weighed by difference and transferred quantitatively with $CH_2Cl_2$ into a volumetric flask to provide solutions for rotations ($c$ 1–2%). Specific rotations at 25 °C were taken at 578, 546, and 436 nm, and compared with those for optically pure material to determine the chiral storage factor (CSF, see text).

In most runs, the $^1H$ NMR spectra of the $CDCl_3$ layer were determined, and appropriate signals of guest and host integrated to determine G/H ratios. The recombined $CDCl_3$ solutions were diluted to 30 mL with $CH_2Cl_2$ and extracted with three 10-mL portions of 0.1 N HCl to separate host and guest. The combined aqueous layers were washed with two 25-mL portions of $CH_2Cl_2$ to remove host, and the organic layers were saved for host recovery. The amino ester was recovered from this aqueous layer as it was recovered from the original equilibrated $H_2O$ layer, and its specific rotation taken as before to determine the chiral recognition factor (CRF, see text).

The host was recovered as follows. The various organic layers containing host were combined and washed with 50 mL of 0.1 N HCl to remove traces of amino ester. The organic phase was dried with $Na_2SO_4$, the solvent was evaporated, and the residue was chromatographed on 75 g of neutral alumina (activity III) with such solvents as 3:2 $CH_2Cl_2$–pentane (v:v). Typically, 95% of the host was recovered.

The original $D_2O$ solutions containing $LiClO_4\cdot3H_2O$ were prepared as usual. Preparation of approximately 2 M $LiPF_6$–$D_2O$ solution is illustrated. To 3.04 g of $LiPF_6$ weighed in a drybox into a 10-mL graduated cylinder was slowly and cautiously added at 0 °C 5 mL of $D_2O$ in such a way that the temperature never rose above 10 °C. The pH of the solution was adjusted to 4 by addition of a few drops of LiOH in $D_2O$ (saturated). Finally, $D_2O$ was added to bring the volume to 10.0 mL, and the solution was filtered to remove a small amount of LiF. This and other solutions like it were stored at 0 °C, and were diluted with $D_2O$ as needed. The values for the $LiPF_6$ concentrations listed in Table II are maximal since $LiPF_6$ hydrolyzes somewhat during preparation of its solutions.

The original $CDCl_3$ was of NMR grade, and was filtered through a short neutral alumina column (activity 1) prior to use. The $CD_3CN$ was of NMR quality and was used directly. The $D_2O$ was of NMR quality and was used directly. The $CH_2Cl_2$ solvent was doubly distilled, the second time from $CaH_2$.

**Sample of Data Obtained in a Specific Run.** Run 27 involved 711.4 mg (0.96 mmol) of ($SS$)-**2** in 5.6 mL of $CDCl_3$ solution (0.17 M) and 604.5 mg (3.00 mmol) of racemic $C_6H_5CH(CO_2CH_3)NH_3Cl$ in 3 mL of $D_2O$ (1.0 M) which was 0.75 M in $LiPF_6$. The two layers were equilibrated, and 213.3 mg of free amino ester was recovered from

the $D_2O$ layer and was used to prepare 10 mL of a $CH_2Cl_2$ (*c* 2.13) solution which gave the following rotations.

| λ nm | α obsd | $[\alpha]_x^{25}$ | % opt purity | CSF |
|---|---|---|---|---|
| 578 | −1.003 | −47.1° | 29.3 | 1.83 |
| 546 | −1.153 | −54.1° | 29.3 | 1.83 |
| 436 | −2.093 | −98.3° | 28.9 | 1.81 |

From the original equilibrated $CDCl_3$ layer was recovered 91.7 mg of free amino ester, which was used to prepare a 5-mL solution of amino ester in $CH_2Cl_2$ (*c* 1.83), whose rotations were as follows.

| λ, nm | α obsd | $[\alpha]_x^{25}$ | % opt purity | CRF |
|---|---|---|---|---|
| 578 | 2.623 | 143.3 | 89.0 | 17.18 |
| 546 | 3.020 | 165.0 | 89.2 | 17.51 |
| 436 | 5.515 | 301.4 | 88.6 | 16.54 |

Since EDC = CRF·CSF, then EDC = 17.08 × 1.82 = 31.1.

**Deviations from Standard Procedure in EDC Determinations.** In runs 7, 8, and 15–22, $CDCl_3$–$CD_3CN$ (9:1 v:v) was employed as the organic medium, instead of the $CDCl_3$ alone used in the other runs. In runs 30 and 40, $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ was employed in the aqueous solution directly in the absence of $LiClO_4$. In runs 4–8, 13, 14, 33, 34, and 38, the G/H ratios were determined only by integrations of $^1$H NMR signals of the $CDCl_3$ layer. In all other runs, the G/H ratios reported in Table II were determined from CRF and CSF factors and eq 3. Many were checked by $^1$H NMR integrations and were found to be within 0.1. In runs 2–8, 9–14, 16–18, and 20–22, the EDC values were calculated from CRF and CSF values based on rotations of the vacuum dried hydrochloride salts precipitated from final dry (HCl gas saturated) $CH_2Cl_2$ extracts of the amino esters obtained from each layer in the distribution experiments. In representative runs, the CRF and CSF values were determined from both the free amino ester and HCl salts. The optical purities of the amino esters came out about 1% higher than those of the HCl salts. In runs 15, 19, 31, and 32 that involved *p*-$HOC_6H_4CH(CO_2CH_3)NH_2$, which is a solid, the ethyl acetate extraction procedure outlined for run 7 of Table II[4] was used to avoid optical fractionation during recovery of amino ester. In runs that involved $CH_3SCH_2CH_2CH(CO_2CH_3)NH_2$ (34 and 38), the CRF values were calculated from $^1$H NMR integrations of the $CDCl_3$ phases because of the low rotations of this ester and its salts. The $CH_3S$ diastereomeric singlets differed by about 0.08 ppm and were integrated against each other to determine CRF values. With these and the $^1$H NMR determined G/H ratios, the CSF values in the aqueous phase were calculated by difference. The signs of rotations of material isolated from each layer identified the more stable diastereomer in the $CDCl_3$ layer.

**Determination of EDC for α-Phenylethylamine Salts.** Host (SS)-2 (741 mg, 1.00 mmol) in 5.0 mL of $CDCl_3$ solution (0.20 M) was used to extract at 0 °C 6.0 mL of a $D_2O$ solution that was 0.50 M in α-phenylethylammonium perchlorate (665.2 mg, 3.00 mmol). From the aqueous layer was obtained 105 mg of free amine that provided CSF = 1.18 with a preponderance of *S*-(−) enantiomer. From the $CDCl_3$ layer was obtained 30.4 mg of amine enriched in the *R*-(+) enantiomer to give CRF = 1.61. The EDC value was 1.9 and G/H = 0.78. Optically pure (*R*)-(+)-α-phenylethylamine[6] gave $[\alpha]_{578}^{25}$ 36.9°, $[\alpha]_{546}^{25}$ 43.7°, $[\alpha]_{436}^{25}$ 73.5° (*c* 2.6, $CH_2Cl_2$), and our rotations were taken at the same concentrations in the same solvent.

Host (SS)-2 (741 mg, 1.00 mmol) in 5 mL of $CDCl_3$ solution was used to extract at 0 °C 3 mL of a $D_2O$ solution (0.75 M in $LiPF_6$) containing 473 mg (3.00 mmol) of racemic α-phenylethylammonium chloride (1.0 M). From the aqueous layer was obtained 171 mg of amine which gave a CSF of 1.13 (enriched in the *S*=(−) enantiomer). From the $CDCl_3$ was obtained 36 mg of amine which gave a CRF of 1.57 (enriched in the *R*-(+) enantiomer). The values produced an EDC of 1.8 and G/H = 0.65.

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# Cyclopeptide Alkaloids. Synthesis of the Ring System and Its Ion Affinity

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**Abstract:** Several examples of the 14-membered, para-bridged ring system of the cyclopeptide alkaloids have been synthesized via an active ester cyclization. The yield of monomeric cyclopeptide varied from 1 to 33% and was affected by the amino acid substitution pattern and amide conformation of the linear peptide precursors. Both the synthetic models and a naturally occurring cyclopeptide alkaloid, ceanothine B, bind monovalent (Li⁺) and divalent (Ca²⁺, Mg²⁺) cations.

Since the confirmation of the structure of pandamine (**1**) in 1966,[1] reports of the isolation and structure elucidation of more than 70 cyclopeptide alkaloids have appeared.[2] This class of natural product, particularly prevalent in plants of the Rhamnaceae family, is structurally well illustrated by frangulanine (**2**). The 14-membered ring, containing two amides

and incorporating a variously functionalized benzylic position (**3**), is the feature common to almost all of these natural products.

Although antibiotic, hypotensive, and antitussive properties have been ascribed to the cyclopeptide alkaloids, no definitive pharmacological activity has been demonstrated[2a] for this class

   