Host–Guest Complexation. 23. High Chiral Recognition of Amino Acid and Ester Guests by Hosts Containing One Chiral Element[1]

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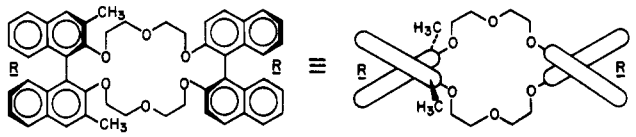
The chiral recognition properties of ten enantiomerically pure hosts toward the enantiomers of six different amino acids and their methyl esters have been examined. The hosts possessed the general structure $(A)_2D(OEOEO)_2E$, in which D is the chiral 1,1′-dinaphthyl group substituted in the 2,2′-positions with oxygens (O) attached through ethylene groups (E) to form a macrocycle. The A groups are substituted in the 3,3′-positions of the 1,1′-dinaphthyl unit to extend the chiral barrier, restrict the conformations available to the macroring, and provide the compounds with C_2 axes. The A groups are H, CH_3, CH_2OCH_3, $CH_2OC_6H_5$, $CH_2OC_6H_4OCH_3$-*p*, $CH_2SC_6H_5$, $CH_2SCH_2C_6H_5$, $\overset{\frown}{C{=}NN{=}C(C_6H_5)O}$ (I), C_6H_5, and $C_6(CH_3)_5$. The guests possessed the structure, $RCH(CO_2R')NH_3ClO_4$, in which R is CH_3, $CH_3SCH_2CH_2$, $(CH_3)_2CH$, $C_6H_5CH_2$, $C_8H_6NCH_2$, and C_6H_5, and R′ is H or CH_3. The chiral recognition was measured by distributing racemic amino acid or ester between D_2O–$CDCl_3$ layers at 0 °C (CD_3CN was sometimes present), the organic layer of which contained host. The layers were separated, the amino acid or ester was isolated from each layer, and their optical purities were determined. From the results, the differences in free energies of the diastereomeric complexes in the organic layers ($-\Delta\Delta G°$ values) were calculated, and the configurations of the more stable diastereomeric complexes were determined. The (*R*)(D) or (*S*)(L) complexes were always the more stable, except when A = H. Host $(C_6H_5)_2D(OEOEO)_2E$ was the most discriminating. It gave $-\Delta\Delta G°$ values for the six amino acids and six amino esters that ranged from a high of 1.6 kcal/mol with R = C_6H_5 and R′ = H or CH_3 to a low of 0.7 kcal/mol with R = CH_3 and R′ = CH_3. A five-step synthesis of racemic $(C_6H_5)_2D(OEOEO)_2E$ from $H_2D(OH)_2$ was developed (31% overall), as well as the resolution of this host into its enantiomers by crystallization of its diastereomeric complexes with enantiomerically pure $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ or $C_6H_5CH(CO_2H)NH_3ClO_4$. Only the (*R*)(D) or (*S*)(L) complexes crystallized. Thus the direction of the chiral bias in the extraction and crystallization separations was the same. The direction and extent of chiral recognition in these experiments is interpreted in terms of molecular model structures of the diastereomeric complexes and of model X-ray structures of complexes. The model structures are based on comparisons between the ^1H NMR spectra of the diastereomeric complexes. Comparisons are made between the intrinsic binding abilities of hosts toward NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ picrates in $CHCl_3$ at 25 °C and the hosts' capacity for chiral recognition.

Structural recognition in complexation is a useful new name given to a phenomenon as old as the discovery of catalysts for specific organic reactions. Chiral recognition in ground-state complexation in the crystalline state is as old as the discovery that racemic organic amines or acids could be enantiomerically resolved by differential crystallization of diastereomeric salts. Chiral recognition in ground-state complexation in solution has long been recognized, but only recently has it been subjected to systematic scrutiny and rationalization. The 2,2′-disubstituted 1,1′-dinaphthyl and 2,2′-disubstituted 1,1′-ditetralyl units have been incorporated into multiheteromacrocycles to provide chiral hosts that complex differentially enantiomers of amino ester and amino acid salts as guests.[2] In liquid–liquid extraction, enantiomer distribution constants (EDC) as high as 30 have been observed.[2i] Total enantiomer resolutions of both hosts and guests have been realized in liquid–liquid and liquid–solid chromatography with separation factors as high as 24.[3] Chiral recognition by hosts of amino ester salts in transport from one aqueous solution through bulk chloroform for delivery to a second aqueous solution has been used as the basis for constructing an amino ester resolving machine.[4] Enantiomeric selectivity rate factors in transport were as high as 19.[4b] Hosts such as 1, which contained two chiral elements,



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provided the highest chiral recognition in complexation. The two methyl groups of 1 extended the chiral barriers of the naphthalene rings and enforced conformations in this host, thus providing greater binding of the guest.[2j]

Other research groups have incorporated different chiral units into multiheteromacrocycles for studies of chiral recognition in ground-state complexation. Stoddart et al. have used saccharides,[5] Lehn et al.[6] and Stoddart et al.[5a]

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Scheme I

$$D(OH)_2 \xrightarrow[K_2CO_3]{CH_3I} D(OCH_3)_2 \xrightarrow[2.\ Br_2]{1.\ BuLi,\ TMEDA} (Br_2)_2D(OCH_3)_2$$

15

$$\xrightarrow[2.\ C_6H_5MgBr]{1.\ Ni[P(C_6H_5)_3]_2Cl_2} (C_6H_5)_2D(OCH_3)_2 \xrightarrow{BBr_3} (C_6H_5)_2D(OH)_2$$

16 17

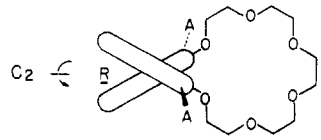
$$\xrightarrow[KOH,\ THF]{TsO(CH_2CH_2O)_5Ts} (C_6H_5)_2D(OEOEO)_2E$$

11

have used units derived from tartaric acid, and Prelog[7] has employed the 9,9′-spirobifluorene unit. Interestingly, the modified natural product desvalinoboromycin, which is also a macrocyclic polyether, shows enantiomeric selectivity for the same amino ester salts used with the totally synthetic systems.[7]

Hosts that are ideal for enantiomer separations by extraction should exhibit the following properties. (1) They should be strong complexing agents that discriminate between enantiomers of a variety of guests by large factors. (2) Both host enantiomers should be available to aid in producing either or both enantiomers of guests in optically pure form. This requirement eliminates the use of most naturally occurring, optically active starting material. (3) The hosts should be easily preparable and resolvable. This requirement eliminates the introduction of more than one chiral element into the host. (4) The compounds should be stable, recoverable, and reusable. (5) The compounds should contain C_2 axes so that the same complex is produced by complexation from either face of the macrocyclic ring. Although 1 satisfies many of these requirements, it suffers from being a weaker complexing agent than is desirable, and its synthesis is complicated by the presence of two different chiral elements.

This paper reports the results of a survey of monolocular hosts (one chiral unit) containing the general structure 2.



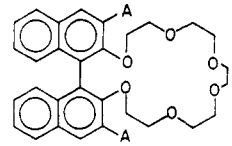
(*R*)-2, (*R*)-A$_2$D(OEOEO)$_2$E

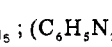
The strategy of the investigation was to prepare a variety of hosts from the same or from similar optically active starting materials and to test their resolving power by extractions of standard racemic guests. The best host was then tested as a resolving agent for a variety of guests. Finally, racemic host was prepared, and a guest commonly available in both enantiomeric forms was employed to resolve the host by crystallization.

It is convenient to use line formulas for hosts such as 2. In these formulas, D stands for the 1,1′-dinaphthyl unit substituted in the 2,2′-positions by oxygens and in the 3,3′-positions by A groups. The letter O represents oxygens, and the letter E represents CH_2CH_2 units.

Results

Syntheses. Host 3 was available from an earlier study.[8] Hosts 4–12 were prepared by conventional procedures from (*R*)- or (*S*)-D(OH)$_2$, (*R*)- or (*S*)-(CH$_3$)$_2$D(OH)$_2$, or (*R*)- or (*S*)-(HOCH$_2$)$_2$D(OH)$_2$ of maximum rotations and known configurations.[9,10] Cycle (*S*)-(ClCH$_2$)$_2$D(OEOEO)E[10]



3, A = H; D(OEOEO)$_2$E
4, A = CH$_3$; (CH$_3$)$_2$D(OEOEO)$_2$E
5, A = CH$_2$OCH$_3$; (CH$_3$OCH$_2$)$_2$D(OEOEO)$_2$E
6, A = CH$_2$OC$_6$H$_5$; (C$_6$H$_5$OCH$_2$)$_2$D(OEOEO)$_2$E
7, A = CH$_2$OC$_6$H$_4$OCH$_3$-*p*; (*p*-CH$_3$OC$_6$H$_4$OCH$_2$)$_2$-D(OEOEO)$_2$E
8, A = CH$_2$SC$_6$H$_5$; (C$_6$H$_5$SCH$_2$)$_2$D(OEOEO)$_2$E
9, A = CH$_2$SCH$_2$C$_6$H$_5$; (C$_6$H$_5$CH$_2$SCH$_2$)$_2$D(OEOEO)$_2$E
10, A =  ; (C$_6$H$_5$N$_2$OC$_2$)$_2$D(OEOEO)$_2$E
11, A = C$_6$H$_5$; (C$_6$H$_5$)$_2$D(OEOEO)$_2$E
12, A = C$_6$(CH$_3$)$_5$; ((CH$_3$)$_5$C$_6$)$_2$D(OEOEO)$_2$E

served as a key intermediate for preparing (*S*)-5 through (*S*)-9, whereas (*S*)-(CN)$_2$D(OEOEO)$_2$E (13) was prepared from (*S*)-(HOCH$_2$)$_2$D(OEOEO)$_2$E by the same procedure as that applied to racemic materials[11] (see Experimental Section). This dicyano compound (13), when treated with hydrazoic acid,[12] gave the corresponding ditetrazole (14). This substance, with benzoyl chloride, rearranged[13] to produce (*S*)-10.

$$(CN)_2D(OEOEO)_2E \xrightarrow{HN_3} \left(\text{tetrazole}\right)_2D(OEOEO)_2E \xrightarrow{C_6H_5COCl}$$

13 14

$$\left(C_6H_5\text{-}C\text{(oxadiazole)}\right)_2D(OEOEO)E$$

10

By far, the best host of the group proved to be (C$_6$H$_5$)$_2$D(OEOEO)$_2$E (11). The compound was synthesized from both racemic and optically pure D(OH)$_2$ by the sequence outlined in Scheme I in 31% yield. The racemic material was resolved into its enantiomers, making use of the fact that the enantiomeric complexes (*R*)-(C$_6$H$_5$)$_2$D(OEOEO)$_2$E·D-C$_6$H$_5$CH(CO$_2$H)NH$_3$ClO$_4$ and (*S*)-(C$_6$H$_5$)$_2$D(OEOEO)$_2$E·L-C$_6$H$_5$CH(CO$_2$H)NH$_3$ClO$_4$ are substantially more stable than their diastereomeric complexes[14a] (see next section). The commericially available enantiomeric phenylglycines were converted to their per-

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Table I. Effect of Host Structure on Chiral Recognition of Enantiomers of Standard Guests in $CDCl_3$ at 0 °C

run	A group of host $A_2D(OEOEO)_2E$	R group of guest $RCH(CO_2CH_3)$-NH_3ClO_4	org layer at equilib G^*/H^* by wt	G^*/H^* calcd[a]	dominant complex	EDC[b]	$-\Delta\Delta G°$,[c] kcal/mol
1	H	$(CH_3)_2CH$	1.0	1.0	(R)(L)	1.1	0.1
2	H	C_6H_5	0.9	1.0	(R)(L)	1.6	0.3
3	CH_3	$(CH_3)_2CH$	1.0	1.0	(R)(D)	3.3	0.6
4	CH_2OCH_3	$(CH_3)_2CH$	0.9	0.8	(S)(L)	3.7	0.7
5	$CH_2OC_6H_5$[d]	$(CH_3)_2CH$	0.9	0.9	(S)(L)	7.1	1.1
6	$CH_2OC_6H_5$	$(CH_3)_2CH$	1.0	0.9	(S)(L)	6.6	1.0
7	$CH_2OC_6H_5$	C_6H_5	0.9	1.0	(S)(L)	3.4	0.7
8	$CH_2OC_6H_4OCH_3$-p	$(CH_3)_2CH$	0.9	0.9	(S)(L)	5.7	0.9
9	$CH_2SC_6H_5$	$(CH_3)_2CH$	0.9	0.9	(S)(L)	4.5	0.8
10	$CH_2SCH_2C_6H_5$	$(CH_3)_2CH$	0.9	0.8	(S)(L)	3.5	0.7
11	$C_2ON_2C_6H_5$[e]	$(CH_3)_2CH$	0.9	0.9	(S)(L)	3.7	0.7
12	C_6H_5	$(CH_3)_2CH$	1.0	1.0	(R)(D)	7.7	1.1
13	C_6H_5	C_6H_5	1.0	1.0	(R)(D)	19.5	1.6
14	$C_6(CH_3)_5$	C_6H_5	0.9	0.7	(S)(L)	1.3	0.2

[a] Equation 5. [b] Equations 1-3. [c] Equation 4. [d] Run at 0.8 scale for all materials. [e] $C_2ON_2C_6H_5$ is I (see Discussion); run at 0.5 scale for all materials.

chlorate salts. One mole of racemic host **11** was mixed in ethyl acetate with 0.5 mol of (L)-salt, and only the (*S*)(L) complex crystallized (93%). This material was decomplexed by an extraction procedure to give (*S*)-**11** (85%). From the filtrates of the original crystallization, the host was recovered and mixed in ethyl acetate with a molar quantity of (D)-salt equal to the molar amount of (*R*)-host left in the mixture. The (*R*)(D) complex crystallized (82%) and was decomplexed (91%) to give (*R*)-host. The magnitudes of the rotations of (*R*)- and (*S*)-**11** prepared by this resolution and the sample of (*R*)-**11** prepared from (*R*)-D-$(OH)_2$ of maximum rotation were within 1.6% of one another.

The much more hindered host, (*S*)-$[C_6(CH_3)_5]_2D(OEOEO)_2E$, was prepared from (*S*)-$Br_2D(OCH_3)_2$ ((*S*)-**15**). The aryl–aryl coupling reaction of $C_6(CH_3)_5MgBr$ with (*S*)-**15** went in only 35% yield, probably due to steric effects. The yield with C_6H_5MgBr was 79%.

Determinations of the Enantiomer Distribution Constants (EDC's) and Differences in Free Energies for Diastereomeric Complexes ($-\Delta\Delta G°$). The chiral recognition of enantiomeric amino methyl ester perchlorate salts by hosts of maximum rotation was measured by distributing racemic salt between D_2O and $CDCl_3$ containing host at 0 °C. The equilibrated layers were separated, and the amounts and rotations of the ester samples recovered from each layer were determined as their hydrochloride salts. Appropriate control experiments established that no enantiomeric fractionation or racemization occurred during isolation. The method used is a refinement of that reported previously[2i] (see Experimental Section). From the results, values of the *enantiomer distribution constants* (EDC's) and values of the differences in free energies of the diastereomeric complexes in $CDCl_3$ at 0 °C ($-\Delta\Delta G°$) were calculated.[2j] Equations 1–4

$$\mathrm{CSF} = [G_B]/[G_A] \tag{1}$$

$$\mathrm{CRF}^* = \frac{[H{\cdot}G_AX^*] + [G_AX^*]}{[H{\cdot}G_BX^*] + [G_BX^*]} \tag{2}$$

$$\mathrm{EDC} = \mathrm{CSF} \times \mathrm{CRF}^* \tag{3}$$

$$\Delta\Delta G° = -RT \ln \mathrm{EDC} \tag{4}$$

$$G^*/H^* = \frac{G_i(\mathrm{CRF}^* + 1)(\mathrm{CSF} - 1)}{2H_i(\mathrm{EDC} - 1)} \tag{5}$$

were used in which CSF is the *chiral storage factor* in the aqueous phase, $[G_A]$ and $[G_B]$ are concentrations in that phase at equilibrium of guest enantiomers (A and B, the more and the less complexed in the organic phase, respectively), CRF* is the *chiral recognition factor* in the organic phase, $[H{\cdot}G_AX^*]$ and $[H{\cdot}G_BX^*]$ are the concentrations at equilibrium of the more and the less stable complexes in the organic phase, respectively, and $[G_AX^*]$ and $[G_BX^*]$ are the concentrations at equilibrium of the two uncomplexed enantiomeric salts A and B in the organic phase, respectively. The ratios of guest to host in the organic phase at equilibrium (G^*/H^*) were measured gravimetrically and corrected for losses during isolation, as determined by control runs. These values were also calculated from eq 5. In eq 5, G_i is the initial molar amount of guest and H_i is the initial molar amount of host used. The proximity of values of G^*/H^* obtained by the two independent methods provided an internal check on the validity of each experiment. The derivations and assumptions pertaining to these equations have been published.[2j] Table I reports the G^*/H^*, EDC, and $-\Delta\Delta G°$ values for hosts **3**–**12** used with either or both the standard guests, the methyl ester perchlorate salts of phenylglycine and (or) valine.

Of the hosts surveyed, the enantiomers of $(C_6H_5)_2A(OEOEO)_2E$ showed the highest chiral recognition toward the two standard guests. Accordingly, the chiral recognition shown by an enantiomer of this host toward the enantiomers of six different methyl amino ester perchlorates and their corresponding amino acid perchlorates was determined. The extraction method described above was also used with the amino ester salts except that for alanine the D_2O phase was 2 M in $LiClO_4$, which served as a salting out agent. In the amino acid perchlorate extractions, $CDCl_3$ (0.45 mol fraction in CD_3CN) was used as the organic phase, and D_2O (2 M in $LiClO_4$) was employed. The amino acids isolated from each layer were converted to their amino esters, and their weights and rotations were determined as their hydrochloride salts. Appropriate control experiments were run to demonstrate the absence of either enantiomeric fractionation or racemization during these operations. Table II reports the results.

The effect of solvent composition on chiral recognition was also studied by the extraction method with (*R*)-$(C_6H_5)_2D(OEOEO)_2E$ as host and the enantiomers of ester, $C_6H_5CH(CO_2CH_3)NH_3ClO_4$, and acid, $C_6H_5CH(CO_2H)NH_3ClO_4$, as guests. The mole fraction of CD_3CN in $CDCl_3$ was varied from 0 to 0.51. Table III reports the results. In all runs, (*R*)-host complexed (D)-ester or (D)-acid in the

Table II. Effect of Guest Structure on Chiral Recognition of Their Enantiomers by Standard Host (*R*)- or (*S*)-$(C_6H_5)_2D(OEOEO)_2E$ at 0 °C in $CDCl_3$ or $CDCl_3$-CD_3CN

run	guest, $RCH(CO_2R')NH_3ClO_4$ R	R'	mol fract of CD_3CN[a]	$[LiClO_4]$,[b] M	org layer at equilib G^*/H^* by wt	G^*/H^* calcd[c]	dominant complex	EDC[d]	$-\Delta\Delta G°$,[e] kcal/mol
1	C_6H_5	CH_3	0	0	1.0	1.0	(*R*)(D)	19.5	1.6
2	C_6H_5	H	0.45	2.0	1.0	1.1	(*R*)(D)	19.2	1.6
3	$(CH_3)_2CH$	CH_3	0	0	1.0	1.0	(*R*)(D)	7.7	1.1
4	$(CH_3)_2CH$	H	0.45	2.0		1.0	(*R*)(D)	8.1	1.1
5[f]	$C_8H_6NCH_2$[g]	CH_3	0	0	0.9	1.0	(*R*)(D)	7.9	1.1
6	$C_8H_6NCH_2$	H	0.45	2.0		1.4	(*R*)(D)	5.1	0.9
7	$C_6H_5CH_2$	CH_3	0	0	1.2	1.0	(*R*)(D)	4.4	0.8
8	$C_6H_5CH_2$	H	0.45	2.0	1.0	1.1	(*S*)(L)	6.4	1.0
9	$CH_3SCH_2CH_2$	CH_3	0	0	1.0	1.0	(*R*)(D)	6.0	1.0
10	$CH_3SCH_2CH_2$	H	0.45	2.0	1.0	1.0	(*R*)(D)	13.5	1.4
11	CH_3	CH_3	0	2.0	1.1	1.2	(*R*)(D)	3.9	0.7
12	CH_3	H	0.45	2.0	1.1	1.1	(*R*)(D)	6.4	1.0

[a] In $CDCl_3$. [b] In D_2O layer. [c] Equation 5. [d] Equations 1-3. [e] Equation 4. [f] Low solubility of guest required its initial concentration to be 0.25 M. [g] $C_8H_6NCH_2$ is

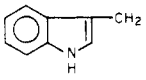


Table III. Effect of Solvent Composition on the Magnitude of Preference of Host (*R*)-$(C_6H_5)_2D(OEOEO)_2E$ for Complexing D Enantiomers of Ester $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ and of Acid $C_6H_5CH(CO_2H)NH_3ClO_4$ at 0 °C in $CDCl_3$-CD_3CN Mixtures

run	guest salt	mol fract of CD_3CN	G^*/H^*[a] by wt	G^*/H^*[a] calcd[b]	EDC[c]	$-\Delta\Delta G°$,[d] kcal/mol
1	ester	0	1.0	1.0	19.5	1.6
2	ester	0.28	0.9	1.1	13.2	1.4
3	ester	0.51	1.2	1.3	7.5	1.1
4	acid	0.15	1.0	0.8	19.9	1.6
5	acid	0.28	0.7	0.9	21.1	1.7
6	acid	0.40	0.8	0.9	23.4	1.7
7	acid	0.51	0.9	0.9	23.3	1.7

[a] Guest to host molar ratio at equilibrium in organic layer. [b] Equation 5. [c] Equation 3. [d] Equation 4.

Table IV. Free Energies of Association of Hosts ($-\Delta G°$) with NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ Picrates in $CDCl_3$ at 25 °C

host	$-\Delta G°$, kcal/mol NH_4^+	$CH_3NH_3^+$	*t*-$BuNH_3^+$	$-\Delta\Delta G°$, kcal/mol NH_4^+, $CH_3NH_3^+$	$CH_3NH_3^+$, *t*-$BuNH_3^+$	NH_4^+, *t*-$BuNH_3^+$
$Nap(OEOEO)_2E$[a]	9.5	7.5	6.9	2.0	0.6	2.6
$P(OEOEO)_2E$[b,c]	7.3	5.4	3.9	1.9	1.5	3.4
$D(OEOEO)_2E$[d]	7.8	5.5	4.1	2.3	1.4	3.7
$(CH_3)_2D(OEOEO)_2E$[a]	8.9	6.9	6.4	2.0	0.5	2.5
$(C_6H_5)_2D(OEOEO)_2E$	8.0	6.2	4.6	1.8	1.6	3.4
$[C_6(CH_3)_5]_2D(OEOEO)_2E$	7.8	5.5	2.8	2.3	2.7	5.0
$D(OEOEO)_2D$[c]	5.5	3.8	2.7	1.7	1.1	2.8
$(CH_3)_2D(OEOEO)_2P$[b,e]	6.6	4.1	2.5	2.5	1.6	4.1
$(CH_3)_2D(OEOEO)_2D$[f]	7.4	4.4	2.7	3.0	1.7	4.7
$(CH_3)_2D(OEOEO)_2D(CH_3)_2$[f]	6.2	4.2	2.5	2.0	1.7	3.7

[a] Reference 11. [b] P is the 2,2'-disubstituted biphenyl unit. [c] Reference 8. [d] Reference 15. [e] Reference 2j. [f] Reference 9.

organic layer better than the L enantiomers, with EDC factors ranging from 7.5 to 23.3. In runs 2 and 3, which involved ester and mole fractions of CD_3CN in $CDCl_3$ of 0.28 and 0.51, the EDC values decreased (from 19.5 in $CDCl_3$ alone, run 1) to 13.2 and 7.5, respectively. This decrease probably reflects the presence of substantial amounts of *uncomplexed* ester salts in the organic layer at equilibrium, for which the EDC values are not corrected.

In runs 4–7, which involved $C_6H_5CH(CO_2H)NH_3ClO_4$ as the guest, the EDC values were essentially constant at ~22 as the mole fraction of CD_3CN in $CDCl_3$ was varied. The distribution constants in the absence of host had been determined previously for this acid salt between D_2O solutions (2 M in $LiClO_4$) and solutions of CD_3CN in $CDCl_3$ at 0 °C for mole fractions ranging from 0 to 0.58.[2j] Only negligible amounts of guest were distributed in the organic phase in the absence of host. In the present study, host (*R*)-$(C_6H_5)_2D(OEOEO)_2E$ was a powerful enough complexing agent so that no $LiClO_4$ was needed in the aqueous phase to salt out the guest.

Determinations of the Free Energies of Complexation of Biaryl Hosts with Ammonium, Methylammonium, and *tert*-Butylammonium Picrates. Table IV reports the free energies ($-\Delta G°$ values) of association[14b] of a variety of hosts containing biaryl units in chloroform at 25 °C. The extraction technique was used in which the picrate salts in water were equilibrated with chloroform both in the presence and in the absence of host.[11,2j] The $-\Delta G°$ values were calculated from the extraction, distribution, and association constants[16] and are

significant to about ±0.1 kcal/mol.

Discussion

A Chiral-Breeding Cycle. The hosts used in this investigation all contained only one chiral unit and were therefore monolocular. The steric barriers of their single dinaphthyl units occupy space in only one place that otherwise would be available to parts of guest bound to a face of the macroring. The *dilocular* host of the previous investigation (1)[2j] contained two dinaphthyl units, each of which was different. This structural feature complicated the synthesis of 1. Either two different enantiomerically pure dinaphthols had to be prepared prior to ring closure in a stereodirected synthesis or diastereomers had to be separated, followed by an enantiomeric resolution of the desired racemate.

Since host $(C_6H_5)_2D(OEOEO)_2E$ showed the highest chiral recognition toward standard guests (Table II), a simple chiral-breeding cycle was developed for the substance to facilitate its synthesis. Host $(R)(S)$-$(C_6H_5)_2D(OEOEO)_2E$, prepared in 31% yield from readily available starting materials, was resolved by *crystallizations* of (R)(D) and (S)(L) complexes with commercially available D- and L-$C_6H_5CH(CO_2H)NH_3ClO_4$ as guests. The diastereomerically pure complexes were readily decomposed by extractions to give (R)- and (S)-$(C_6H_5)_2D(OEOEO)_2E$. These enantiomeric hosts could then be used to resolve DL-$C_6H_5CH(CO_2H)NH_3ClO_4$ into its enantiomers by either crystallization or extraction procedures (eq 6 and 7). These operations constitute a simple, chiral-breeding cycle. Alternatively, ester $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ could be substituted for the acid in this scheme.

$$(R)(S)\text{-host} \xrightarrow[\text{with D- or L-guest and decomplexation}]{\text{crystallization}} (R)\text{- or } (S)\text{-host} \quad (6)$$

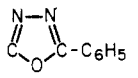
$$\text{DL-guest} \xrightarrow[(R)\text{- or } (S)\text{-host and decomplexation}]{\text{countercurrent extraction or crystallization with}} \text{D- or L-guest} \quad (7)$$

In the crystallizations, 0.5 mol of pure enantiomer and 1 mol of racemate were always used, and, in all cases, only the (R)(D) or (S)(L) complexes crystallized. The direction of the chiral bias in the crystallizations and extraction experiments was the same. Although the positions of equilibria between diastereomeric complexes in solution favor crystallization of the more abundant complex, either the kinetics of crystallization or thermodynamic stability of diastereomeric crystals ultimately determines the stereochemical outcome of the crystallization experiments.

Effect of Side Chains Attached to Hosts on Their Chiral Recognition of Standard Guests. The methyl ester perchlorates of valine and phenylglycine were chosen as standard guests to screen hosts for chiral recognition. These hosts were selected because their hydrocarbon side chains ($(CH_3)_2CH$ and C_6H_5) have high steric requirements. The enantiomer distribution constants (EDC values) of Table I range from a low of 1.1 for $D(OEOEO)_2E$ with $(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$ to a high of 19.5 for $(C_6H_5)_2D(OEOEO_2)E$ with $C_6H_5CH(CO_2CH_3)NH_3ClO_4$. These extremes provide a range in free-energy differences ($-\Delta\Delta G°$) for the diastereomeric complexes in $CDCl_3$ at 0 °C of 0.1–1.6 kcal/mol.

All hosts with substituents in the 3,3′-positions on the dinaphthyl unit gave the same direction of chiral bias in complexation with the two standard guests (Table I). The (R)(D) or (S)(L) complexes proved more stable than the (R)(L) or (S)(D) diastereomers. What little chiral recognition host (R)-$D(OEOEO)_2E$ (no 3,3′-substituents) exhibited favored the (R)(L) complex. Although chiral recognition varied between 0.2 and 1.6 kcal/mol as nine different substituents were introduced into the 3,3′-positions of the host, none of the substituents changed the direction of the chiral bias.

The values (in kcal/mol) of $-\Delta\Delta G°$ for complexation of ester $(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$ decreased as the host substituents were changed as follows: C_6H_5 and $CH_2OC_6H_5$, 1.1; $CH_2OC_6H_4OCH_3$-*p*, 0.9; $CH_2SC_6H_5$, 0.8; CH_2OCH_3, $CH_2SCH_2C_6H_5$, and I, 0.7; CH_3, 0.6. With $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ as guest, they decreased as the



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host substituents were changed as follows: C_6H_5, 1.6; $CH_2OC_6H_5$, 0.7; $C_6(CH_3)_5$, 0.2. Thus with valine ester salt as the guest, only a 0.5-kcal spread in $-\Delta\Delta G°$ values was observed as substituents in the host were changed. With phenylglycine ester salt, the spread was 1.4 kcal/mol, which is about three times as large. These results indicate that $(C_6H_5)_2D(OEOEO)_2E$ provides the highest chiral recognition toward standard guests of the monolocular systems examined to date. This host was therefore used in a survey of chiral recognition of a broader spectrum of guests.

Survey of the Chiral Recognition by Hosts (R)- and (S)-$(C_6H_5)_2D(OEOEO)_2E$ of Enantiomers of Amino Acid and Ester Salt Guests. The results of Table II indicate that for the six racemic ester and six racemic acid perchlorate salts examined, the EDC values ranged from a high of 19.5 with the guest $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ to a low of 3.9 with $CH_3CH(CO_2CH_3)NH_3ClO_4$. The corresponding differences in free energy for the diastereomeric complexes were 1.6 and 0.7 kcal/mol. These $-\Delta\Delta G°$ values are the highest that have been observed for amino *acid* salts. The only value for an amino *ester* salt higher than the 1.6 kcal/mol observed for $(C_6H_5)_2D(OEOEO)_2E$ binding $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ was the value of 1.9 kcal/mol reported for $(CH_3)_2D(OEOEO)_2D$ or $(CH_3)_2D(OEOEO)_2T$ binding $C_6H_5CH(CO_2CH_3)NH_3PF_6$.[2i] In $(CH_3)_2D(OEOEO)_2T$, T is the 2,2′-disubstituted 1,1′-ditetralyl unit. When $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ was the guest and $(CH_3)_2D(OEOEO)_2D$ the host, $-\Delta\Delta G°$ = 1.7 kcal/mol.[2i] Thus the hexafluorophosphate salt gave a higher value than the perchlorate with $(CH_3)_2D(OEOEO)_2D$, and the same might be true for $(C_6H_5)_2D(OEOEO)_2E$. Toward the six acid guests, $C_6H_5CH(CO_2H)NH_3ClO_4$, $(CH_3)_2CHCH(CO_2H)NH_3ClO_4$, $C_6H_5CH_2CH(CO_2H)NH_3ClO_4$, $C_8H_6NCH_2CH(CO_2H)NH_3ClO_4$, $CH_3SCH_2CH_2CH(CO_2H)NH_3ClO_4$, and $CH_3CH(CO_2H)NH_3ClO_4$, the host $(C_6H_5)_2D(OEOEO)_2E$ showed higher chiral recognition than $(CH_3)_2D(OEOEO)_2D$ by 0.3, 0.6, 0.3, 0.5, 0.9, and 0.5 kcal/mol, respectively.[2j] Clearly, $(C_6H_5)_2D(OEOEO)_2E$ is the best overall host for chiral recognition that has yet been designed and tested.

Interestingly, the chiral recognition exhibited by $(C_6H_5)_2D(OEOEO)_2E$ toward the amino *acid* salts was generally equal to or higher than that shown toward the amino *ester* salts. The differences depended on the nature of the side chain (R) of the guest (Table II). Thus with R = C_6H_5, both acid and ester gave $-\Delta\Delta G°$ = 1.6 kcal/mol,

(16) R. C. Helgeson, T. L. Tarnowski, and D. J. Cram, *J. Org. Chem.* 44, 2538–2550 (1979).

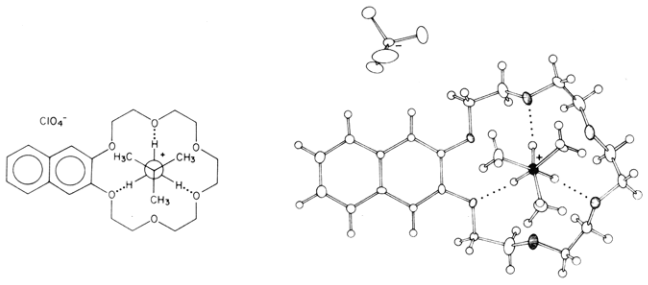


Figure 1. Concept of structure for the complex between Nap(OEOEO)$_2$E and $(CH_3)_3CNH_3ClO_4$ and the observed X-ray structure.

and with R = $(CH_3)_2CH$, they both gave 1.1 kcal/mol. When R was $C_6H_5CH_2$, $CH_3SCH_2CH_2$, or CH_3, the $-\Delta\Delta G°$ values of the acids exceeded those of the corresponding esters by 0.2, 0.4, and 0.3 kcal/mol, respectively. This behavior contrasts with that of the host $(CH_3)_2$D(OEOEO)$_2$D, which showed somewhat higher chiral recognition toward esters than acids. The same was true with $(C_6H_5)_2$D(OEOEO)$_2$E complexing the tryptophane ester vs. the acid.

In most of the runs of Tables I and II, the ratios of guest to host in the organic phase at equilibrium were close to unity ($G^*/H^* \approx 1$). This indicates that one-to-one complexes were formed and that the host was a strong enough binder to draw approximately 1 equiv of guest into the organic layer. Values of G^*/H^* in similar experiments with $(CH_3)_2$D(OEOEO)$_2$D ranged from 0.2 to 1.0.[2i,j] Thus the monolocular systems are more efficient binders than the dilocular system.

Effect of Solvent on Chiral Recognition in Complexation by Host $(C_6H_5)_2$D(OEOEO)$_2$E of Guest $C_6H_5CH(CO_2H)NH_3ClO_4$. Table III contains $-\Delta\Delta G°$ values for formation of the diastereomeric complexes. These values remained essentially constant as the organic phase was changed from 0.15 to 0.51 mol fraction of CD_3CN in $CDCl_3$. This result contrasts with those involving the dilocular system $(CH_3)_2$D(OEOEO)$_2$D complexing the same guest. With this system, as the mole fraction of CD_3CN in $CDCl_3$ changed from 0.35 to 0.40 to 0.45 to 0.52 to 0.58, the $-\Delta\Delta G°$ values decreased from 1.41 to 1.38 to 1.32 to 1.25 to 1.14 kcal/mol, respectively (see runs 10–14 of Table III of ref 2j). This difference between the monolocular and dilocular hosts is attributed to the stronger binding power of the former, whose complexes remain highly structured even in $CDCl_3$ rich in CD_3CN.

Structural Recognition in Complexation through Opposition of Electronic and Steric Effects. Table IV reports the results of a survey of the free energies of complexation in $CDCl_3$ at 25 °C of ten hosts and three guests. The guests were picrate salts of NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$, whose steric requirements for complexation are expected to vary over a wide range. The roughly planar and lipophilic crown compound Nap(OEOEO)$_2$E was used as a standard host because it was expected to minimize steric inhibition of complexation with the most sterically hindered $(CH_3)_3CNH_3^+$ ion. The anticipated tripod crystal structure for the complex between $(CH_3)_3CNH_3ClO_4$ and Nap(OEOEO)$_2$E of Figure 1[17] indicates there is little repulsion between the *tert*-butyl group and the support structure for the binding oxygens of the hosts. A similar tripod crystal structure was observed for the complex between $(CH_3)_3CNH_3ClO_4$ and $(CH_3)_2$D(OEOEO)$_2$E (see Figure 2).[18] In this structure,

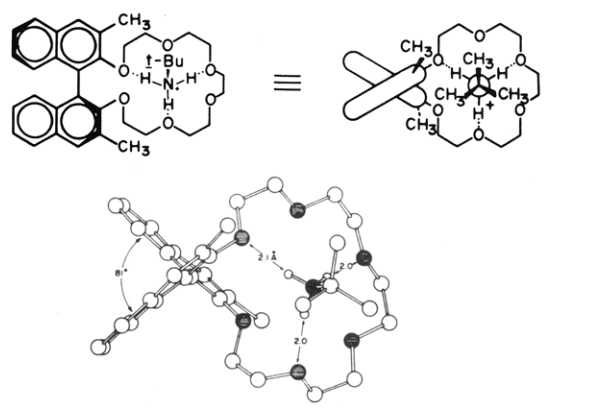


Figure 2. Concept of structure for the complex between $(CH_3)_2$D(OEOEO)$_2$E and $(CH_3)_3CNH_3ClO_4$ and the observed X-ray structure.

one methyl group of the host contacts two of the guest, and the steric requirements of these groups are accommodated by there being a larger than 90° dihedral angle between the best plane of the macroring and the plane of the naphthalene ring on the complexed face of the host.[19] Similar tripod structures for hosts with NH_4X probably contain contact ion pairs bound through the hydrogen bond, $NH^+\cdots X^-$.[20] A tripod structure for the complexes involving CH_3NH_3X or $(CH_3)_3CNH_3X$ would require a partially host-separated ion pair, $\overset{+}{N}$ Cl^-, similar to those observed in the X-ray structures of Figures 1 and 2.

The values of $-\Delta G°(CH_3NH_3^+)$ (in kcal/mol) decrease as the structures of the hosts are changed in the following order: Nap(OEOEO)$_2$E, 7.5; $(CH_3)_2$D(OEOEO)$_2$E, 6.9; $(C_6H_5)_2$D(OEOEO)$_2$E, 6.2; $[C_6(CH_3)_5]_2$D(OEOEO)$_2$E, 5.5; D(OEOEO)$_2$E, 5.5; P(OEOEO)$_2$E, 5.4; $(CH_3)_2$D(OEOEO)$_2$D, 4.4; $(CH_3)_2$D(OEOEO)$_2$D$(CH_3)_2$, 4.3; $(CH_3)_2$D(OEOEO)$_2$P, 4.1; D(OEOEO)$_2$D, 3.8. Thus substitution of $(CH_3)_2$D, $(C_6H_5)_2$D, $[C_6(CH_3)_5]_2$D, or D units for the Nap unit in Nap(OEOEO)$_2$E decreases binding by 0.6, 1.3, 2.0, and 2.0 kcal/mol, respectively. Any substituent in the 3,3′-positions of the 1,1-dinaphthyl unit in CPK molecular models forces a conformation on the two OCH_2 substituents attached at the 2,2′-positions which resembles that of a gauche ethylene glycol unit. This enforced structure is good for binding both because the two oxygens are well placed to cooperatively contact the NH^+ group and because complexing probably compensates for electron–electron repulsion.[21] This effect explains why $(CH_3)_2$D(OEOEO)$_2$E and $(C_6H_5)_2$D(OEOEO)$_2$E are better binders than D(OEOEO)$_2$E. The increased steric requirements of the 3-substituents in the sequence CH_3, C_6H_5, and $C_6(CH_3)_5$ correlate with the order, $(CH_3)_2$D(OEOEO)$_2$E > $(C_6H_5)_2$D(OEOEO)$_2$E > $C_6(CH_3)_5$D(OEOEO)$_2$E in binding. Steric inhibition of binding starts to become important with the introduction of phenyl and, particularly, pentamethylphenyl groups in the 3-positions. As expected, the four dilocular systems are poorer receptors of $CH_3NH_3^+$ than their monolocular counterparts by 1.7–2.7 kcal/mol. Substitution of a biphenyl (P) unit for a dinaphthyl (D) unit in $(CH_3)_2$D(OEOEO)$_2$D leads to a

(17) We warmly thank Professor K. N. Trueblood for information regarding this structure in advance of publication.

(18) I. Goldberg, *J. Am. Chem. Soc.*, **102**, 4106 (1980).

(19) For an X-ray structure of an alkylammonium–crown complex designed not to form, see I. Goldberg, *J. Am. Chem. Soc.*, **99**, 6049–6057 (1977).

(20) Prelog[7] has reported an X-ray structure of a host complexed with NH_4SCN, which contains the $NH^+\cdots N^-CS$ moiety.

(21) (a) K. E. Koenig, G. M. Lein, P. Stückler, T. Kaneda, and D. J. Cram, *J. Am. Chem. Soc.*, **101**, 3553–3566 (1979); (b) D. J. Cram. T. Kaneda, R. C. Helgeson, and G. M. Lein, *ibid.*, **101**, 6752–6754 (1979).

0.2–0.8-kcal/mol drop in binding toward the three guests NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ (Table IV). The greater rigidity of the dinaphthyl compared to the diphenyl unit provides hosts better organized for binding prior to complexation.

The $-\Delta\Delta G(NH_4^+, CH_3NH_3^+)$ parameters for the six monolocular systems vary between 1.8 and 2.3 kcal/mol and between 1.7 and 3.0 kcal/mol for the dilocular systems. The fact that there is no visible correlation of this parameter with structure suggests the existence of many cancelling effects, none of which dominate, particularly in the dilocular series. The lack of variation in the monolocular series strongly suggests that all their $CH_3NH_3^+$ complexes possess the tripod structure.

The values of the $-\Delta\Delta G°(CH_3NH_3^+, t\text{-}BuNH_3^+)$ parameter provide an interesting probe of the outcome of the opposition of binding and steric effects on binding free energies. As expected from the X-ray structures in Figures 1 and 2, Nap(OEOEO)$_2$E and $(CH_3)_2$D(OEOEO)$_2$E can bind $(CH_3)_3CNH_3^+$ without development of serious repulsions. Accordingly, these hosts provide the lowest values of this parameter, 0.6 and 0.5 kcal/mol, respectively. Interestingly, the less preorganized P(OEOEO)$_2$E hosts provide values of 1.5 and 1.4 kcal/mol, respectively. These increases in value may reflect the higher degree of organization required for hosts to complex $(CH_3)_3CNH_3^+$ than to complex $CH_3NH_3^+$.

The most orderly and informative sequence in the series involves the parameter values (kcal/mol) of 0.5 for $(CH_3)_2$D(OEOEO)$_2$E, 1.6 for $(C_6H_5)_2$D(OEOEO)$_2$E, and 2.7 for $[C_6(CH_3)_5]_2$D(OEOEO)$_2$E. Steric inhibition to complexation of $(CH_3)_3CNH_3^+$ is clearly visible in this series and correlates with what is observed in molecular models. The tripod structure for the complex with $(C_6H_5)_2$D-(OEOEO)$_2$E can be assembled but is tight, whereas that structure for $[C_6(CH_3)_5]_2$D(OEOEO)$_2$E cannot be assembled. The complex between the latter host and $(CH_3)_3CNH_3^+$ probably involves only one or two hydrogen bonds to oxygens remote from the steric barrier.

The $-\Delta\Delta G°(CH_3NH_3^+, t\text{-}BuNH_3^+)$ values (in kcal/mol) for the dilocular systems were as follows: D(OEOEO)$_2$D, 1.1; $(CH_3)_2$D(OEOEO)$_2$P, 1.6; $(CH_3)_2$D(OEOEO)$_2$D, 1.7; $(CH_3)_2$D(OEOEO)$_2$D$(CH_3)_2$, 1.7. The proximity of these values to one another suggests that the $CH_3NH_3^+$ complexes possess the tripod structure and the $(CH_3)_3CNH_3^+$ complexes less ordered structures, possibly involving only one or two hydrogen bonds. This interpretation is compatible with the fact that all four dilocular hosts have $-\Delta G°(t\text{-}BuNH_3^+)$ values of only 2.5–2.7 kcal/mol, close to that observed for $[C_6(CH_3)_5]$D(OEOEO)$_2$E (2.8 kcal/mol). Complexes with only one or two hydrogen bonds are relatively nonstructured and, therefore, are relatively insensitive to steric effects.

The value of the $-\Delta\Delta G°(NH_4^+, t\text{-}BuNH_3^+)$ parameter provides a measure of the ability of a host to recognize the difference between complexing NH_4X and $(CH_3)_3CNH_3X$. This parameter measures the maximum structural recognition available to a host. The hosts arranged in decreasing order of the values of this parameter (in kcal/mol) are as follows: $[C_6(CH_3)_5]_2$D(OEOEO)$_2$E, 5.0; $(CH_3)_2$D-(OEOEO)D, 4.7; $(CH_3)_2$D(OEOEO)$_2$P, 4.1; D(OEOEO)$_2$E, 3.7; $(CH_3)_2$D(OEOEO)$_2$D$(CH_3)_2$, 3.7; $(C_6H_5)_2$D(OEOEO)$_2$E, 3.4; P(OEOEO)$_2$E, 3.4; D(OEOEO)$_2$D, 2.8; Nap-(OEOEO)$_2$E, 2.6; $(CH_3)_2$D(OEOEO)$_2$E, 2.5. These values reflect both the intrinsic hydrogen bonding affinity of the host toward NH_4X and the maximum steric inhibition it offers to binding $(CH_3)_3CNH_3X$. High values represent a good balance between these effects, and low values represent the dominance of one over the other. The highly hindered and yet fairly strongly binding monolocular system $[C_6(CH_3)_5]_2$D(OEOEO)$_2$E has the highest value for this parameter (5.0 kcal/mol). Of the total binding capacity of this system for NH_4X, 64% emerges as structural recognition. The dilocular yet fairly strongly binding system $(CH_3)_2$D(OEOEO)$_2$D, with its steric barriers more evenly distributed throughout the binding system, has the next highest value of 4.7 kcal/mol. Thus 63% of its binding capacity is available for structural recognition. Host $(C_6H_5)_2$D(OEOEO)$_2$E gives a middle value of 3.4 kcal/mol, which represents 43% of its total potential binding capacity. Standard systems Nap(OEOEO)$_2$E and $(CH_3)_2$D(OEOEO)$_2$E are at the low end of the scale with values of 2.6 and 2.5 kcal/mol, respectively. Only 27–28% of their total binding potential turns up as structural recognition. They are hardly hindered enough to greatly inhibit complexation of $(CH_3)_3CNH_3X$.

The important question arises as to whether any of these parameters correlate with chiral recognition of the amino acid and amino ester salts discussed in the other sections. We had hoped that the $-\Delta\Delta G°(CH_3NH_3^+, t\text{-}BuNH_3)$ parameters would correlate with chiral recognition well enough to serve as a simple screen for hosts.[22] Unfortunately, no correlation is evident. The hosts designed thus far for chiral recognition of enantiomers of alkylammonium salts divide roughly into the three classes of good, average, and poor. Of the hosts in Table IV, $(C_6H_5)_2$D(OEOEO)$_2$E and $(CH_3)_2$D(OEOEO)$_2$D are good and give values for the parameter of 1.6 and 1.7 kcal/mol, respectively. Hosts $(CH_3)_2$D(OEOEO)$_2$E, D(OEOEO)$_2$D, and $(CH_3)_2$D-(OEOEO)$_2$D$(CH_3)_2$ are average and give values of 0.5, 1.1, and 1.7 kcal/mol, respectively. The poorest hosts for chiral recognition are D(OEOEO)$_2$E and $[C_6(CH_3)_5]$D-(OEOEO)$_2$E, which give values of 1.4 and 2.7 kcal/mol, respectively. The absence of a correlation probably reflects the absence of a single dominating effect and cancellation of many small effects. One feature that probably destroys any possible correlation of chiral recognition with the values of $-\Delta\Delta G°(CH_3NH_3^+, t\text{-}BuNH_3^+)$ is that as steric inhibition of complexation increases, complexes probably change their structures by losing some of their hydrogen bonds. Another is that π–π and van der Waals attractive forces probably contribute to the binding of ester and acid salt guests to hosts, and these are absent or of less importance with the simple alkylammonium complexes.

Structural Basis for Chiral Recognition by (*R*)- or (*S*)-$(C_6H_5)_2$D(OEOEO)$_2$E of the Enantiomers of the Amino Acid and Ester Salts. Ideally, X-ray structures of both diastereomeric complexes of (*R*)-$(C_6H_5)_2$D-(OEOEO)$_2$E and D- and L-$C_6H_5CH(CO_2H)NH_3ClO_4$ would be available and could serve as the basis of discussion. In practice, the often whimsical propensities of the complexes to crystallize provided only the more stable diastereomer, and that in a form unsuitable for simple structure determination. The discussion will correlate facts concerning ^1H NMR spectra and stereochemical results with expectations based on CPK molecular model examination and with X-ray structures of model complexes.

The X-ray structure of the complex between $(CH_3)_3C-NH_3ClO_4$ and $(CH_3)_2$D(OEOEO)$_2$E in Figure 2[18] is in full accord with expectations based on CPK molecular model examination of the complex. It is held together by three $NH^+\cdots O$ and three $N^+\cdots O$ interactions. The best plane of the macroring is normal to the axis of the C–N bond. The dihedral angles of the H–N–C–C groups are about 60°.

(22) R. C. Helgeson, T. L. Tarnowski, J. M. Timko, and D. J. Cram. *J. Am. Chem. Soc.*, **99**, 6411–6418 (1977).

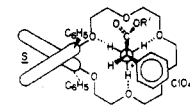
The dihedral angle around the naphthyl–naphthyl bond (82°) is such as to allow the aryl oxygen-to-naphthyl oxygen distance to adjust to 3.26 Å, close to those of the OCH_2CH_2O oxygens. The angle between the naphthyl–naphthyl bond and the best plane of the macroring is about 40°, which leaves the naphthyl methyl of the host and two of the three methyl groups of the guest close to one another but uncompressed. These three methyls possess a "gear"-type arrangement, which might dictate which set of three oxygens the host selects for hydrogen bonding. The alternative tripod structure sets the guest deeper into the hole of the host, compresses one methyl of the guest somewhat against one naphthyl of the host, compresses a second methyl of the guest against the methyl of the host, and eclipses the three N–H with the three CH_3–C bonds. Finally, the methyl of the host close to the unbound face of the complex sterically inhibits conformations of the proximate atoms 2–7 of the macroring system ($ArOC^2H_2C^3H_2O^4C^5H_2C^6H_2O^7$) which might otherwise increase the distance between the host's and guest's methyl groups on the opposite face.

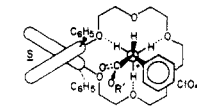
The complexes of the present investigation probably are similarly structured. The exceptions are that in place of the three CH_3 groups of the guest are substituted an H, an R group, and either a CO_2H or a CO_2CH_3 group. In place of the methyl group in all hosts but $(CH_3)_2$D-(OEOEO)$_2$E are substituted bulkier groups. Those located on the complexing face extend the chiral barrier and crowd the guest substituents. Those attached on the opposite side force the chiral center of the bound guest closer to the chiral barrier of the host. Both effects should increase the chiral recognition as the bulk of the substituents increases up to the point where the tripod binding of the more stable diastereomer is still sterically feasible. After that point, both diastereomeric complexes should go to less structured and less bound complexes involving fewer hydrogen bonds, and chiral recognition should decrease.

The pattern of results is generally consistent with these expectations. As the 3,3′-substituents of the hosts are changed from H to CH_3 to $CH_2OC_6H_5$ to C_6H_5 to $C_6(CH_3)_5$, the chiral recognition toward the standard guests increases, reaches a maximum with C_6H_5, and then decreases sharply with $C_6(CH_3)_5$. Although molecular models of the diastereomeric complexes of the tripod variety between $[C_6(CH_3)_5]_2$D(OEOEO)$_2$E and $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ can be assembled, considerable steric compression is visible. The actual complexes of this host–guest combination are probably held together by fewer than three $NH^+\cdots O$ bonds.

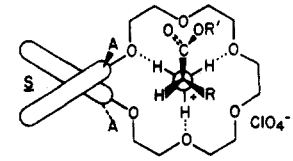
The direction of the chiral bias in complexation of all amino acid or ester salts by hosts of the structure A_2D-(OEOEO)$_2$E favors the (*R*)(D) or (*S*)(L) over the (*R*)(L) or (*S*)(D) diastereomers. The fact that nine different A groups of the host A_2D(OEOEO)$_2$E and six different R groups, each with two different R′ groups, of the guest RCH-(CO_2R′)NH_3ClO_4 are involved in this generalization suggests that certain structural interactions common to all their complexes dominate other opposing interactions. The additional fact that complexes with D(OEOEO)$_2$E as host give very low chiral recognition with the opposite chiral bias suggests that interactions between the A groups and guest substituents govern the direction of the chiral bias. Of the substituents attached to the asymmetric center of guests RC*H(CO_2R′)NH_3ClO_4, the H and NH_3ClO_4 groups are constant, the CO_2R′ groups are nearly constant, and the R group varies widely in both its steric requirements and electronic character. The NH_3ClO_4 group is occupied with the macroring of the host, which leaves the interactions of the H and CO_2R′ with the A groups as the feature that controls the direction of the chiral bias. It therefore seems reasonable to locate the H and CO_2R′ groups close to and the R groups distant from the A groups in hypothetical structures for the diastereomeric complexes, (*S*)(L)-18 and (*S*)(D)-18. These structures generally resemble the X-ray structure of Figure 2.

Chart I

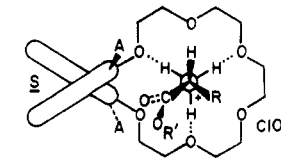




Guest	(S)(L)-19 R′=CH_3	(S)(L)-19 R′=H	Free Guests R′=CH_3	Free Guests R′=H	(S)(D)-19 R′=CH_3	(S)(D)-19 R′=H
NCH	4.49	4.47	5.13	5.09	4.51	4.38
	6.58	6.52	7.47	7.47	6.95	7.02
OCH_3	3.70		3.80		3.65	



(*S*)(L)-18 (more stable)



(*S*)(D)-18 (less stable)

These diastereomeric structures differ only in the positions of the H and CO_2R groups relative to the naphthyl–A groups. In the more stable (*S*)(L)-18 structures, the CO_2R and A groups extend roughly in the same directions, whereas in the (*S*)(D)-18 structures, they extend in opposite directions. In CPK models of (*S*)(L)-18 structures, the A groups contact the face of the CO_2R′ and the C*H groups to provide what we interpret to be van der Waals attractive interactions. Because of the electron-attracting effects of the attached NH_3^+ and the two oxygens, the C*HC group as a whole is positive, and its attractive interaction with the polarizable A groups in effect provides a weak additional binding site for the complexes. A similar type of interaction appeared to be present in the X-ray structure of the complex, (*SS*)(*R*)-D(OEOEO)$_2$D·C_6H_5CH-(CO_2CH_3)NH_3PF_6.[2i,19]

In molecular models of the less stable (*S*)(*R*)-18 diastereomer, this additional binding site is less effective because the CO_2R′ group extends in a direction opposite to that in which the A group extends and less contact points are available. This hypothesis, although compatible with the facts, is tentative and oversimplified. The hydrogen bonds act as the main binding interactions which provide a tripod structure. Once together, the sum of secondary contact interactions between parts of the host and guest modify the overall binding energies and are the source of the chiral recognition. The highest chiral efficiency observed thus far is only about 33%[2j] which indicates that these secondary contact interactions are weaker than the primary hydrogen bonding interactions.

Host $(C_6H_5)_2$D(OEOEO)$_2$E shows the highest chiral recognition toward a variety of guests that has been observed thus far. In general, $C_6H_5CH(CO_2R')NH_3ClO_4$ as guest has elicited the highest chiral recognition by those hosts that have been examined. Accordingly, the ^1H NMR spectra in $CDCl_3$–CD_3CN of the diastereomeric complexes

between $(C_6H_5)_2D(OEOEO)_2E$ and $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ and between $(C_6H_5)_2D(OEOEO)_2E$ and $C_6H_5CH(CO_2H)NH_3ClO_4$ were taken, as well as those of the free guests. Chart I records the chemical shifts in parts per million upfield from Me_4Si of those guest protons which were assigned, along with structures for the diastereomeric complexes (*S*)(L)-**19** and (*S*)(D)-**19**. The highest EDC's for these complexes were both about 20, and the chiral recognition was about 1.6–1.7 kcal/mol (Table III).

In CPK molecular models of (*S*)(L)-**19** and (*S*)(D)-**19**, the C_6H_5 group of the host on the side remote from the bound guest occupies a plane nearly parallel to the best plane of the macroring. This phenyl group in effect provides a supporting floor for most of the macroring and forces the chiral elements of host and guest on the opposite face close to one another. In the more stable (*S*)(L)-**19** isomers, the faces of the other C_6H_5 of the host and the CO_2 group of the guest contact one another centrally without strain in roughly parallel planes. In the less stable (*S*)(*R*)-**19** isomers, the planes of the CO_2 groups are again roughly parallel to that of the C_6H_5 group of the host, but the contact between the groups is only partial. In both types of diastereomeric structures, the face of the C_6H_5 groups of the guests extends far enough to contact several atoms of the macroring.

These structures are consistent with the ^1H NMR changes in the values of δ of the guest protons upon complexation. Chart I indicates that the NCH proton moves upfield in the four complexes by 0.62–0.71 ppm. In molecular models of all four complexes, this proton is situated in the shielding region of the C_6H_5 group of the host. The ortho protons of the C_6H_5 groups of the guests move upfield upon formation of the (*S*)(L) complexes by 0.89–0.95 ppm and by 0.45–0.52 ppm upon formation of the (*S*)(D) complexes. At ambient temperatures at which the spectra were taken, the two ortho protons are undoubtedly averaging. In the uncomplexed guest, one ortho proton is possibly in the deshielding region of the CO_2 group. In models of the (*S*)(L) structures, this proton moves into the middle of the shielding region and is moved far upfield. In models of the (*S*)(D) structures, this proton moves less centrally into the shielding region of the CO_2 group and is therefore moved upfield by a substantial but lesser extent. Upon formation of the (*S*)(L) complex, the CH_3 of the ester guest moved upfield by only 0.1 ppm and in formation of the (*S*)(*R*) complex by 0.15 ppm. In models for both structures, the methyl groups must occupy positions remote from the macroring and, at best, only on the edge of the shielding region of the C_6H_5 group of the host. Thus the structures postulated for the diastereomeric complexes accommodate the direction of chiral bias, the X-ray structures of other complexes, the ^1H NMR spectra, and expectations based on molecular model examination.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover or Mel-Temp apparatus and are uncorrected. Mass spectra were taken on an AEI MS-9 mass spectrometer at 70 eV. The ^1H NMR spectra were taken on either a Varian T-60 or Bruker WP 200 spectrometer in $CDCl_3$. Chemical shifts are given in δ units with Me_4Si as an internal standard. Optical rotations were determined with a Perkin-Elmer 141 polarimeter in water-jacketed cells maintained at 25 °C. Gel permeation chromatography was performed on a $^3/_8$ in. × 20 ft column of 100-Å Styragel beads (Waters Associates, Inc.; 37–75 μm particle size; exclusion limit mol wt 1500 in CH_2Cl_2; flow rate of 4 mL/min; pressure of 400–600 psi).

(*R*)-2,3:4,5-Bis[1,2-(3-methylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*R*)-4). To a solution of 3.0 g (9.5 mmol) of (*R*)-3,3'-dimethyl-2,2'-dihydroxy-1,1'-dinaphthyl of maximum rotation[9] and 5.3 g (9.7 mmol) of pentaethylene glycol ditosylate[23] in 800 mL of THF stirred under N_2 at 25 °C was added 1.3 g (19.7 mmol) of KOH (85%) in 5 mL of H_2O. The mixture was refluxed for 96 h, and the crude product was isolated by the usual evaporative, extractive, drying, and evaporative procedure.[11] The crude product was chromatographed on alumina, as was racemic **4**,[11] and then submitted to gel-permeation chromatography to give 2.95 g (60%) of (*R*)-**4** as an oil: retention volume of 195 mL; ^1H NMR identical with that of racemic **4**;[11] $[\alpha]^{25}_{589}$ +38.2°, $[\alpha]^{25}_{578}$ +39.1°, $[\alpha]^{25}_{546}$ +45.0°, $[\alpha]^{25}_{436}$ +88.2° (*c* 0.68, $CHCl_3$). Anal. Calcd for $C_{32}H_{36}O_6$: C, 74.40; H, 7.02. Found: C, 74.27; H, 7.00.

(*S*)-2,3:4,5-Bis[1,2-[3-(methoxymethyl)naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-5). To a suspension of 1.0 g of (*S*)-$(HOCH_2)_2D(OEOEO)_2E$ of maximum rotation[10] and 2.0 g (41.7 mmol) of NaH (50% mineral oil suspension) in 150 mL of THF stirred under N_2 at 25 °C was added 4.0 g (28 mmol) of iodomethane. The mixture was refluxed for 12 h and cooled, and the excess NaH was decomposed by the dropwise addition of CH_3OH. The mixture was shaken with 400 mL of $CHCl_3$ and 1 L of H_2O. The organic layer was separated, and the water layer was extracted with two 100-mL portions of $CHCl_3$. The combined organic layers were dried and evaporated under reduced pressure. The residue was dissolved in 30 mL of CH_2Cl_2 and chromatographed on 150 g of MCB alumina suspended in CH_2Cl_2. Elution of the column with 1 L of CH_2Cl_2 and 1 L of 1:19 (v/v) ether–CH_2Cl_2 gave traces of impurities. Elution of the column with 2-L mixtures of ether–CH_2Cl_2 (1:9 and 1:4, v/v) gave product which was subjected to gel-permeation chromatography to give 1.0 g (95%) of (*S*)-**5** as a white foam: retention volume 184 mL of CH_2Cl_2; mass spectrum, *m/e* 576 (M^+); ^1H NMR (60 MHz) δ 3.58 (m, OCH_2, OCH_3, 26 H), 4.52 (AB q, $ArCH_2$, 4 H), 7.33 (m, Ar H, 6 H), 7.83 (m, Ar H, 4 H); $[\alpha]^{25}_{589}$ −28.2°, $[\alpha]^{25}_{578}$ −29.8°, $[\alpha]^{25}_{546}$ −34.6°, $[\alpha]^{25}_{436}$ −71.6° (*c* 1.14, $CHCl_3$). Anal. Calcd for $C_{34}H_{40}O_8$: C, 70.81; H, 6.99. Found: C, 70.68; H, 6.95.

(*S*)-2,3:4,5-Bis[1,2-[3-(phenoxymethyl)naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-6). A suspension stirred under N_2 of 1.2 g (2.1 mmol) of (*S*)-$(ClCH_2)_2D(OEOEO)_2E$ of maximum rotation,[10] 1.2 g (12.8 mmol) of phenol, and 2.0 g (14.5 mmol) of K_2CO_3 in 75 mL of DMF was heated at 110 °C for 18 h. The following procedure (procedure A) is a general method for extractive isolation of substitution products prepared from (*S*)-$(ClCH_2)_2D(OEOEO)_2E$ (see below). The mixture was cooled and then shaken with 400 mL of $CHCl_3$ and 1 L of H_2O. The layers were separated, and the organic layer was washed with three 500-mL portions of water, dried, and evaporated under reduced pressure. The residue was dissolved in 30 mL of CH_2Cl_2 and chromatographed on 100 g of MCB 80–325-mesh chromatographic grade basic alumina suspended in CH_2Cl_2. The column was eluted with 5 L of CH_2Cl_2 to give crude product which was chromatographed on the gel-permeation column to give 1.38 g (96%) of (*S*)-**6** as a white foam: retention volume 183 mL of CH_2Cl_2; mass spectrum, *m/e* 700 (M^+); ^1H NMR (60 MHz) δ 3.49 (m, OCH_2, 20 H), 5.50 (s, $ArCH_2$, 4 H), 7.20 (m, Ar H, 16 H), 7.88 (m, Nap H^5, 2 H), 8.17 (m, Nap H^4, 2 H); $[\alpha]^{25}_{589}$ −17.0°, $[\alpha]^{25}_{578}$ −18.3°, $[\alpha]^{25}_{546}$ −21.8°, $[\alpha]^{25}_{436}$ −51.8° (*c* 1.04, $CHCl_3$). Anal. Calcd for $C_{44}H_{44}O_8$: C, 75.41; H, 6.33. Found: C, 75.59; H, 6.48.

(*S*)-2,3:4,5-Bis[1,2-[3-[(4-methoxyphenoxy)methyl]-naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-7). A mixture of 1.2 g (2.1 mmol) of (*S*)-$(ClCH_2)_2D(OEOEO)_2E$ of maximum rotation,[10] 1.5 g (12.1 mmol) of *p*-methoxyphenol, and 1.7 g (12.3 mmol) of K_2CO_3 in 100 mL of DMF was stirred under N_2 at 110 °C for 16 h. Application of procedure A to the mixture gave 0.85 g (54%) of (*S*)-**7** as a white foam: gel-permeation chromatographic retention volume 177 mL of CH_2Cl_2; mass spectrum, *m/e* 760 (M^+); ^1H NMR (60 MHz) δ 3.64 (m, OCH_2, OCH_3, 26 H), 5.43 (s, $ArCH_2$, 4 H), 7.10 (m, Ar H, 14 H), 7.92 (m, Nap H^5, 2 H), 8.18 (s, Nap H^4, 2 H); $[\alpha]^{25}_{589}$ −15.0°, $[\alpha]^{25}_{578}$ −16.2°, $[\alpha]^{25}_{546}$ −19.3°, $[\alpha]^{25}_{436}$ −46.9° (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{46}H_{48}O_{10}$: C, 72.61; H, 6.36. Found: C, 72.43; H, 6.37.

(*S*)-2,3:4,5-Bis[1,2-[3-(phenylthio)methyl]naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-8). A mixture

(23) M. Newcomb, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, 99, 6405–6410 (1977).

of 1.0 g (1.7 mmol) of (*S*)-$(ClCH_2)_2D(OEOEO)_2E$ of maximum rotation,[10] 1.0 g (9.1 mmol) of thiophenol, and 2.0 g (14.5 mmol) of K_2CO_3 in 70 mL of DMF was stirred under N_2 at 90 °C for 2 h. Application of procedure A to the reaction mixture gave 1.1 g (88%) of (*S*)-8: gel permeation chromatographic retention volume 182 mL of CH_2Cl_2; mass spectrum, *m/e* 732 (M^+); ^1H NMR (60 MHz) δ 3.52 (m, OCH_2, 20 H), 4.83 (s, $ArCH_2$, 4 H), 7.24 (m, Ar H, 16 H), 7.98 (m, Nap $H^{4,5}$, 4 H); $[\alpha]^{25}_{589}$ −13.3°, $[\alpha]^{25}_{578}$ −14.8°, $[\alpha]^{25}_{546}$ −17.5°, $[\alpha]^{25}_{436}$ −52.1° (*c* 1.22, $CHCl_3$). Anal. Calcd for $C_{44}H_{44}O_6S_2$: C, 72.12; H, 6.05. Found: C, 72.09; H, 6.02.

(*S*)-2,3:4,5-Bis[1,2-[3-[(benzylthio)methyl]naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-9). A mixture of 1.4 g (2.4 mmol) of (*S*)-$(ClCH_2)_2D(OEOEO)_2E$ of maximum rotation,[10] 1.4 g (10.1 mmol) of benzyl mercaptan, and 2.0 g (14.5 mmol) of K_2CO_3 in 70 mL of DMF was stirred under N_2 at 90 °C for 12 h. By application of procedure A, the product was isolated as 1.2 g (66%) of a white foam: gel-permeation retention volume 180 mL of CH_2Cl_2; mass spectrum, *m/e* 760 (M^+); ^1H NMR (60 MHz) δ 3.60 (m, OCH_2, $C_6H_5CH_2$, 24 H), 4.07 (AB q, Nap CH_2, 4 H), 7.34 (m, Ar H, 16 H), 7.91 (m, Nap $H^{4,5}$, 4 H); $[\alpha]^{25}_{589}$ +9.0°, $[\alpha]^{25}_{578}$ +9.0°, $[\alpha]^{25}_{546}$ +9.7° (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{46}H_{48}O_6S_2$: C, 72.61; H, 6.36. Found: C, 72.30; H, 6.44.

(*S*)-2,3:4,5-Bis[1,2-(3-cyanonaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-13). The reported procedure for preparing racemic material was employed.[11] The crude product obtained from the reaction of 4.0 g (7.3 mmol) of optically pure (*S*)-$(HOCH_2)_2D(OEOEO)_2E$ with 8.0 g (92 mmol) of activated MnO_2 in 300 mL of CH_2Cl_2 was dissolved in 30 mL of CH_2Cl_2 and chromatographed on 150 g of silica gel suspended in CH_2Cl_2. The column was washed with 1 L of CH_2Cl_2 and 1:19 (v/v) ether–CH_2Cl_2, and product was eluted with 2-L portions of CH_2Cl_2–ether (4:1, 3:2, and 1:3 v/v) to give material that was subjected to gel-permeation chromatography, which gave 192 mL of CH_2Cl_2 as its elution volume. The pure product, (*S*)-$(OCH)_2D(OEOEO)_2E$, was obtained as 3.1 g (78%) of a white foam whose 200-MHz ^1H NMR spectrum was identical with that of authentic racemic material.[11] This (*S*)-aldehyde (1.8 g, or 3.3 mmol) was converted to (*S*)-$(CN)_2D(OEOEO)_2E$ (1.5 g, 84%) by the same procedure used on racemic aldehyde.[11] The product, (*S*)-**13**, was isolated as a white foam: gel-permeation chromatographic retention volume 194 mL of CH_2Cl_2; ^1H NMR spectrum (200 MHz) was identical with that of racemic material; $[\alpha]^{25}_{589}$ −148.2°, $[\alpha]^{25}_{578}$ −155.9°, $[\alpha]^{25}_{546}$ −182.1°, $[\alpha]^{25}_{436}$ −365° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{32}H_{30}N_2O_6$: C, 71.36; H, 5.61. Found: C, 71.29; H, 5.65.

(*S*)-2,3:4,5-Bis[1,2-(3-tetrazolylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-14). A mixture of 1.4 g (2.6 mmol) of (*S*)-**13**, 4.2 g (65 mmol) of NaN_3, 3.6 g (70 mmol) of NH_4Cl, and 1.0 g (23.5 mmol) of LiCl in 60 mL of DMF was heated to 130 °C for 30 h.[12] The mixture was cooled to 25 °C, diluted with $CHCl_3$ (150 mL) and H_2O (800 mL), and shaken, and the aqueous layer was adjusted to pH 1 by addition of concentrated hydrochloric acid. The mixture was shaken again, the layers were separated, and the aqueous layer was extracted with two 50-mL portions of $CHCl_3$. The organic layers were combined, dried, and evaporated at 70 °C (30 mm) to give a pale yellow foam. This material was subjected to gel-permeation chromatography to give 1.3 g (80%) of (*S*)-14: retention volume 180 mL of CH_2Cl_2; mass spectrum, *m/e* 624 (M^+); ^1H NMR (200 MHz) δ 3.40 (m, OCH_2, 20 H), 7.45 (m, Ar H, 6 H), 8.11 (m, Ar H^5, 2 H), 9.07 (s, Ar H^4, 2 H); $[\alpha]^{25}_{589}$ +319.7°, $[\alpha]^{25}_{578}$ +335.6°, $[\alpha]^{25}_{546}$ +394.6°, $[\alpha]^{25}_{436}$ +795.9° (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{32}H_{32}N_8O_6$: C, 61.53; H, 5.16. Found: C, 61.52; H, 5.24.

(*S*)-2,3:4,5-Bis[1,2-[3-(5-phenyl-2-oxadiazinyl)-naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-10). To a solution of 1.2 g (1.9 mmol) of tetrazole (*S*)-**14** in 16 mL of pyridine was added 1.3 g (9.3 mmol) of benzoyl chloride, and the mixture was heated to 130 °C (30 min) and then refluxed (oil bath, 130 °C) for 1.5 h.[13] The solution was cooled to ~50° and then evaporated at 60 °C (30 mm). The residue was shaken with 100 mL of $CHCl_3$ and water (1 L), the layers were separated, and the organic layer was dried and concentrated under vacuum to 10 mL. This solution was added to an alumina column (75 g, MCB basic) suspended in CH_2Cl_2. The column was washed with two 1-L portions of CH_2Cl_2–Et_2O (19:1 and 9:1, v/v) to give unidentified material (traces). Product was eluted with 3 L of CH_2Cl_2–Et_2O (4:1, v/v) and was subjected to gel-permeation chromatography to give (*S*)-**10**: 1.32 g (89%); white foam; retention volume 175 mL of CH_2Cl_2; mass spectrum, *m/e* 776 (M^+); ^1H NMR (200 MHz) δ 3.50 (m, OCH_2, 20 H), 7.40 (m, Ar H, 12 H), 8.14 (m, Ar H, 6 H), 8.79 (s, Nap H^4, 2 H); $[\alpha]^{25}_{589}$ +47.4°, $[\alpha]^{25}_{578}$ +49.4°, $[\alpha]^{25}_{546}$ +59.0°, $[\alpha]^{25}_{436}$ +143.0° (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{46}H_{40}N_4O_8$: C, 71.12; H, 5.19. Found: C, 71.35; H, 5.40.

(*R*)- and (*S*)-2,2′-Dimethoxy-1,1′-dinaphthyl. A suspension of 25.0 g (8.7 mmol) of (*R*)-2,2′-dihydroxy-1,1′-dinaphthyl of maximum rotation[8] was heated in 800 mL of acetone to give a homogeneous solution. To this solution stirred under N_2 was added 40.0 g (29 mmol) of K_2CO_3 and 60.0 g (0.42 mol) of CH_3I, and the mixture was refluxed for 24 h. An additional 20.0-g (0.14 mol) portion of CH_3I was added, and the mixture was refluxed for an additional 12 h. The solvent was evaporated to leave a volume of 150 mL, which was cooled to 25 °C, and 900 mL of water was added to the stirred suspension. The mixture was stirred for 8 h, and the solid was collected, washed with water, and dried under vacuum first at 25 °C and then at 95 °C (20 mm, for 24 h) to give 26.7 g (97%) of the desired product as a white powder that was used without further purification in the next reaction and gave a ^1H NMR spectrum identical with that of racemic material.[24a] An analytical sample was prepared by recrystallization from CH_2Cl_2–C_6H_6: mp 224–225 °C (after drying at 100 °C and 0.1 mm); ^1H NMR (60 MHz) δ 3.69 (s, OCH_3, 6 H), 7.27 (m, Ar H, 8 H), 7.89 (m, Ar H, 4 H); $[\alpha]^{25}_{589}$ +72.8°, $[\alpha]^{25}_{578}$ +77.4°, $[\alpha]^{25}_{546}$ +96.0°, $[\alpha]^{25}_{436}$ +280.6° (*c* 1.2, THF) (lit.[24b] $[\alpha]^{21}_{589}$ +79.5° (*c* 1.0, THF)). Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.95; H, 5.66.

Application of this procedure to (*S*)-2,2′-dihydroxy-1,1′-dinaphthyl of maximum rotation[8] gave (*S*)-2,2′-dimethoxy-1,1′-dinaphthyl, whose properties were identical with those of its enantiomer except in sign of rotation.

(*R*)(*S*)-, (*R*)-, and (*S*)-3,3′-Dibromo-2,2′-dimethoxy-1,1′-dinaphthyl ((*R*)(*S*)-15, (*R*)-15, and (*S*)-15). To a solution of 7.8 g (67 mmol) of tetramethylethylenediamine in 500 mL of ether stirred under N_2 was added 30 mL (72 mmol) of 2.4 M *n*-butyllithium in hexane. The mixture was stirred at 25 °C for 15 min, 10.0 g (31.8 mmol) of solid racemic 2,2′-dimethoxy-1,1′-dinaphthyl[24a] was added, and the mixture was stirred for 3 h. The suspension was cooled to −78 °C, and 15 mL (0.3 mol) of bromine in 50 mL of pentane was added over a 10-min period. The suspension was warmed to 25 °C, and after 4 h, 300 mL of a saturated solution of Na_2SO_3 in water was cautiously added. The mixture was stirred for an additional 4 h and shaken with 1 L of $CHCl_3$ and 1 L of H_2O, and the layers were separated. The organic layer was dried and evaporated under reduced pressure, and the residue was dissolved in 40 mL of hot benzene. This solution was added to an alumina column (200 g, MCB) suspended in cyclohexane. Product was eluted from the column with cyclohexane–benzene mixtures (2 L each of 4:1, 3:2, 2:3 and 1:4, v/v) to give the desired dibromide contaminated with monobromide. The latter compound was identified by its ^1H NMR and mass spectra but was not fully characterized. The combined fractions of the mixture were recrystallized from 250 mL of CH_2Cl_2–pentane to give 10.8 g (72%) of dibromide: mp 158–159 °C; mass spectrum, *m/e* 470 (M^+, ^{79}Br); ^1H NMR (200 MHz) δ 3.51 (s, OCH_3, 6 H), 7.30 (m, ArH, 6 H), 7.82 (m, Ar H^5, 2 H), 8.27 (s, Ar H^4, 2 H). Anal. Calcd for $C_{22}H_{16}Br_2O_2$: C, 55.96; H, 3.42. Found: C, 55.83; H, 3.31.

Application of the above procedure to 10.0 g of (*R*)-2,2′-dimethoxy-1,1′-dinaphthyl gave 9.2 g (64%) of (*R*)-**15**, mp 174–175 °C [after recrystallization from CH_2Cl_2–pentane and drying at 100 °C (0.1 mm) for 12 h]. The ^1H NMR (200 MHz) spectra of the (*R*)(*S*)- and (*R*)-**15** samples were identical. The (*R*)-**15** gave $[\alpha]^{25}_{589}$ +13.2°, $[\alpha]^{25}_{578}$ +14.1°, $[\alpha]^{25}_{546}$ +15.4°, and $[\alpha]^{25}_{436}$ +25.4° (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{22}H_{16}Br_2O_2$: C, 55.96; H, 3.42. Found: C, 56.02; H, 3.44.

Similarly, (*S*)-2,2′-dimethoxy-1,1′-dinaphthyl was converted in 65% yield into dibromide (*S*)-**15**, whose properties were identical with those of its enantiomer except for its sign of rotation.

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(*R*)(*S*)- and (*R*)-3,3′-Diphenyl-2,2′-dihydroxy-1,1′-dinaphthyl ((*R*)(*S*)-17 and (*R*)-17). To a suspension of 7.7 g (16.3 mmol) of racemic 3,3′-dibromo-2,2′-dimethoxy-1,1′-dinaphthyl and 0.6 g (0.92 mmol) of $Ni[P(C_6H_5)_3]_2Cl_2$[25] in 100 mL of ether stirred under N_2 was added (20 min) a solution of 45 mmol of phenylmagnesium bromide in 60 mL of ether. The mixture was refluxed for 20 h, cooled, and shaken with 600 mL each of $CHCl_3$ and 1 M hydrochloric acid. The organic layer was dried, evaporated, dissolved in 50 mL of hot C_6H_6, and chromatographed on 300 g of silica gel suspended in C_6H_6. Washing of the column with 6 L of C_6H_6 gave a forerun of biphenyl followed by phenylated binaphthyl. The combined fractions (~7 g) were dissolved in 600 mL of CH_2Cl_2 and cooled to 0 °C, and 24.0 g (96 mmol) of BBr_3 was added. After being stirred for 24 h at 25 °C, the mixture was cooled to 0 °C, and the excess BBr_3 was decomposed by dropwise addition of H_2O. The mixture was shaken with 300 mL of water, and the organic layer was dried, concentrated to 30 mL, and chromatographed on 300 g of silica gel suspended in benzene. Washing of the column with 3-L portions of benzene and 19:1 benzene–ether (v/v) gave 5.6 g (79% overall) of (*R*)(*S*)-17: mp 204–205 °C (after recrystallization from CH_2Cl_2–cyclohexane); mass spectrum, *m/e* 438 (M^+); ^1H NMR (200 MHz) δ 5.38 (s, OH, 2 H), 7.60 (m, Ar H, 20 H). Anal. Calcd for $C_{32}H_{22}O_2$: C, 87.64; H, 5.06. Found: C, 87.84; H, 4.92.

Application of the same procedure to 7.0 g of (*R*)-**15** gave 4.2 g (65%) of (*R*)-17, mp 197–198 °C [after recrystallization from CH_2Cl_2–cyclohexane and heating at 90 °C (0.1 mm) for 12 h]. The ^1H NMR (200 MHz) spectrum of (*R*)-17 was identical with that of (*R*)(*S*)-17. The sample gave $[\alpha]^{25}_{589}$ +106.5°, $[\alpha]^{25}_{578}$ +112.1°, $[\alpha]^{25}_{546}$ +132.4°, $[\alpha]^{25}_{436}$ +283.1° (*c* 1.0, THF). Anal. Calcd for $C_{32}H_{20}O_2$: C, 87.64; H, 5.06. Found: C, 87.55; H, 4.96.

(*R*)(*S*)- and (*R*)-2,3:4,5-Bis[1,2-(3-phenylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*R*)(*S*)-11 and (*R*)-11). To a solution of 1.1 g (2.5 mmol) of (*R*)(*S*)-17 and 1.5 g (2.7 mmol) of pentaethylene glycol ditosylate[23] in 200 mL of THF stirred under N_2 at 25 °C was added 0.36 g (5.5 mmol) of solid KOH (85%). The mixture was refluxed for 72 h, cooled, and shaken with 500 mL each of $CHCl_3$ and H_2O. The organic layer was dried and evaported under reduced pressure, and the residue was dissolved in 30 mL of CH_2Cl_2. This material was chromatographed on 150 g of alumina (MCB) suspended in CH_2Cl_2. Product was eluted from the column with 1 L of CH_2Cl_2 and 2-L portions of CH_2Cl_2–ether mixtures (49:1 and 24:1, v/v) to give crude (*R*)(*S*)-11, which was further purified by gel-permeation chromatography to give a retention volume of 178 mL of CH_2Cl_2. This material was a white foam: 0.9 g (56%); mass spectrum, *m/e* 640 (M^+); ^1H NMR (60 MHz) δ 3.41 (m, OCH_2, 20 H), 7.64 (m, Ar H, 20 H). Anal. Calcd for $C_{42}H_{40}O_6$: C, 78.73; H, 6.29. Found: C, 78.46; H, 6.45.

Application of the above procedure to 1.13 g (2.6 mmol) of (*R*)-17, 1.6 (2.9 mmol) of pentaethylene glycol ditosylate,[23] 0.38 g (5.8 mmol) of KOH (85%), and 200 mL of THF gave 0.95 g (58%) of (*R*)-11 as a white foam. The retention volume and ^1H NMR (60 MHz) spectrum were identical with those of (*R*)(*S*)-11. The sample of (*R*)-11 gave $[\alpha]^{25}_{589}$ −20.7°, $[\alpha]^{25}_{578}$ −23.4°, $[\alpha]^{25}_{546}$ −27.2°, $[\alpha]^{25}_{436}$ −63.6° (*c* 1.0, THF). Anal. Calcd for $C_{42}H_{40}O_6$: C, 78.73; H, 6.29. Found: C, 78.53; H, 6.23.

Enantiomeric Resolution of (*R*)(*S*)-2,3:4,5-Bis[1,2-(3-phenylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*R*)(*S*)-11) into (*R*)-11 and (*S*)-11. Hot solutions of 2.154 g (3.36 mmol) of (*R*)(*S*)-11 and 0.422 g (1.68 mmol or 0.5 equiv) of (L)-$C_6H_5CH(CO_2H)NH_3ClO_4$ of maximum rotation (see below) in a total of 30 mL of EtOAc were mixed to give a gummy precipitate. The mixture when heated to reflux gave a homogeneous solution. When the mixture cooled, the (*S*)(L) complex crystallized, which after being allowed to stand for 15 min was collected, rinsed with EtOAc, and dried at 25 °C and 0.2 mm to give 1.40 g (1.57 mmol or 93%) of complex. This material was shaken with a mixture of 200 mL each of CH_2Cl_2, Et_2O, cyclohexane, and water. The organic layer was washed with three additional 200-mL portions of water, the last of which gave a negative ninhydrin test (see below). The aqueous extracts were combined and back-extracted with two 200-mL portions of CH_2Cl_2, which were combined with the original layer. This solution was dried with $MgSO_4$, filtered, evaporated, and dried at 0.2 mm and 100 °C for 2 h as a glass to give 0.914 g (85% overall) of (*S*)-11: $[\alpha]^{25}_{589}$ +21.8°, $[\alpha]^{25}_{578}$ +23.0°, $[\alpha]^{25}_{546}$ +27.8°, $[\alpha]^{25}_{436}$ +64.7° (*c* 0.91, THF).

The mother liquors from the original filtrate from the crystallization of the (*S*)(L) complex were evaporated under reduced pressure, and the free host was regenerated by the above procedure (five water washes gave a negative ninhydrin test). Hot solutions of this foam and of 0.424 g (1.68 mmol) of (D)-$C_6H_5CH(CO_2H)NH_3ClO_4$ (see below) were mixed in a total of 30 mL of EtOAc. The gum that separated dissolved when the mixture was refluxed. The (*R*)(D) complex that separated on cooling was collected, washed, and dried to give 1.235 g (1.38 mmol or 82%) of material, which was decomplexed (see above) to provide 0.88 g (82% overall) of (*R*)-11 as a glass: $[\alpha]^{25}_{589}$ −21.1°, $[\alpha]^{25}_{587}$ −22.5°, $[\alpha]^{25}_{546}$ −27.1°, $[\alpha]^{25}_{436}$ −63.4° (*c* 1.06, THF).

To demonstrate that maximum rotation had been reached, we recrystallized the (*R*)(D) complex twice from ethyl acetate to give after the first recrystallization the following rotations: $[\alpha]^{25}_{589}$ −21.4°, $[\alpha]^{25}_{578}$ −23.0°, $[\alpha]^{25}_{546}$ −27.5°, $[\alpha]^{25}_{436}$ −64.1° (*c* 1.1, THF); after the second recrystallization, $[\alpha]^{25}_{589}$ −20.8°, $[\alpha]^{25}_{578}$ −22.3°, $[\alpha]^{25}_{546}$ −27.0°, $[\alpha]^{25}_{436}$ −62.8° (*c* 1.06, THF). The proximity to one another of the magnitudes of rotation of the samples of the enantiomers of 11 indicates that maximum rotation essentially was reached during the first crystallization.

Preparation of (D)-Phenylglycine Methyl Ester Perchlorate Complex of (*R*)-11 for Possible X-ray Crystal Structure Determination. A hot solution of 0.934 g (1.45 mmol) of (*R*)-11 and 0.386 g (1.45 mmol) of (D)-phenylglycine methyl ester perchlorate in 25 mL of EtOAc was cooled, and after 15 min the crystals of the (*R*)(D) complex that separated were collected and dried to give 1.157 g (1.28 mmol, 87%) of material, which was recrystallized from 50 mL of methanol to give 0.629 g (54%) of tiny rods. These were dissolved in 25 mL of methanol at 60 °C, and the solution was passed through a sintered-glass filter and very slowly cooled to 25 °C over a 72-h period to give large rod-shaped, X-ray-quality crystals. They were collected, rapidly washed with methanol, and dried at 0.1 mm for 30 min to give 0.215 g (34%) of complex, mp 147–149 °C (gas liberated). Before analysis of the complex, the solvent of crystallization was removed by heating the sample. Anal. Calcd for $C_{51}H_{52}O_{12}NCl$: C, 67.58; H, 5.78; N, 1.55. Found: C, 67.41; H, 5.84; N, 1.52.

(*S*)-3,3′-Bis(pentamethylphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl. To a suspension of 2.0 g (83 mmol) of Mg in 25 mL of dry ether stirred under N_2 was added 0.5 g (2.7 mmol) of 1,2-dibromoethane, and the mixture was heated to activate the Mg surface. The mixture was cooled to 25 °C, and over a 10-min period, a solution of 7.0 g (31 mmol) of pentamethylbromobenzene and 5.5 g (29.2 mmol) of 1,2-dibromoethane in 150 mL of ether was added. The mixture was refluxed for 4 h and cooled to 25 °C, and 0.6 g (0.92 mmol) of $Ni[P(C_6H_5)_3]_2Cl_2$ was added. To this mixture stirred under N_2 was added 2.2 g (4.7 mmol) of (*S*)-$(Br)_2D(OCH_3)_2$ dissolved in a mixture of 20 mL of THF and 75 mL of ether. The mixture was refluxed for 40 h, cooled, and shaken with a mixture of 500 mL of $CHCl_3$ and 1 N hydrochloric acid. The organic layer was dried and evaporated, and the residue was dissolved in 50 mL of CH_2Cl_2. This solution was passed through an alumina filtration column (100 g of alumina suspended in CH_2Cl_2) to give a crude mixture which was dissolved in 400 mL of CH_2Cl_2, cooled to 0 °C, and treated with 12.0 g (48 mmol) of BBr_3. The mixture was stirred for 24 h at 25 °C and cooled to 0 °C, and H_2O was added dropwise to decompose the excess BBr_3. The mixture was shaken with 300 mL of water, and the organic layer was dried and evaporated under reduced pressure. The residue was dissolved in 50 mL of hot C_6H_6 and chromatographed on 400 g of silica gel suspended in 3:1 (v/v) cyclohexane–benzene. Elution of the material with the same solvent gave unidentified materials, and further elution with 3 L of 1:1

(25) A detailed discussion of this aryl–aryl coupling reaction is given: K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, *Bull. Chem. Soc. Jpn.*, 49(7), 1958–1969 (1976).

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Table V. Specific Rotations of Optically Pure Methyl Ester Hydrochlorides of Amino Acids in Methanol at c 1.0 at 25 °C

amino ester of	mp, °C	[α], deg 589 nm	578 nm	546 nm	436 nm	365 nm
D-phenylglycine[a]	200-201	−132.0	−138.3	−159.4	−288.3	−491.3
L-valine[b]	165-166	24.2	25.2	29.2	53.7	92.6
L-tryptophane[c]	209-210	16.8	17.4	20.5	42.4	85.8
L-phenylalanine[d]	158-162	17.3	18.0	20.9	41.5	78.1
L-methionine[e]	151-153	25.0	26.0	29.6	52.8	87.7
D-alanine[f]	110	−6.5	−6.6	−7.8	−16.2	−30.7

[a] Lit.[27] $[\alpha]^{25}_{589}$ −133.1 (c 1.0, MeOH); mp 199-200 °C. [b] Lit.[28] mp 167.5-168 °C. [c] Lit.[28] mp 214 °C. [d] Lit.[28] mp 159-161 °C. [e] Lit.[28] mp 150 °C. [f] Lit.[28] mp 109-110 °C. A melting point of 154-155 °C has also been reported.[29]

(v/v) cyclohexane–benzene and benzene (2 L) gave 0.95 g (35% overall) of (S)-$[C_6(CH_3)_5]_2D(OH)_2$ as an oil: mass spectrum, m/e 578 (M^+); ^1H NMR (60 MHz) δ 2.20 (m, $ArCH_3$, 30 H), 5.13 (s, OH, 2 H), 7.38 (m, Ar H, 6 H), 7.84 (m, Ar H, 4 H); $[\alpha]^{25}_{589}$ −36.4°, $[\alpha]^{25}_{578}$ −38.4°, $[\alpha]^{25}_{546}$ −45.1° (c 1.25, $CHCl_3$). Anal. Calcd for $C_{42}H_{42}O_2$: C, 87.16; H, 7.31. Found: C, 87.12; H, 7.35.

(S)-2,3:4,5-Bis[1,2-[3-(pentamethylphenyl)naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((S)-12). To a solution of 0.9 g (1.6 mmol) of (S)-$[C_6(CH_3)_5]_2D(OH)_2$ and 0.9 g (1.65 mmol) of pentaethylene glycol ditosylate[23] in 225 mL of THF stirred under N_2 at 25 °C was added 0.225 g (3.4 mmol) of 85% KOH. The mixture was refluxed for 72 h, and the product was isolated and purified as were the other hosts (see above) by chromatography on 150 g of alumina suspended in CH_2Cl_2 and by gel-permeation chromatography to give 0.50 g (41%) of (S)-12 as a white foam: retention volume 188 mL of CH_2Cl_2; mass spectrum, m/e 780 (M^+); ^1H NMR (60 MHz) δ 2.25 (m, $ArCH_3$, 30 H), 3.30 (m, OCH_2, 20 H), 7.33 (m, Ar H, 6 H), 7.84 (m, Ar H, 4 H); $[\alpha]^{25}_{589}$ −103.1°, $[\alpha]^{25}_{578}$ −108.8°, $[\alpha]^{25}_{546}$ −125.8°, $[\alpha]^{25}_{436}$ −251.2° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{52}H_{60}O_6$: C, 79.97; H, 7.74. Found: C, 80.01; H, 7.68.

Perchlorate Salts of Amino Acids. The perchlorate salts of the racemic acids used here have been previously described, as well as the methyl ester perchlorate of phenylglycine and phenylalanine.[3d] The same procedure was applied to the preparation of the methyl ester perchlorates of the following amino acids. Valine, 55%, mp 82–83.5 °C. Anal. Calcd for $C_6H_{14}O_6ClN$: C, 31.11; H, 6.09; N, 6.05. Found: C, 31.10; H, 6.01; N, 6.02. Tryptophane, 83%, mp 139–140 °C. Anal. Calcd for $C_{12}H_{15}O_6ClN_2$: C, 45.22; H, 4.74; N, 8.79. Found: C, 45.16; H, 4.71; N, 8.82. Methionine, 14%, mp 60–62 °C. Anal. Calcd for $C_6H_{14}O_6ClNS$: C, 27.33; H, 5.35; N, 5.31. Found: C, 27.40; H, 5.27; N, 5.29. The perchlorate methyl ester of alanine was formed by ion exchange and was used directly since it did not crystallize.

Determination of Standard Specific Rotations of Guests. In all of the chiral recognition–extraction experiments, rotations of final products isolated from both the aqueous and organic layers were taken on the methyl ester hydrochloride salts. Accordingly, the methyl ester hydrochloride salts were prepared by the same method from standard amino acids, the rotations were taken on three separately prepared solutions three times for each wavelength, and the nine rotations were averaged. The error with 66% confidence was always less than 0.5% and was less than 0.1% for $C_6H_5CH(CO_2CH_3)NH_3Cl$. Table V records the values obtained.

For determination of the sensitivity of the specific rotations of these ester salts to their concentrations, their rotations were taken at c 0.5 and c 2.0 in MeOH and compared to those taken at c 1.0. The average percent variations (at c 0.5 and c 2.0, respectively) as the R groups of $RCH(CO_2CH_3)NH_3Cl$ were varied were as follows: C_6H_5, −0.9 and −0.8; $(CH_3)_2CH$, 2.8 and −1.9; $C_8H_6NCH_2$, −1.3 and 5.0; $C_6H_5CH_2$, −0.6 and 3.8; $CH_3SCH_2CH_2$, 0.5 and 0.5. Thus to accurately determine the optical purity of the guest methyl ester salts, the rotations had to be taken at the same concentrations as those used for the standard determinations.

Amino Ester Hydrochloride and Amino Acid Perchlorate Extraction Control Experiments, General Procedures and Exceptions. The general procedure applied to $RCH(CO_2CH_3)NH_3Cl$ was as follows (procedure B). A solution in 15 mL of water of 1.0 mmol of an optically pure or about 50% optically pure sample of $RCH(CO_2CH_3)NH_3Cl$ was washed with two successive 10-mL portions of reagent grade CH_2Cl_2. The aqueous layer was basified with ca. 1 mL of a saturated aqueous solution of Na_2CO_3 to pH 9 and extracted with four or five 10-mL portions of CH_2Cl_2. The organic extracts were combined and dried with ca. 1 g of $MgSO_4$ for 30 min and passed through a medium-porosity glass filter. The filter and all glassware were dried at 150 °C before use. Into the filtrate was bubbled dry HCl gas for 2 min, the solvent was evaporated under vacuum at 25 °C to give a powder, which was dried at <0.2 mm for 30 min and weighed, and the percent recovery was calculated. Specific rotations were taken on these samples at c 1.0 in pure methanol in jacketed tubes at 25 °C, and where appropriate, the optical purities were calculated on the basis of the values of Table V, whose salts had been identically prepared. Table VI records the variations from theory of these control runs.

Table VI. Variation from Theory of Specific Rotations of $RCH(CO_2CH_3)NH_3Cl$ Samples Isolated in Control Runs for EDC Determination Procedures[a]

starting $RCH(CO_2R')NH_3X$ R	R'	X	% opt purity	recovd $RCH(CO_2CH_3)NH_3Cl$ %	% diff[b] theory
C_6H_5	CH_3	Cl	100	92	−0.9
C_6H_5	CH_3	Cl	50	89	−1.4
C_6H_5	H	ClO_4	50	84	−0.6
$(CH_3)_2CH$	CH_3	Cl	100	95	−0.3
$(CH_3)_2CH$	CH_3	Cl	50	86	0.3
$(CH_3)_2CH$	H	ClO_4	50	88	0.2
$C_8H_6NCH_2$	CH_3	Cl	100	91	−0.9
$C_8H_6NCH_2$	CH_3	Cl	50	89	2.1
$C_8H_6NCH_2$	H	ClO_4	50	12[c]	2.6
$C_6H_5CH_2$	CH_3	Cl	100	94	−0.3
$C_6H_5CH_2$	CH_3	Cl	50	90	1.5
$C_6H_5CH_2$	H	ClO_4	100	93	1.8
$C_6H_5CH_2$	H	ClO_4	50	78	2.5
$CH_3SCH_2CH_2$	CH_3	Cl	100	94	−1.3
$CH_3SCH_2CH_2$	CH_3	Cl	50	98	−0.8
$CH_3SCH_2CH_2$	H	ClO_4	50	72	0.6
CH_3	CH_3	Cl	100	80	2.4
CH_3	H	ClO_4	50	53	−5.2

[a] Based on rotations of Table V. [b] Observed optical purity minus calculated optical purity based on optical purity of starting material. [c] Further experiments demonstrated this recovery to be variable.

The procedure applied to $CH_3CH(CO_2CH_3)NH_3Cl$ was modified as follows. The concentrate from the dried, filtered, acidified CH_2Cl_2-extracted solution was a glass, and it was impossible to dry. Consequently, it was sublimed from the bottom to the top of the flask at 100 °C and <0.2 mm. Furthermore, this salt was very hygroscopic. Consequently, the whole sample was weighed and dissolved in a measured amount of MeOH to give c ~1.0.

The general procedure applied to $RCH(CO_2H)NH_3ClO_4$ was as follows (procedure C). A 1.0-mmol sample of either optically pure or 50% optically pure $RCH(CO_2H)NH_3ClO_4$ dissolved in 15 mL of H_2O was extracted twice with 10-mL portions of reagent grade CH_2Cl_2. The aqueous phase was placed under vacuum to remove the remaining CH_2Cl_2 and lyophilized at less than 0.1 mm. The dry residue was dissolved in 25 mL of MeOH, and at 25 °C dry HCl was bubbled through the solution until it was saturated

(2 min). The mixture was refluxed under argon for 30 min, and the solvent and HCl were evaporated under vacuum at 40 °C. The residue was subjected to procedure B. The results are recorded in Table VI.

The procedure as applied to $C_8H_6NCH_2CH(CO_2H)NH_3ClO_4$ was modified since the racemic salt did not have a weighable form. To a mixture of 1.0 mmol of the amino acid in 15 mL of water was added 1.0 equiv (90 μl) of 70% $HClO_4$ to give a solution. This salt solution was lyophilized. To the residue was added a solution prepared by adding cautiously at −35 °C 1.5 ml (20 equiv) of reagent grade $SOCl_2$ to 15 mL of MeOH. The homogenous solution was allowed to stand for 15 min and then evaporated under vacuum at 40 °C. The residue was dissolved in 15 mL of water and subjected to procedure B. Anomalously high rotations were obtained when CH_3OH–HCl procedures were used to make the ester salt.

Since racemic $CH_3SCH_2CH_2CH(CO_2H)NH_3ClO_4$ could not be isolated in a dry, weighable form, it was prepared in solution as was the tryptophane salt, and then procedure C was followed.

Since racemic $CH_3CH(CO_2H)NH_3ClO_4$ could not be weighed in a dry state, it was prepared in solution (see below) and submitted to esterification procedure C, and the $CH_3CH(CO_2CH_3)NH_3Cl$ was isolated by the modification under procedure B.

Ninhydrin Test for Detection of Guest during Decomplexation. The decomplexation–extraction by which hosts and guests were separated was monitored to determine how many extractions were needed to complete the separation. The organic solution was shaken with 5 mL of water. A drop of the water extract was spotted onto a small square of a glass silica gel TLC plate. The plate was sprayed to saturation with an atomizer containing a 0.2% ethanol solution of ninhydrin. The square was heated with a heat gun. If more than 5 μmol of guest was present in the extract, a red color appeared. The extractions were carried out until the color was absent, which meant that less than 1% of the original guest was still present in the organic layer.

Regeneration of Guest-Free Hosts. Hosts were reused repeatedly and had to be rendered completely guest free. The host was dissolved in 10 mL of CH_2Cl_2, 10 mL of Et_2O, and 10 mL of cyclohexane, and the solution was extracted with successive 5-mL portions of water until a negative ninhydrin test was obtained (four or five extractions). The aqueous extracts were combined and extracted with two 10-mL portions of CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ for 30 min and filtered through a medium glass filter, and the filtrate was vacuum evaporated. The concentrate was subjected to gel permeation chromatography and isolated as a foam or oil which was dried at 60–100 °C for 2 h at 0.1 mm.

Amino Ester Perchlorate Chiral Recognition. General Procedure D. A solution of 3.0 mmol of amino ester perchlorate in 6 mL of D_2O was added to 5.0 mL of a solution of 1.0 mmol of host in NMR grade $CDCl_3$ in a 25-mL graduated centrifuge tube, which was placed in a cold room (0 ± 2 °C) for 1 h. The mixture was vortexed for 30 s and centrifuged in the cold room for 15 min. With a Pasteur pipette, ca. 5.5 mL of the aqueous solution was carefully withdrawn and placed in a 12-mL graduated centrifuge tube. The 25-mL tube was lightly tapped to break the meniscus and expose the organic layer. With a second Pasteur pipette, ca. 4.5 mL of the organic layer was carefully withdrawn and placed in a graduated 12-mL centrifuge tube. These separations were carried out in the cold room, but subsequent operations were carried out under ambient conditions.

The aqueous phase was washed into a separatory funnel with three 5-mL portions of additional water, and this solution was washed with two 10-mL portions of CH_2Cl_2. The organic layers were set aside, and the aqueous layer was submitted to procedure B. The amino ester hydrochloride salts isolated were weighed, their rotations were determined, and the CSF values calculated.

The organic phase was washed into a separatory funnel with 5 mL of CH_2Cl_2 and diluted with 10 mL of Et_2O and 10 mL of cyclohexane. This solution was extracted with four or five successive 5-mL volumes of water until the last extract gave a negative ninhydrin test. The host-containing organic layer was combined with the organic extracts set aside earlier. The combined aqueous layers were washed with two 10-mL portions of CH_2Cl_2, and the organic extracts were combined with the organic extracts set aside earlier. The aqueous solution was subjected to procedure B to give amino ester hydrochloride which was used to determine CRF* values. The combined organic phase was subjected to the above procedure for recovery of host.

When racemic $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ served as the guest, the volume of the organic phase had to be trebled in each component to keep the complex in solution during extractions with water. When racemic $C_8H_6NCH_2CH(CO_2CH_3)NH_3ClO_4$ served as the guest, the original D_2O volume had to be increased to 12 mL to allow the salt to be dissolved at 0 °C. Since $CH_3CH(CO_2CH_3)NH_3ClO_4$ was not crystalline, $CH_3CH(CO_2CH_3)NH_3Cl$ (3.0 mmol) was dissolved in D_2O that was 2.0 M in $LiClO_4$ to give a volume of 3.0 mL. This solution was then submitted to procedure D.

Amino Acid Perchlorate Chiral Recognition. General Procedure E. A solution of 3.0 mmol of amino acid perchlorate in 3 mL of D_2O or in D_2O that was 2.0 M in $LiClO_4$ was added to 5.0 mL of the appropriate CD_3CN–$CDCl_3$ (spectral grade) mixture containing 1.0 mmol of host in a 25-mL graduated centrifuge tube. The tube was placed in a cold room at 0 ± 2 °C for 1 h, vortexed for 30 s, and then centrifuged for 15 min in the cold room. With a Pasteur pipette, ca. 2.5 mL of the aqueous phase was withdrawn and placed in a 12-mL graduated centrifuge tube. The original centrifuge tube was lightly tapped to break the remaining meniscus of the aqueous phase, leaving a ring around the top of the organic layer. With a second Pasteur pipette, ca. 4.5 mL of the organic phase was withdrawn and placed in a graduated 12-mL centrifuged tube. All these operations were carried out in the cold room.

At ambient temperature, the isolated aqueous phase was washed into a separatory funnel with three 5-mL portions of H_2O and washed with two 10-mL portions of CH_2Cl_2. The organic layer was set aside. The aqueous layer was submitted to procedure C to give the ester hydrochloride salt, from whose rotation the CSF value was determined.

The isolated organic phase was transferred to a separatory funnel with 5 mL of CH_2Cl_2 and diluted with 10 mL of Et_2O and 10 mL of cyclohexane. The organic layer was washed four or five times with successive 5-mL volumes of H_2O until the last extract gave a negative ninhydrin test. The host-containing organic layer was combined with the organic extracts set aside earlier.

The aqueous extracts were combined and washed with two 10-mL portions of CH_2Cl_2. These organic extracts were combined with those set aside above for host recovery. The aqueous phase was then submitted to procedure C for conversion to the amino ester hydrochloride, whose rotation provided its CRF* value. Host was recovered by the procedure outlined earlier. Host recoveries were nearly quantitative.

When racemic $C_6H_5CH(CO_2H)NH_3ClO_4$ served as guest, six drops of concentrated hydrochloric acid had to be added to the D_2O solution to obtain a homogenous solution.

When racemic $C_8H_6NCH_2CH(CO_2H)NH_3ClO_4$, $CH_3SCH_2CH_2CH(CO_2H)NH_3ClO_4$, or $CH_3CH(CO_2H)NH_3ClO_4$ were guests, 3.0 mmol of free amino acid in 2.5 mL of D_2O that was 2 M in $LiClO_4$ was diluted with 90 μL (1.0 equiv) of 70% $HClO_4$. After the amino acid dissolved, enough additional D_2O that was 2.0 M in $LiClO_4$ was added to provide 3.0 mL of solution that was then extracted with host solution as above.

Determination of the Free Energies of Association of the Hosts with Ammonium, Methylammonium, and *tert*-Butylammonium Picrates. The procedures and equations reported earlier[11,2j] were followed, and Table IV reports the results.

Nuclear Magnetic Resonance Spectra of Diastereomeric Complexes between (*R*)- and (*S*)-$(C_6H_5)_2D(OEOEO)_2E$ and D-$C_6H_5CH(CO_2R')NH_3ClO_4$. A solution of 56 mg (87 mmol) of (*S*)-host and 24.5 mg (92 mmol, 1.1 equiv) of D-$C_6H_5CH(CO_2CH_3)NH_3ClO_4$ in EtOAc was evaporated under vacuum to give a foam, which was dried at 100 °C at 0.2 mm for 30 min (transition temperature, 105 °C). Similarly a solution of 46.2 mg (72 mmol) of (*R*)-host and 19.1 mg (76 mmol) of L-$C_6H_5CH(CO_2H)NH_3ClO_4$ in 10 mL of EtOAc was evaporated under vacuum to give a foam, which was dried at 100 °C and 0.2 mm for 30 min (transition temperature, 110 °C). The complex between (*S*)-$(C_6H_5)_2D(OEOEO)_2E$ and L-$C_6H_5CH(CO_2H)NH_3ClO_4$ has been described above in connection with the resolution of the host. The guest D-$C_6H_5CH(CO_2CH_3)NH_3ClO_4$ was equally effective as a resolving agent of this host, and in this connection, the (*R*)-$(C_6H_5)_2D$-

$(OEOEO)_2E$·D-$C_6H_5CH(CO_2CH_3)NH_3ClO_4$ complex was prepared. Into separate ^1H NMR tubes were placed 10-mg samples of each of the above complexes to which were added 500 μL of 0.45 mol fraction solution of CD_3CN in $CDCl_3$. The ^1H NMR spectra were taken on these four solutions at ambient temperature on a Bruker WP 200 spectrometer.

Registry No. (*S*)-**2** (A = CH_2OH), 55516-00-2; (*S*)-**2** (A = CH_2Cl), 55516-09-1; (*S*)-**2** (A = CHO), 75684-68-3; (*R*)-**3**·L-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75684-70-7; (*R*)-**3**·L-$PhCH(CO_2CH_3)NH_3ClO_4$, 75684-71-8; **3**·NH_4^+·picrate, 75640-37-8; **3**·$CH_3NH_3^+$·picrate, 75640-38-9; **3**·*t*-$BuNH_3^+$·picrate, 75640-39-0; (*R*)-**4**, 75684-72-9; (*R*)-**4**·D-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75684-73-0; **4**·$NH_4^+$·picrate, 75640-40-3; **4**·$CH_3NH_3^+$·picrate, 75640-41-4; **4**·*t*-$BuNH_3^+$·picrate, 75640-42-5; (*S*)-**5**, 75640-43-6; (*S*)-**5**·L-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75640-45-8; (*S*)-**6**, 75640-46-9; (*S*)-**6**·L-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75640-47-0; (*S*)-**6**·L-$PhCH(CO_2CH_3)NH_3ClO_4$, 75640-48-1; (*S*)-**7**, 75640-49-2; (*S*)-**7**·L-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75640-50-5; (*S*)-**8**, 75640-51-6; (*S*)-**8**·L-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75640-52-7; (*S*)-**9**, 75640-53-8; (*S*)-**9**·L-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75640-54-9; (*S*)-**10**, 75640-55-0; (*S*)-**10**·L-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75640-56-1; (*R,S*)-**11**, 75640-57-2; (*R*)-**11**, 75684-74-1; (*S*)-**11**, 75684-75-2; (*R*)-**11**·D-$C_6H_5CH(CO_2H)NH_3ClO_4$, 75684-76-3; (*R*)-**11**·D-$(CH_3)_2CHCH(CO_2CH_3)NH_3ClO_4$, 75684-77-4; (*R*)-**11**·D-$C_6H_5CH(CO_2CH_3)NH_3ClO_4$, 75684-78-5; (*R*)-**11**·D-$(CH_3)_2CHCH(CO_2H)NH_3ClO_4$, 75684-80-9; (*R*)-**11**·D-$C_8H_6NCH_2CH(CO_2CH_3)NH_3ClO_4$, 75684-82-1; (*R*)-**11**·D-$C_8H_6NCH_2CH(CO_2H)NH_3ClO_4$, 75684-84-3; (*R*)-**11**·D-$C_6H_5CH_2CH(CO_2CH_3)NH_3ClO_4$, 75684-85-4; (*S*)-**11**·L-$C_6H_5CH_2CH(CO_2H)NH_3ClO_4$, 75684-86-5; (*R*)-**11**·D-$CH_3SCH_2CH_2CH(CO_2CH_3)NH_3ClO_4$, 75684-88-7; (*R*)-**11**·D-$CH_3SCH_2CH_2CH(CO_2H)NH_3ClO_4$, 75684-90-1; (*R*)-**11**·D-$CH_3CH(CO_2CH_3)NH_3ClO_4$, 75714-58-8; (*R*)-**11**·D-$CH_3CH(CO_2H)NH_3ClO_4$, 75684-91-2; **11**·NH_4^+·picrate, 75640-59-4; **11**·$CH_3NH_3^+$·picrate, 75640-60-7; **11**·*t*-$BuNH_3^+$·picrate, 75640-61-8; (*S*)-**12**, 75640-62-9; (*S*)-**12**·L-$C_6H_5CH(CO_2CH_3)NH_3ClO_4$, 75640-63-0; **12**·$NH_4^+$·picrate, 75640-65-2; **12**·$CH_3NH_3^+$·picrate, 75640-66-3; **12**·*t*-$BuNH_3^+$·picrate, 75640-67-4; (*S*)-**13**, 75684-92-3; (*S*)-**14**, 75640-68-5; (*R,S*)-**15**, 75640-69-6; (*R*)-**15**, 75714-59-9; (*S*)-**15**, 75714-60-2; (*R,S*)-**17**, 75640-70-9; (*R*)-**17**, 75684-93-4; (*S*)-L-**19** ($R^1 = CH_3$), 75684-94-5; (*S*)-L-**19** (R^1 = H), 75684-95-6; (*S*)-D-**19** ($R^1 = CH_3$), 75684-96-7; (*S*)-D-**19** (R^1 = H), 75684-97-8; L-$C_6H_5CH(CO_2H)NH_3ClO_4$, 74292-06-1; D-$C_6H_5CH(CO_2H)NH_3ClO_4$, 74345-75-8; (*S*)-$[C_6(CH_3)_5]_2D(OH)_2$, 75640-71-0; $Nap(OEOEO)_2E$·NH_4^+·picrate, 64916-33-2; $Nap(OEOEO)_2E$·$CH_3NH_3^+$·picrate, 75640-72-1; $Nap(OEOEO)_2E$·*t*-$BuNH_3^+$·picrate, 64916-32-1; $P(OEOEO)_2E$·NH_4^+·picrate, 75640-73-2; $P(OEOEO)_2E$·$CH_3NH_3^+$·picrate, 75640-74-3; $P(OEOEO)_2E$·*t*-$BuNH_3^+$·picrate, 75640-75-4; $D(OEOEO)_2D$·NH_4^+·picrate, 75640-76-5; $D(OEOEO)_2D$·$CH_3NH_3^+$·picrate, 75640-77-6; $D(OEOEO)_2D$·*t*-$BuNH_3^+$·picrate, 75640-78-7; $(CH_3)_2D(OEOEO)_2P$·NH_4^+·picrate, 75640-80-1; $(CH_3)_2D(OEOEO)_2P$·$CH_3NH_3^+$·picrate, 75640-81-2; $(CH_3)_2D(OEOEO)_2P$·*t*-$BuNH_3^+$·picrate, 75640-82-3; $(CH_3)_2D(OEOEO)_2D$·NH_4^+·picrate, 75640-83-4; $(CH_3)_2D(OEOEO)_2D$·$CH_3NH_3^+$·picrate, 75640-84-5; $(CH_3)_2D(OEOEO)_2D$·*t*-$BuNH_3^+$·picrate, 75640-85-6; $(CH_3)_2D(OEOEO)_2D(CH_3)_2$·$NH_4^+$·picrate, 75684-99-0; $(CH_3)_2D(OEOEO)_2D(CH_3)_2$·$CH_3NH_3^+$·picrate, 75685-00-6; $(CH_3)_2D(OEOEO)_2D(CH_3)_2$·*t*-$BuNH_3^+$·picrate, 75685-93-7; D-$C_6H_5CH(CO_2CH_3)NH_3Cl$, 19883-41-1; L-$(CH_3)_2CHCH(CO_2CH_3)NH_3Cl$, 6306-52-1; L-$(CH_3)_2CHCH(CO_2H)NH_3ClO_4$, 74292-12-9; L-$C_8H_6NCH_2CH(CO_2CH_3)NH_3Cl$, 7524-52-9; L-$C_8H_6NCH_2CH(CO_2H)NH_3ClO_4$, 74292-14-1; L-$C_6H_5CH_2CH(CO_2CH_3)NH_3Cl$, 7524-50-7; L-$C_6H_5CH_2CH(CO_2H)NH_3ClO_4$, 74292-10-7; L-$CH_3SCH_2CH_2CH(CO_2CH_3)NH_3Cl$, 2491-18-1; L-$CH_3SCH_2CH_2CH(CO_2H)NH_3ClO_4$, 74292-16-3; D-$CH_3CH(CO_2CH_3)NH_3Cl$, 14316-06-4; D-$CH_3CH(CO_2H)NH_3ClO_4$, 75640-86-7; (*R*)-3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl, 55515-98-5; pentaethylene glycol ditosylate, 41024-91-3; iodomethane, 74-88-4; phenol, 108-95-2; *p*-methoxyphenol, 150-76-5; thiophenol, 108-98-5; benzyl mercaptan, 100-53-8; benzoyl chloride, 98-88-4; (*R*)-2,2′-dimethoxy-1,1′-dinaphthyl, 35294-28-1; (*S*)-2,2′-dimethoxy-1,1′-dinaphthyl, 75640-87-8; (*R*)-2,2′-dihydroxy-1,1′-dinaphthyl, 18531-94-7; (*S*)-2,2′-dihydroxy-1,1′-dinaphthyl, 18531-99-2; (*R,S*)-2,2′-dimethoxy-1,1′-dinaphthyl, 75685-01-7; phenyl bromide, 108-86-1; pentamethylbromobenzene, 5153-40-2; DL-valine methyl ester perchlorate, 75640-88-9; DL-tryptophane methyl ester perchlorate, 75640-89-0; DL-methionine methyl ester perchlorate, 75640-90-3.

Pressure-Induced Cyclotrimerization of Electron-Deficient Nitriles. Catalysis by Acidic Alcohols and Phenols

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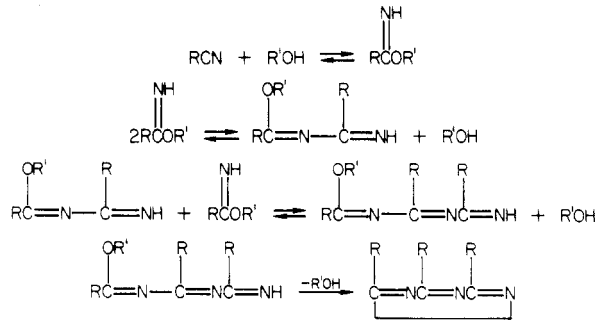
Fluorodinitroacetonitrile (1) was pressurized at 1 GPa in the presence of a variety of ROH catalysts. Cyclotrimerization of 1 occurred in several cases, but the observed triazines contained RO groups in place of one or several $CF(NO_2)_2$ groups. Some mechanistic aspects of this reaction are explored by comparison with the results of the pressurization of preformed fluorodinitroacetimidates.

Nitriles differ considerably in their ability to undergo cyclotrimerization to 1,3,5-triazines under the influence of acidic or basic catalysts. Facile trimerization has been reported for some nitriles[1] (e.g., CCl_3CN and 2-cyanonaphthalene but not 1-cyanonaphthalene with HCl/PCl_5;[2] *F*-alkyl nitriles with NH_3[3]), but in general the scope of this reaction has been limited. The use of high pressure, as first reported by Cairns,[1a] allowed a larger variety of nitriles to be cyclotrimerized. This pressure effect is probably a consequence of the negative volume of activation of addition reactions in general and of cycloadditions in particular.[4] Subsequently, Kurabayashi[5a] et al., Korte,[1b] and Zhulin[5b] provided additional examples and showed that a probable mechanism is formation of imidate ester (or amidine) and its self-condensation to triazine (Scheme I).

Scheme I



Triazines derived from nitro- and polynitroacetonitriles have been sought as high-energy compounds for some time, but several representative nitriles, difluoronitro- and fluorodinitroacetonitrile (1), have resisted attempts at

(1) For leading references see: (a) Cairns, T. L.; Larchar, A. W.; McKusick, B. C. *J. Am. Chem. Soc.* **1952**, *74*, 5633; (b) Jarre, W.; Bienik, D.; Korte, F. *Tetrahedron* **1975**, *31*, 619.
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