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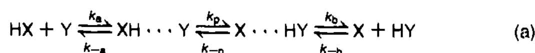

$$\mathrm{HX + Y} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \mathrm{XH \cdots Y} \underset{k_{-p}}{\overset{k_p}{\rightleftharpoons}} \mathrm{X \cdots HY} \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} \mathrm{X + HY} \qquad (a)$$

$$k_f = \frac{k_a k_p k_b}{k_p k_b + k_b k_{-a} + k_{-a} k_{-p}} \qquad (b)$$

Assuming that $k_p \gg k_{-a}$, $k_{-a} \simeq k_b$, and $\log K_p = \Delta pK$ [where $\Delta pK = pK(\text{catalyst}) - pK(\text{intermediate})$] gives

$$k_f = \frac{k_a}{1 + 10^{-\Delta pK}} \qquad (c)$$

Setting $k_f = k_{-d}$ (in eq 6) and $k'_{-s} = 0$ yields eq 8. The same method was used for the derivation of eq 9, except that it was assumed that $k_p \approx k_{-a}$, giving

$$k_f = \frac{k_a}{1 + \frac{k_{-a}}{k_p} + 10^{-\Delta pK}} \qquad (d)$$

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Host–Guest Complexation. 14. Host Covalently Bound to Polystyrene Resin for Chromatographic Resolution of Enantiomers of Amino Acid and Ester Salts[1,2]

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Abstract: A host, $CH_3OCH_2PSCH_2OED(CH_3)_2(OEOEO)_2D$ ((*R,R*)-**12**), was synthesized for preparative or analytical chromatographic resolution of racemic amino acids and esters. In (*R,R*)-**12**, PS is cross-linked polystyrene, ~12% of whose phenyl groups are substituted in the para position with a CH_3OCH_2 group, and 0.8% with a spacer unit ($CH_2OCH_2CH_2$), which in turn is attached to a designed complexing site. This site is a macrocycle composed of two 1,1′-dinaphthyl or D units of the same *R* configuration attached to one another at their 2,2′ positions by two OEOEO units (E is CH_2CH_2). The spacer is attached to the remote 6 position of that D unit which contains two methyl groups substituted in its 3,3′ positions. Columns of this material were used in chromatographic resolutions in $CHCl_3$-CH_3CN of racemic mixtures of $C_6H_5CH(CO_2H)NH_3ClO_4$, *p*-$HOC_6H_4CH(CO_2H)NH_3ClO_4$, $C_6H_5CH_2CH(CO_2H)NH_3ClO_4$, $C_8H_6NCH_2CH(CO_2H)NH_3ClO_4$, $(CH_3)_2CHCH(CO_2H)NH_3ClO_4$, $C_2H_5(CH_3)CHCH(CO_2H)NH_3ClO_4$, $(CH_3)_3CCH(CO_2H)NH_3ClO_4$, $CH_3CH(CO_2H)NH_3ClO_4$, $CH_3SCH_2CH_2CH(CO_2H)NH_3ClO_4$, $C_6H_5CH(CO_2CH_3)NH_3ClO_4$, *p*-$HOC_6H_4CH(CO_2CH_3)NH_3ClO_4$, *p*-$CH_3O_2CC_6H_4CH(CO_2CH_3)NH_3ClO_4$, *p*-$ClC_6H_4CH(CO_2CH_3)NH_3ClO_4$, $C_6H_5CH_2CH(CO_2CH_3)NH_3ClO_4$, and *p*-$HOC_6H_4CH_2CH(CO_2CH_3)NH_3ClO_4$. Separation factors ranged from 26 to 1.4, and resolution factors from 4.5 to 0.21. Host of the *R,R* configuration bound D guest more firmly than L guest by from 1.8 to 0.18 kcal/mol in all cases. A column packed with 9.5 g of (*R,R*)-**12** containing the equivalent of 0.42 g of complexing site gave base-line separation of enantiomers of $C_6H_5CH(CO_2H)NH_3ClO_4$ in runs that involved as much as 15 mg to as little as 0.013 mg of racemate. A host similar to (*R,R*)-**12** in which the two methyl groups are absent, $CH_3OCH_2PSCH_2OED(OEOEO)_2D$ ((*R,R*)-**11**), was found to give lower separation factors than (*R,R*)-**12**. The results are discussed in terms of complementary vs. noncomplementary stereoelectronic diastereomeric relationships between host and guest.

Amino ester salt racemates as a family have been resolved preparatively by solid–liquid and liquid–liquid chromatography that involved designed host-guest complexation. Separation factors varied from 1.52 to 6.4.[4] Derivatives of amino acid racemates have been resolved analytically as gases on long capillary columns of very high plate value in which optically active, derivatized peptides served as liquid phases. Separation factors between enantiomers as high as 1.7 have been observed.[5] Sephadex, covalently bound to L-arginine as a solid phase, was used to resolve preparatively solutions of 3,4-dihydroxyphenylalanine with a separation factor of 1.6. A complementary relationship between ion-pairing sites of the bound amino acid and one enantiomer of the racemate was envisioned.[5c]

This paper reports the first example of the synthesis of designed solid phase hosts useful for both preparative and analytical chromatographic resolution of amino acid and ester racemates as a family.[2] Macromolecules (*R,R*)-**11** and (*R,R*)-**12** (Chart I) are composed of a macroreticular cross-linked polystyrene *p*-divinylbenzene resin on which have been grafted the chiral hosts (*R,R*)-**1** and (*R,R*)-**2**, respectively. About 0.8% of the para positions of the C_6H_5 groups available

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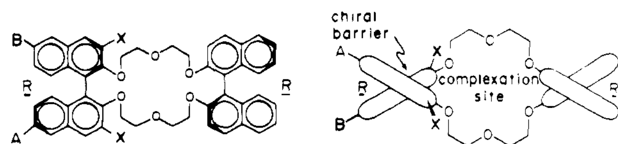
Chart I[a]



[a] (R,R)-1, A = B = X = H; (R,R)-2, A = B = H, X = CH_3; (R,R)-3, A = B = Br, X = H; (R,R)-4, A = B = Br, X = CH_3; (R,R)-5, A = B = CH_2CH_2OH, X = H; (R,R)-6, A = B = CH_2CH_2OH, X = CH_3; (R,R)-7, A = CH_2CH_2OH, B = X = H; (R,R)-8, A = CH_2CH_2OH, B = H, X = CH_3; (R,R)-9, A = $CH_2CH_2OCH_2$-PS-CH_2Cl (PS = polystyrene), B = X = H; (R,R)-10, A = $CH_2CH_2OCH_2$-PS-CH_2Cl_3, B = H, X = CH_3; (R,R)-11, A = $CH_2CH_2OCH_2$-PS-CH_2OCH_3, B = X = H; (R,R)-12 = $CH_2CH_2OCH_2$-PS-CH_2OCH_3, B = H, X = CH_3.

in the polymer are occupied in (*R,R*)-**12** by the (*R,R*)-**2** binding sites to provide ~0.056 mmol of host/g, or ~17 800 mass units for an average site.

Results

Syntheses of the Host-Bound Resins. Optically pure (*R*)-2,2'-dihydroxy-1,1'-dinaphthyl[6a] and (*R*)-2,2'-dihydroxy-3,3'-dimethyl-1,1'-dinaphthyl[6b] were brominated to give (*R*)-6,6'-dibromo-2,2'-dihydroxy-1,1'-dinaphthyl (94%) and (*R*)-6,6'-dibromo-3,3'-dimethyl-2,2'-dihydroxy-1,1'-dinaphthyl (90%), respectively. These substances, with optically pure (*R*)-2,2'-bis(1,4-dioxa-6-tosyloxyhexyl)-1,1'-dinaphthyl[6a] and KOH-THF, gave cycles (*R,R*)-**3** (74%) and (*R,R*)-**4** (69%), respectively. Metallation of (*R,R*)-**3** with BuLi and treatment of the product with ethylene oxide gave optically pure parent cycle (*R,R*)-**1** (30%), diethoxylated cycle (*R,R*)-**5** (10%), and monoethoxylated cycle (*R,R*)-**7** (55%). Similarly, (*R,R*)-**4** gave optically pure (*R,R*)-**2** (25%), (*R,R*)-**6** (6%), and (*R,R*)-**8** (60%).

Hosts (*R,R*)-**7** and (*R,R*)-**8** were attached through their 6-substituted CH_2CH_2O spacer units to a solid phase by reaction of their sodium alkoxides with ~15% chloromethylated macroreticular polystyrene-divinylbenzene copolymer to give (*R,R*)-**9** and (*R,R*)-**10**, respectively. The differences between the amounts of (*R,R*)-**7** and (*R,R*)-**8** used and recovered from the reactions were used to calculate the amounts of cycles covalently bound to the resin. These amounts were consistent within experimental error with the loss in the amounts of chlorine content of the resins during the reactions. To destroy the CH_2Cl groups on the resin unavailable to the large cyclic alkoxides, (*R,R*)-**9** and (*R,R*)-**10** were treated with $NaOCH_3$ to give (*R,R*)-**11** and (*R,R*)-**12**, respectively. Grafted polymer (*R,R*)-**11** contained ~0.048 mmol of cycle/g, 0.17 mequiv of Cl/g, and 0.90 mequiv of CH_3O groups/g. Grafted polymer (*R,R*)-**12** contained ~0.056 mmol of cycle/g, 0.18 mequiv of Cl/g, and 0.87 mequiv of CH_3O groups/g.

Chromatographic Columns. The host-bound resins were sieved, suspended in CH_3CN-$CHCl_3$, and pumped into jacketed and insulated stainless steel columns, which were conditioned by pumping through their beds, in turn, degassed CH_3OH, $CHCl_3$, and, finally, the solvent used for the runs. The columns were fitted with injection loops for sample introduction. The bottoms of the columns led to conductivity cells attached to a recorder. The relative conductivity of the cell was found to be proportional to the concentration of the alkylammonium salt in chloroform-host solutions.[4c] The dead volume of each column was determined by injecting the nonretained compounds methanol, benzene, hexane, and pentane as samples onto the columns, and determining their retention volumes (see Experimental Section).

Column A was 60 by 0.75 (i.d.) cm in dimension and was packed with 9.5 g of 250-325 mesh (*R,R*)-**12**. Column B was 60 by 0.40 (i.d.) cm and was packed with 4.0 g of 325-400 mesh (*R,R*)-**12**. Column C was the same size as B and was packed with 4.0 g of 325-400 mesh (*R,R*)-**11**.

Chromatographic Resolutions of Enantiomers. The runs were made at constant temperature maintained by passing water-ethylene glycol at constant temperature through the jackets of the columns. During the runs, constant flow rates were maintained between 0.27 and 2.0 mL/min with pressure drops between 350 and 900 psi. Between 0.013 and 84 mg/run of racemic $*RNH_3ClO_4$ or $*RNH_3PF_6$ was injected into the loop at the top of the column. Corrections, which were less than one third of the dead volume, were made for the loop, detector, and tubing volumes. The appearance of enantiomers in the column eluate was detected conductometrically. The mobile phases were $CHCl_3$ or CH_2Cl_2 containing 5-25% by volume of CH_3CN or EtO_2CCH_3 to act as salt carriers. The use of ethers or alcohols as the main solvents gave no enantiomer separation. However, small amounts of CH_3OH or $(CH_3)_2CHOH$ as salt carriers in $CHCl_3$ or CH_2Cl_2 gave moderately good results, but were not generally investigated.

Plots of relative conductance (μmho) against volume of column eluate (mL) for each chromatographic run provided the parameters that indicate the effectiveness of the separations.[8] The peaks were Gaussian and showed little tailing. The enantiomer separation factor (α) is defined by eq 1, in which V_{RA} is the retention volume of enantiomer A (more firmly complexed by the stationary phase and appearing last in the column eluate); V_{RB} is the retention volume of enantiomer B (less firmly complexed and appearing first in the eluate); and V_M is the dead volume of the column. The enantiomer resolution factor (R_s) is defined by eq 2, in which W_A is the bandwidth (mL) of enantiomer A and W_B is that of enantiomer B. Under ideal conditions, the differences in free energies of complexed enantiomers A and B are represented by eq 3.[8] In some runs, the conditions were probably not ideal. The results of these runs can be conveniently discussed in terms of the $-\Delta(\Delta G°)$ values even though they are only approximations. The configurational identities and optical purities of the faster (less complexed) and slower (more complexed) moving enantiomers were identified by isolation and characterization of the pure antipodes in runs 9, 20, and 26 of Table I, which records the results obtained with amino acid perchlorates as guests. In runs 6-21 and 27, the identifications of the faster and slower moving enantiomers were made by determinations of the signs of rotation of the eluate fractions. The signs of rotations of authentic L-amino acids salts were taken in the solvents used in these runs, and the signs and configurations correlated. In runs 22-26 and 32-34, each peak was collected, the solvent evaporated, and the residue dissolved in absolute methanol. The signs of rotation were taken. The correlations with configurations reported are based on the signs of rotations of authentic L-amino acid salts taken in absolute methanol. In those runs with base-line separation, the areas under the two bands were essentially equal to one another.

$$\alpha = (V_{RA} - V_M)/(V_{RB} - V_M) \quad (1)$$

$$R_s = 2[(V_{RA} - V_{RB})/(W_A + W_B)] \quad (2)$$

$$-\Delta(\Delta G°) = RT \ln \alpha \quad (3)$$

Table II reports the results of chromatographic runs made with methyl esters of six different amino acid salts and columns A, B, and C. Both perchlorate and hexafluorophosphate salts were examined. Base-line separations were observed for all runs except 12-15. In those runs with base-line separation, the areas under the bands were essentially equal to one another. The more complexed and slower moving enantiomers were identified by isolation and characterization of the pure antipodes in runs 2, 4, and 5 (or ones like them). In the other runs, the more and the less bound enantiomers were identified by their signs of rotation. In runs 1-3 and 7-15, the signs were determined in the column eluate. Configurations were assigned

Table I. Resolution of Enantiomers of $RCH(CO_2H)NH_3ClO_4$ Guests (G) by Solid-Liquid Chromatography with *R,R* Hosts (H)

run no.	column used[a]	guest: structure of R	guest: wt, mg	H/G[b]	mobile phase[c]: solvent	carrier: kind	carrier: %[d]	T, °C	sepn factor: α[e]	sepn factor: kind[f]	$-\Delta(\Delta G^\circ)$, kcal/mol[g]	resl factor, R_s[h]	guest enantiomers: config[i]	more bound: sign of α_{obsd}[j]	more bound: V_{RA}, mL	less bound: sign of α_{obsd}[j]	less bound: V_{RB}, mL
1	A	C_6H_5	0.013	11 000	$CHCl_3$	MeCN	10	0	5.5	base line	0.9	1.99	D		100		38
2	A	C_6H_5	0.13	1 100	$CHCl_3$	MeCN	10	0	8.9	base line	1.2	2.72	D		116		34
3	A	C_6H_5	0.32	420	$CHCl_3$	MeCN	10	0	11.0	base line	1.3	2.89	D		119		32
4	A	C_6H_5	0.60	220	$CHCl_3$	MeCN	10	0	11.6	base line	1.3	2.86	D		114		32
5	A	C_6H_5	1.9	70	$CHCl_3$	MeCN	10	0	12.2	base line	1.4	1.76	D		89		29
6	A	C_6H_5	5.0	27	$CHCl_3$	MeCN	10	0	14.6	base line	1.5	1.13	D	−	72	+	27
7	A	C_6H_5	10.1	13	$CHCl_3$	MeCN	10	0	24.3	base line	1.7	0.74	D	−	54	+	25
8	A	C_6H_5	15.2	8	$CHCl_3$	MeCN	10	0	12.2	base line	1.4	0.76	D	−	51	+	26
9	A	C_6H_5	20.5	6	$CHCl_3$	MeCN	10	0	10.0	minimum	1.25	0.54	D	−	30	+	25
10	A	C_6H_5	84	1.5	$CHCl_3$	MeCN	10	0	10.7	minimum	1.2	0.20	D	−	30	+	24
11	A	C_6H_5	5.08	27	$CHCl_3$	EtOAc	5	25	4.5	base line	0.9	1.35	D	mins	69	+	34
12	A	C_6H_5	5.04	27	$CHCl_3$	EtOAc	5	0	10.9	base line	1.3	1.92	D		134		34
13	A	C_6H_5	16.1	8	$CHCl_3$	EtOAc	10	0	7.4	base line	1.1	1.23	D	−	62	+	28
14	A	C_6H_5	16.0	8	$CHCl_3$	EtOAc	15	0	4.7	minimum	0.8	0.61	D	−	49	+	29
15	A	C_6H_5	5.1	26	$CHCl_3$	EtOAc	25	0	4.3	base line	0.8	0.85	D		45		28
16	A	C_6H_5	15.7	8	CH_2Cl_2	MeCN	5	0	5.3	base line	0.9	1.22	D	−	140	+	45
17	A	C_6H_5	14.5	9	CH_2Cl_2	MeCN	17	0	3.4	minimum	0.7	0.39	D	−	37	+	28
18	A	C_6H_5	14.7	9	Et_2O	MeCN	10	0	1.0	none	0.0	0.00	D		36		36
19	A	*p*-HOC_6H_4	6.6	21	$CHCl_3$	MeCN	10	0	6.1	base line	1.0	2.31	D	−	426		90
20	A	$C_6H_5CH_2$	4.6	31	$CHCl_3$	MeCN	4	0	2.3	base line	0.45	0.97	D	−	123	+	67
21	A	*p*-HOC_6H_4-CH_2	5.8	28	$CHCl_3$	MeCN	10	0	1.9	minimum	0.35	0.42	D	−	89	+	59
22	A	$C_8H_6NCH_2$[k]	2.0	80	$CHCl_3$	MeCN	20	0	6.1	base line	1.0	1.61	D	+[l]	278	−[l]	66
23	A	$(CH_3)_2CH$	1.6	74	$CHCl_3$	MeCN	10	0	2.3	minimum	0.45	0.45	D	−[l]	69	+[l]	44
24	A	$C_2H_5(CH_3)$-CH	2.3	53	$CHCl_3$	MeCN	5	0	1.9	minimum	0.3	0.24	D	−[l]	59	+[l]	42
25	A	$(CH_3)_3C$	2.0	61	$CHCl_3$	MeCN	5	0	1.9	minimum	0.3	0.37	D	−[l]	61	+[l]	44
26	A	CH_3	1.6	63	$CHCl_3$	MeCN	4	0	1.5	minimum	0.2	0.21	D	−[l]	52	+[l]	43
27	A	CH_3SCH_2-CH_2	6.6	20	$CHCl_3$	MeCN	4	0	1.4	minimum	0.8	0.25	D	−	86	+	67
28	B	C_6H_5	1.7	33	$CHCl_3$	MeCN	10	25	4.1	base line	0.8	0.89	D		19		12
29	B	*p*-HOC_6H_4	2.4	25	$CHCl_3$	MeCN	10	25	4.2	base line	0.85	1.55	D		71		24
30	B	$C_6H_5CH_2$	1.0	58	$CHCl_3$	MeCN	10	25	1.2	minimum	0.1	0.25	D		14		13
31	B	$(CH_3)_3C$	1.4	36	$CHCl_3$	MeCN	5	25	1.4	minimum	0.2	0.52	D		25		21
32	C	C_6H_5	2.0	23	$CHCl_3$	MeCN	2.5	0	2.4	minimum	0.5	0.35	D	−[l]	17	+[l]	13
33	C	*p*-HOC_6H_4	1.7	30	$CHCl_3$	MeCN	10	0	1.8	minimum	0.3	0.23	D	−[l]	32	+[l]	22
34	C	*p*-HOC_6H_4-CH_2	1.1	48	$CHCl_3$	MeCN	5	0	1.6	minimum	0.3	0.21	D	−[l]	33	+[l]	24

[a] Column A contained 9.5 g of (*R,R*)-**12** or 0.53 mmol of host (H) sites; column B, 4.0 g of (*R,R*)-**12** or 0.22 mmol of H sites; column C, 4.0 g of (*R,R*)-**11** or 0.19 mmol of H sites. [b] Ratio of moles of H to moles of G. [c] Reagent-grade solvents. $CHCl_3$ contained 0.75% EtOH. [d] By volume. [e] Equation 1. [f] Base line means base line separation. [g] Equation 3. [h] Equation 2. [i] Enantiomer A. [j] λ 578 and 546 nm; solvent is column eluant unless otherwise noted. [k] β-indolylmethyl. [l] MeOH as solvent.

based on the signs of rotation of authentic L-amino ester salts taken in the solvent of the run. In runs 4-6, the two eluant bands were evaporated, and the signs of rotation of their salts were determined in methanol. Runs 4-6 and 11 involved esters not previously resolved.[9] With column A and larger amounts of the salts than in these runs, *p*-$CH_3O_2CC_6H_4CH(CO_2CH_3)NH_3ClO_4$ and *p*-$ClC_6H_4CH(CO_2CH_3)NH_3ClO_4$ were totally resolved. The CD spectra of all four phenylglycine and two phenylalanine methyl ester perchlorate salts were determined in CH_3OH. Each of the six salts gave two Cotton effects, one at 215-220 nm ($\pi \rightarrow \pi^*$ transitions) whose sign was configuration dependent and the other at 250-260 nm whose sign was configuration independent and negative. The L enantiomers of the four salts of known absolute configuration all gave a positive Cotton effect at the lower wavelength, and this correlation was used to assign configurations to the two salts of unknown configuration (see Experimental Section).

Discussion

Utility of Chromatographic Columns for Enantiomer Separations and Analysis. Resin-bound host (*R,R*)-**12** provides a material for effective solid-liquid chromatographic resolution of racemates into enantiomers for amino acid and ester perchlorate or hexafluorophosphate salts. Column A, containing 9.5 g of (*R,R*)-**12**, provided separations in either $CHCl_3$ or CH_2Cl_2 of 16 salts of the type $RCH(CO_2R')NH_3ClO_4$ in which R represents 12 different groups and R′ was either H or CH_3. With the exception of $\alpha = 1$ in run 8 using Et_2O as a solvent, separation factors (α) for enantiomers ranged from 26 (run 1, Table II) to 1.4 (run 27, Table I), which represents a spread of $-\Delta(\Delta G^\circ)$ values for the diastereomeric complexes of ~1.8-0.18 kcal/mol. Resolution factors (R_s) ranged from 4.5 (runs 2 and 3, Table II) to 0.21 (run 26, Table I). Phenylglycine perchlorate gave the highest and alanine the lowest. Even with methionine perchlorate (run 27), which gave the lowest separation factor (α = 1.4), proper cutting of eluate fractions provided substantial amounts of pure enantiomers.

The same column (A) was used, both analytically and preparatively. Since the column contained ~0.53 mmol of host sites, the ratio of host to guest sites (H/G) involved in a run could be calculated. With $C_6H_5CH(CO_2H)NH_3ClO_4$ as G, base-line separation of enantiomers was observed with as little as 0.013 mg of salt (H/G = 11 000, run 1, Table I) or as much as 15.2 mg (H/G = 8, run 8, Table I). Thus, the column performed well when the amount of racemate submitted for res-

Table II. Resolution of Enantiomers of $RCH(CO_2CH_3)NH_3X$ Guests (G) by Solid–Liquid Chromatography on *R,R* Hosts (H)

run no.	column used[a]	guest structure R	guest structure X	guest wt, mg	H/G[b]	% CH_3CN in $CHCl_3$ as mobile phase[c]	*T*, °C	sepn factor α[d]	$-\Delta(\Delta G°)$, kcal/mol[e]	resln factor R_s[f]	guest enantiomers, more bound: config[g]	more bound: sign of α_{obsd}[h]	more bound: V_{RA}, mL	less bound: sign of α_{obsd}[h]	less bound: V_{RB}, mL
1	A	p-HOC_6H_4	ClO_4^-	9.5	16	10	0	26	1.8	3.0	D	−		+	
2	A	C_6H_5	ClO_4^-	9.5	15	10	0	18.5	1.6	4.5	D	−		+	
3	A	C_6H_5	PF_6^-	2.1	77	5	0	18.2	1.6	4.5	D	−	39	+	22
4	A	p-CH_3O_2C-C_6H_4	ClO_4^-	9.5	18	10	0	12.6	1.4	2.3	D	−[i]		+[i]	
5	A	p-ClC_6H_4	ClO_4	9.5	17	10	0	8.5	1.2	2.2	D	−[i]		+[i]	
6	A	p-ClC_6H_4	PF_6^-	5.0	37	10	0	8.1	1.1	1.2	D	−[i]	76	+[i]	30
7	A	$C_6H_5CH_2$	ClO_4^-	9.5	16	10	0	6.4	1.0	1.9	D	−		+	
8	A	p-HOC_6H_4-CH_2	ClO_4^-	9.5	17	10	0	4.7	0.8	1.7	D	−		+	
9	B	C_6H_5	ClO_4^-	2.0	29	10	25	4.3	0.9	1.02	D	−	28	+	14
10	B	C_6H_5	PF_6^-	2.5	28	5	25	4.3	0.9	0.77	D	−	23	+	13
11	B	p-CH_3O_2-CC_6H_4	PF_6^-	2.2	36	5	25	9.0	1.3	0.84	D	−	30	+	25
12	B	$C_6H_5CH_2$	ClO_4^-	2.6	24	5	25	3.2	0.7	0.58	D	−	15	+	11
13	B	p-HOC_6H_4-CH_2	ClO_4^-	2.7	24	10	25	2.2	0.6	0.24	D	−	14	+	12
14	C	C_6H_5	PF_6^-	5.4	11	5	0	4.1	0.8	0.48	D	−	20	+	12
15	C	C_6H_5	PF_6^-	0.5	116	10	0	1.7	0.3	0.25	D	−	15	+	13

[a] Column A contained 9.5 g of (*R,R*)-**12**, or 0.53 mmol of host (H) sites; column B, 4.0 g of (*R,R*)-**12**, or 0.22 mmol of H sites; column C, 4.0 g of (*R,R*)-**11**, or 0.19 mmol of H sites. [b] Ratio of moles of H to moles of G. [c] Reagent-grade solvents. $CHCl_3$ contained 0.75% EtOH, percent by volume. [d] Equation 1. [e] Equation 3. [f] Equation 2. [g] Enantiomer A. [h] λ 578 and 546 nm; solvent is column eluant, unless otherwise noted. [i] CH_3OH as solvent.

olution varied by a factor of $>10^3$. Even when badly overloaded with 84 mg of salt (run 10, Table I), over half of each enantiomer was obtained in an optically pure state.

Although these chromatographic columns were designed to separate and differentiate enantiomers, they probably could be used to identify different amino acids as well. Solvent composition and pressure were not kept constant for all the different amino acids examined, so general comparisons of changes in their retention volumes with changes in structure cannot be made. Usually, solvent composition and pressure were adjusted to give convenient retention volumes. What comparisons can be made suggest that, had standard conditions been maintained, retention volumes would have varied markedly with changes in the structures of the amino acid. For example, runs 20 and 24–27 were all made on column A with ~95% $CHCl_3$–5% CH_3CN at about the same pressure (650–700 psi). As the side chain varied in the order $C_6H_5CH_2$, $CH_3SCH_2CH_2$, $(CH_3)_3C$, $C_2H_5(CH_3)CH$, and CH_3, V_{RA} (mL) changed in the order 123, 86, 61, 59, and 52. Runs 6, 19, 21, and 23 were conducted with 90% $CHCl_3$–10% CH_3CN. As the side chain varied in the order p-HOC_6H_4, p-$HOC_6H_4CH_2$, C_6H_5, and $(CH_3)_2CH$, V_{RA} (mL) changed in the order, 426, 89, 72, and 69. Tryptophan had such a large V_{RA} with this solvent mixture that the CH_3CN carrier had to be increased to 20%, which gave a V_{RA} of 278.

The Question of Whether All Host Sites Bound to Polymer Exhibit the Same Degree of Chiral Recognition. The important question arises as to whether, in a host-polymer such as (*R,R*)-**12**, each binding site shows the same chiral recognition toward a particular guest. The character of the polymer-host is material to a discussion of this question. The macroreticular resin used possessed an average pore diameter of 90 Å and a surface area of 330 m^2/g, and was cross-linked enough not to swell noticeably when wet with the solvents used. In the preparations of the host-polymers used in the separations, the conditions were designed to maximize the number of host sites. In the preparation of (*R,R*)-**12**, ~0.8% of the C_6H_5 groups theoretically available in the original polymer became attached to the macrocycle.

Host **2** has a molecular weight of 740. It is fairly rigid and possesses molecular dimensions of ~18 by 11 by 10 Å (CPK molecular model examination). Apparently, even with the $CH_2OCH_2CH_2$ spacer group between the polymer and host, only a relatively small number of sites on the polymer surface were sterically available to this large reactant. For (*R,R*)-**12**, the average number of mass units per host site is ~17 800, and ~4.4% of it by weight is the macrocyclic binding site. The remainder appears to be support structure. In this sense, (*R,R*)-**12** resembles the smaller of the enzyme systems. They possess molecular weights in the 10 000–20 000 range, only a fraction of which involves binding and catalytic sites, the rest being support structure.

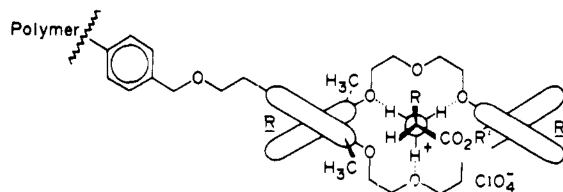
The molecular weights of the guest cations used in the chromatograms ranged from ~140 to 224 and their molecular dimensions are much less than those of the host sites. Thus it seems reasonable to expect that any place on the polymer sterically available to the relatively large host molecules should also be available to the smaller guest molecules. However, it is possible that the chiral recognition exhibited by host binding sites attached to the more sterically confined aryl groups in the narrower pores of the polymer might be different from the nonconfined sites more surrounded by solvent. The results of runs 1–10 of Table I that involve (*R,R*)-**12** and $C_6H_5CH(CO_2H)NH_3ClO_4$ bear on this question.

If all the host sites in (*R,R*)-**12** produced the same chiral recognition, the $\Delta(\Delta G°)$ values that measure chiral recognition should be independent of H/G values. In runs 1–10, $-\Delta(\Delta G°)$ varied from 0.9 kcal/mol at H/G = 11 000 to a maximum of 1.7 at H/G = 13, and decreased to 1.25 kcal/mol at H/G = 1.5. These results are explained by the presence of the following two opposing effects, one operative at high and the other at low H/G values. When very small amounts of guest were put on the column (e.g., H/G = 11 000), only 1:1 complexes were formed at the sterically most available sites, and these sites exhibited lower chiral recognition than the more confined host sites. This explanation presumes the reasonable assumption that the more exposed complexed sites possess a more negative free energy of binding toward both enantiomers

than do the more confined complexing sites. As the amounts of guest were increased, the sterically more confined sites which exhibited higher chiral recognition were engaged in binding, and the $-\Delta(\Delta G°)$ values increased to 1.7 kcal/mol at H/G = 13. When H/G values decreased further, complexes formed at the top of the column that involved two guests to one host. These complexes were less structured, and lower chiral recognition resulted.

As a result of this study with $C_6H_5CH(CO_2H)NH_3ClO_4$ as guest, the H/G ratios employed in runs that involved the other guests were kept mainly in the 8-80 range. Thus the amounts of guest involved were practical from the point of view of solubility and identification, and this range gave the most representative chiral recognition. However, the fact that the free energies of complexation were somewhat dependent on H/G values makes fine distinctions in comparisons between guests impossible.

Racemate Resolution by Rational Design of Chiral Complexing Agent. Unlike conventional resolutions of racemates into their enantiomers, those described here are rational in the sense that in most cases the more bound enantiomer was predicted in advance of experiment based on complementary stereoelectronic compatibility between host and guest and on results of complexation studies in solution.[10a,b] Molecular model (CPK) examination of diastereomeric complexes led to generalized complex (*R,R*)-D-**13** as being the more stable.



(R,R)-D-13

Therefore, the D-amino acid or ester salt was expected to be the more retained enantiomer on the columns.

In molecular models of the host, the four naphthalene rings occupy planes that are roughly perpendicular to the best plane of the macroring. Two of the naphthalene rings extend above and tangent and two below and tangent to the macroring. The naphthalene rings provide walls or chiral barriers that divide into two cavities on each face of the macroring, the space available to the R, CO_2R', and H groups attached to the asymmetric center of the potential guests. The methyl groups attached to one of the dinaphthyls extend the chiral barrier, and inhibit folding of the macroring. Aside from the side chain (spacer) attached at the remote 6 position, the chiral binding site possesses a C_2 axis, so that essentially the same complex is formed by the approach of a guest to either face. The visualized complex is held together by three $NH^+ \cdots O$ interactions in a tripod arrangement, by three $N^+ \cdots O$ interactions in a triangular arrangement, and by π-π CO_2R' to naphthalene attractions. In (*R,R*)-D-**13**, these latter two groups occupy parallel planes that contact one another. In (*R,R*)-D-**13**, the H and CO_2R' groups attached to the chiral center occupy the lower cavity and the bulky R group occupies the upper cavity on the top face of the host.

Comparison of Chiral Recognition in Solution and at a Polymer-Solution Interface. The directions of the configurational bias and degrees of chiral recognition in complexation in $CHCl_3$ solution with (*R,R*)-**2** toward a variety of guests[10] are similar to those observed for (*R,R*)-**12** at the polymer-$CHCl_3$ interface. Thus, in $CHCl_3$-CH_3CN at 0 °C, (*R,R*)-**2** complexed D-$RCH(CO_2H)NH_3ClO_4$ better than it complexed L-$RCH(CO_2H)NH_3ClO_4$, by $-\Delta(\Delta G°)$ values that decreased in magnitude as the R groups were changed as follows: $C_6H_5 > p\text{-}HOC_6H_4 > C_8H_6NCH_2 > C_6H_5CH_2 \sim (CH_3)_2CH > CH_3SCH_2CH_2 \sim CH_3$.[10c,d] A comparable order with comparable $-\Delta(\Delta G°)$ magnitudes is visible in runs 6, 19, 22, 20, 23, 26, and 27 of Table I, where complexation occurs at 0 °C at the polymer-$CHCl_3$ interface.

With the amino ester salts, $RCH(CO_2CH_3)NH_3PF_6$, in solution in $CHCl_3$ at 0 °C, the (*R,R*)-D complex was favored over the (*R,R*)-L complex, by $-\Delta(\Delta G°)$ values that decreased in magnitude as the R group was changed as follows: $C_6H_5 \sim p\text{-}HOC_6H_4 > C_6H_5CH_2$.[10b] At the polymer-$CHCl_3$ interface at 0 °C for $RCH(CO_2CH_3)NH_3ClO_4$, the same order applied (see runs 1, 2, and 7 in Table II).

Other similarities exist between the results in solution (one-plate extractions)[10] and those at the polymer-solvent interface. For both environments, higher chiral recognition was observed with binding sites whose chiral barriers were extended by two methyl groups (see (*R,R*)-**2** and (*R,R*)-**12**) compared with those without the methyls such as (*R,R*)-**1** and (*R,R*)-**11** (compare, Table I, run 6 with 32, 19 with 33, and 21 with 34, and appropriate pairs of runs in ref 10b with those in 10a). For both environments, higher chiral recognition was observed at 0 °C than at 25 °C (compare, Table I, run 6 with 28, 19 with 29, 20 with 30, and 25 with 31; Table II, run 2 with 9, 4 with 11, 7 with 12, and 8 with 13; and appropriate pairs of runs in ref 10a,b). For both environments, PF_6^- or ClO_4^- as counterions gave nearly comparable results (compare, Table II, run 2 with 3, 5 with 6, and 9 with 10, and appropriate runs in ref 10b). For both environments, $CHCl_3$ or $CHCl_3$-CH_3CN mixtures as solvent or mobile phase gave the highest chiral recognition. Substitution of CH_2Cl_2 for $CHCl_3$ as in runs 16 and 17 of Table I resulted in lower chiral recognition and larger retention volumes, particularly for the more firmly bound isomer. Substitution of Et_2O for $CHCl_3$ eliminated chiral recognition altogether (run 18). Other ethers or alcohols as the main mobile phase also gave no enantiomer separation. Apparently ethers and alcohols as solvents themselves provide good enough hydrogen bonding sites to inhibit complexation. Similar responses to these solvent changes have been observed in one-plate extraction experiments with $C_6H_5CH(CO_2CH_3)NH_3PF_6$ and (*R,R*)-**2**.[11] Small amounts of CH_3OH (3%) or $(CH_3)_2CHOH$ (10%) can be used as guest carriers in $CHCl_3$ or CH_2Cl_2. Although lower chiral recognition was observed, lower volumes of solvent were needed to place the guest on the column. Interestingly, runs 11-15 of Table I indicate that $CHCl_3$-EtOAc can be substituted for $CHCl_3$-CH_3CN with $C_6H_5CH(CO_2H)NH_3ClO_4$ as guest with little change in chiral recognition. Unfortunately, no comparisons are available in one-plate extraction experiments.

Effect on Chiral Recognition of Para Substituents (X) in Guests $p\text{-}XC_6H_4CH(CO_2CH_3)NH_3ClO_4$ and $p\text{-}XC_6H_4CH_2CH(CO_2CH_3)NH_3ClO_4$. Substitution of *p*-HO groups in place of hydrogen in the phenyl rings of guests $C_6H_5CH(CO_2H)NH_3ClO_4$ and $C_6H_5CH_2CH(CO_2H)NH_3ClO_4$ produced a marked effect on the chiral recognition of (*R,R*)-**12** for these guests. This substitution in phenylglycine reduced the chiral recognition from about $-\Delta(\Delta G°)$ of 1.5 to 1.0 kcal/mol (runs 6 and 19, Table I), but the direction of the chiral bias was not changed. The same substitution in phenylalanine to give tyrosine changed $-\Delta(\Delta G°)$ from 0.45 to 0.35 kcal/mol (runs 20 and 21, Table I). General model (*R,R*)-D-**13** for the more stable diastereomeric complexes takes no account of substituent effects in positions in the guest remote from the binding sites. Consequently substituent effects were examined somewhat more thoroughly in the ester series.

In runs 1, 2, 4, and 5 of Table II with (*R,R*)-**12** as host, X of $p\text{-}XC_6H_4CH(CO_2CH_3)NH_3ClO_4$ was varied from HO to H to CH_3O_2C to Cl. In the four runs carried out under identical conditions, the D enantiomer was always the more complexed, but the $-\Delta(\Delta G°)$ values changed in the respective

order 1.8, 1.6, 1.4, and 1.2 kcal/mol. This order correlates very roughly with the Hammett σ values for these substituents (correlation coefficient of 0.84)[12] with $\rho = -0.54$. In the X-ray structure of the less stable diastereomeric complex between (*S,S*)-**1** and D-$C_6H_5CH(CO_2CH_3)NH_3PF_6$, the rather acidic hydrogen attached to the asymmetric center of the guest "hydrogen bonds" one of the oxygens of the macroring of the host.[13] This hydrogen is acidified by the NH_3^+, CO_2CH_3, and *p*-XC_6H_4 groups attached to the asymmetric carbon. A plausible explanation for the above order of $\Delta(\Delta G°)$ values is the effect of the X substituent on the acidity of this carbon acid, which directly affects the stability of the *less stable* diastereomeric complex. Thus the more acidifying the X substituent, the more stable the (*R,R*)-**12**-(*S*)-guest complexes should become. The thermodynamically favored (*R,R*)-**12**-(*R*)-guest complexes should be relatively insensitive to this particular remote substituent effect, as is suggested by the general model, (*R,R*)-D-**13**.

In runs 7 and 8 of Table II with (*R,R*)-**12** as host, the behavior of *p*-$XC_6H_4CH_2CH(CO_2CH_3)NH_3ClO_4$ guests was examined under standard conditions. With X = H and HO, the D enantiomer was again the more complexed,[14] with $-\Delta(\Delta G°)$ values of ~1.2 and ~0.8 kcal/mol, respectively. In the X-ray structure[13] of (*S,S*)-**1**-D-$C_6H_5CH(CO_2CH_3)$-NH_3PF_6, the CO_2CH_3, and oxynaphthyl groups lie in parallel planes, and probably π bind one another. An examination of CPK molecular models of (*R,R*)-D-**13** indicates a geometry ideal for a similar electronic effect for this more stable diastereomer, as well. This π binding should be subject to remote substituent effects in complexes for each diastereomer of the ester salts of both phenylglycine and phenylalanine. However, it is impossible to guess which diastereomer is more subject to this π binding.

The overall binding energies in these complexes are small, and the $-\Delta(\Delta G°)$ values reflect the net of several different opposing binding effects. In view of the complexities, the surprising feature of this study is that model (*R,R*)-D-**13** qualitatively correlates all of the results.

Experimental Section

General. All chemicals and solvents were reagent grade. Tetrahydrofuran (THF) and 1,2-dimethoxyethane were distilled from sodium benzophenone ketyl immediately prior to use. Thin-layer chromatography was performed on silica-gel-coated glass plates (0.25-mm thickness) with 1% Du Pont Phosphor as UV indicator. Melting points below 200 °C were measured on a Thomas-Hoover apparatus, those above 200 °C were measured on a Mel-Temp apparatus, and all are uncorrected. Mass spectra were recorded on an AEI Model MS-9 double-focusing spectrometer. The ^1H NMR spectra were recorded in $CDCl_3$ on a Varian T-60 or HA-100 NMR spectrometer, and the chemical shifts are given in δ (parts per million) with internal Me_4Si as standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter in a 1 dm thermostated cell at 25 °C. The ORD and CD spectra were recorded on a Cary 60 recording spectrophotometer equipped with a circular dichroism accessory, Cary Model 6002. Ultraviolet spectra were taken on a Cary Model 14. All CD spectral recordings were made in a 1-cm jacketed cell at 25.0 ± 1 °C.

(*R*)-6,6′-Dibromo-2,2′-dihydroxy-1,1′-dinaphthyl. In 40 mL of CH_2Cl_2, 2.10 g (7.34 mmol) of optically pure (+)-(*R*)-2,2′-dihydroxy-1,1′-dinaphthyl[6a] was dissolved, and the system cooled to −75 °C. Bromine (1 mL, 19.6 mmol) was added dropwise over 20–30 min with constant stirring at −75 °C. After stirring an additional 2.5 h while warming to 25 °C, the reaction mixture was stirred further for 0.5 h, and the excess Br_2 was destroyed by addition of 50 mL of 10% aqueous solution of sodium bisulfite. The layers were separated, and the organic layer was washed with saturated NaCl solution and dried. Evaporation of the solution gave 3.6 g of solid, which was recrystallized from benzene-cyclohexane to give 3.20 g (99%) of the desired product. When the reaction was repeated using 18.0 g of optically pure (+)-(*R*) diol in 400 mL of CH_2Cl_2 and 9.0 mL (176.4 mmol) of Br_2 in 50 mL of CH_2Cl_2, the desired dibromide diol was obtained in 94% yield as a solvate, which after drying gave $[\alpha]^{25}_{578}$ −129° (*c* 1.0, CH_2Cl_2). Its ^1H NMR spectrum gave δ 5.07 (s, OH, 2 H), 6.85 (d, ArH_8, $J_{7,8}$ = 9 Hz, 2 H) 7.15 (d, ArH_3, $J_{4,3}$ = 9 Hz, 2 H), 7.25 (d of d, ArH_7, $J_{7,8}$ = 9, $J_{5,7}$ = 2 Hz, 2 H), 7.75 (d, ArH_4, $J_{3,4}$ = 9 Hz, 2 H), 7.90 (d, ArH_5, $J_{5,7}$ = 2 Hz, 2 H). Anal. ($C_{20}H_{12}O_2Br_2$) C, H, Br.

(*R*)- and (*S*)-6,6′-Dibromo-3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl. A procedure essentially identical with that described above was used except the reaction temperature was −50 °C. Thus, 11.63 g (37 mmol) of optically pure (*R*)-3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl[6b] in 250 mL of CH_2Cl_2 and 5.0 mL (98 mmol) of Br_2 in 50 mL of CH_2Cl_2 was converted into 15.7 g (90%) of recrystallized ($CHCl_3$–pentane at −60 °C) *R* product as a foam at 25 °C, $[\alpha]^{25}_{578}$ −68.0° (*c* 1.37, CH_2Cl_2). Anal. ($C_{22}H_{16}O_2Br_2$) C, H, Br.

Similarly 3.5 g of optically pure (*S*)-3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl[6b] was dibrominated to give 4.6 g (88%) of desired (*S*)-dibromide as a foam: $[\alpha]^{25}_{578}$ +68.2° (*c* 1.0, CH_2Cl_2); ^1H NMR δ 2.43 (s, CH_3, 6 H), 5.03 (s, OH, 2 H), 6.85 (d, ArH_8, $J_{7,8}$ = 9 Hz, 1 H), 7.27 (d of d, ArH_7, $J_{5,7}$ = 2, $J_{7,8}$ = 9 Hz, 1 H), 7.62 (br s, ArH_4, 1 H), 7.91 (d, ArH_5, $J_{5,7}$ = 2 Hz, 1 H). Anal. ($C_{22}H_{16}O_2Br_2$) C, H.[15]

(*R,R*)-2,3,4,5-Di[1,2-(6-bromo)naphtho]-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((*R,R*-3). In 400 mL of dry THF, 10.3 g (23.2) mmol) of optically pure (*R*)-6,6′-dibromo-2,2′-dihydroxy-1,1′-dinaphthyl was dissolved and stirred under dry nitrogen. Potassium hydroxide pellets (2.88 g) were added and the mixture was refluxed under nitrogen for 4 h during which it became homogeneous. Optically pure (*R*)-2,2′-bis(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl[10a] (18 g or 23.3 mmol) dissolved in 50 mL of pure THF was added dropwise in 0.5 h, and the mixture was refluxed under nitrogen for 17 h. The reaction mixture was cooled and filtered, and the solids were washed with $CHCl_3$. The washings and filtrate were combined, dried, and evaporated to give a viscous oil (21.9 g). This material was chromatographed on 500 g of neutral alumina with 2 L of CH_2Cl_2 to give 17 g of a white foam. This material was crystallized and recrystallized three times from 2:1 (by volume) benzene-cyclohexane to give a solvate, mp 136–137 °C. Removal of the solvent at 80 °C at 0.1 mm of Hg gave a glass, 15.0 g (74%) of (*R,R*)-**3**: $[\alpha]^{25}_{589}$ +157°, $[\alpha]^{25}_{578}$ +166° (*c* 1.0, CH_2Cl_2). The ^1H NMR of the cycle gave δ 3.20 (m, CH_2OCH_2, 8 H), 3.80 (m, $ArOCH_2$, 8 H), 6.80 (d, $BrArH_8$, $J_{7,8}$ = 9 Hz, 2 H), 7.05 (m, ArH, 8 H), 7.13 (d of d, $BrArH_7$, $J_{7,8}$ = 9, $J_{5,7}$ = 2 Hz, 2 H), 7.18 (d, $BrArH_3$, $J_{3,4}$ = 9 Hz, 2 H), 7.75 (d, ArH_4, $J_{3,4}$ = 9 Hz, 4 H), 7.80 (d, ArH_3, $J_{3,4}$ = 9 Hz, 2 H), 7.90 (d, $BrArH_5$, $J_{5,7}$ = 2 Hz, 2 H). Anal. ($C_{48}H_{36}O_6Br_2$) C, H, Br.

(*R,R*)-2,3,4,5-Di[1,2-(6-bromo-3-methyl)naphtho]-13,14,15,16-di(1,2-naphthol)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((*R,R*)-4). By a procedure similar to that described for preparing (*R,R*)-**3**, 10.24 g of optically pure (*R*)-6,6′-dibromo-3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl and 15.1 g of optically pure (*R*)-2,2′-bis(5-tosyloxy-3-oxa-1-pentoxy)-1,1′-dinaphthyl[10a] were coupled to give 12.1 g (69%) of (*R,R*)-**4**, mp 135–143 °C (benzene-cyclohexane solvate). Before crystallization from benzene–cyclohexane, the reaction product was chromatographed on 600 g of neutral alumina-CH_2Cl_2. After drying at 160 °C at 0.01 mm of Hg, (*R,R*)-**4** gave $[\alpha]^{25}_{578}$ +172° (*c* 1.1, CH_2Cl_2). Anal. ($C_{50}H_{42}O_6Br_2$) C, H, Br.

(*R,R*)-2,3-{1,2-[6-(2-Hydroxyethyl)-3-methyl]naphtho}-4,5-[1,2-(3-methyl)naphtho]-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((*R,R*)-8), (*R,R*)-2,3,4,5-Di{1,2-[6-(2-hydroxyethyl)-3-methyl]naphtho}-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((*R,R*)-6), and (*R,R*)-2,3,4,5-Di[1,2-(3-methyl)naphtho]-13,14,-15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,-15-tetraene ((*R,R*)-2). Into a dry, three-necked flask, fitted with a jacketed (calibrated) and refrigerated addition funnel was placed a solution of 6.92 g (7.95 mmol) of optically pure dibromide (*R,R*)-**4** dissolved in dry, purified 1,2-dimethoxyethane containing a trace of triphenylmethane indicator. The solution was cooled to −75 °C, and, with constant stirring under dry nitrogen, 8.05 mL (17.7 mmol) of butyllithium (2.2 M in hexane) was added with a dry hypodermic syringe through a rubber septum. The solution turned pink owing to the triphenylmethane anion. Ethylene oxide gas was dried carefully by passing it through a calcium sulfate tower (12 by 2 in. i.d.), and it was condensed in the addition funnel (1.5 mL or 30 mmol) into 6.5 mL of dry 1,2-dimethoxyethane. After the initial reaction mixture had stirred for 2 h at −75 °C, the ethylene oxide solution was added dropwise (15 min) under nitrogen with stirring. The reaction mixture

then was allowed to warm slowly to 25 °C over a period of 2 h, during which time the pink color disappeared. The mixture was stirred for 30 min at 25 °C, and 200 mL of cold water was added. The mixture was shaken with CH_2Cl_2, and the organic layer was dried and evaporated to give 6.6 g of a white solid. This material was chromatographed on 300 g of neutral alumina and eluted successively with 1 L of CH_2Cl_2 to give 2.00 g (34%) of fully protonated cycle ((*R,R*)-**2**); with 1.5 L of 2% CH_3OH in CH_2Cl_2 to give 3.74 g (60%) of monoethoxylated cycle (*R,R*)-**8**; and with 750 mL of 3% CH_3OH in CH_2Cl_2 to give 0.40 (6%) of diethoxylated cycle (*R,R*)-**6**, which was not characterized. The monoethoxylated cycle was submitted to dry column chromatography on neutral alumina with 25% CH_3OH in CH_2Cl_2 (volume) as solvent. The pure (*R,R*)-**8** was isolated as a white glass which was dried at 90 °C at 0.01 mm of Hg to give 3.50 g (56%): mass spectrum (76 eV) M^+ at *m/e* 784; $[\alpha]^{25}_{578}$ +164° (*c* 1.7, CH_2Cl_2). The compound's complex ^1H NMR spectrum gave an A_2B_2 pattern at δ 2.80 with a coupling constant of J_{AB} = 6 Hz corresponding to the group $ArCH_2CH_2OH$. Anal. ($C_{52}H_{48}O_7$) C, H.

(*R,R*)-2,3-[1,2-(6-Hydroxyethyl)naphtho]-4,5,13,14,15,16-tri(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((*R,R*)-7), (*R,R*)-2,3,4,5-Di[1,2-(6-hydroxyethyl)naphtho]-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((*R,R*)-5), and (*R,R*)-2,3,4,5,13,14,15,16-tetra(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((*R,R*)-1). Optically pure dibromocycle (*R,R*)-**3** was treated by the above procedure first with butyllithium, then with ethylene oxide, and finally with water to give monoethoxylated cycle (*R,R*)-**7** (55%), diethoxylated cycle (*R,R*)-**5** (10%), and protonated cycle (*R,R*)-**1** (30%). Desired (*R,R*)-**7** was obtained as a foam: $[\alpha]^{25}_{578}$ +165° (*c* 1.13, CH_2Cl_2); mass spectrum at 70 eV M^+ *m/e* 756. Anal. ($C_{50}H_{44}O_7$) H; calcd for C, 79.37; found, 78.90. Diethoxylated cycle (*R,R*)-**5** was obtained as a foam: $[\alpha]^{25}_{578}$ +162° (*c* 0.7, CH_2Cl_2); mass spectrum (70 eV) M^+ *m/e* 800. Anal. ($C_{52}H_{48}O_8$) C, H. The protonated cycle (*R,R*)-**1** gave $[\alpha]^{25}_{578}$ +227° (*c* 1, CH_2Cl_2), which indicates that no racemization occurred during the above reactions.[10a]

Chloromethylation of Styrene-Divinylbenzene Macroreticular Resin. Amberlite XAD-2 (porosity 42 vol %, surface area 330 m^2/g, average pore diameter 90 Å, mesh 20-50,[7] was ground in a laboratory mill (Wiley Laboratory Mill, Standard Model No. 3) fitted with a 150 mesh sieve. The sieved material (103.4 g) was mixed with 150 mL of dry ethylene dichloride for 30 min at 25 °C. To this slurry was added dropwise the stirring over a 15-min period 26.82 g (0.30 mol) of chloromethyl methyl ether. Then 7.49 g (0.05 mol) of anhydrous $AlCl_3$ was added. The slurry was stirred at 25-30 °C for 4 h and quenched with 300 mL of CH_3OH as the temperature was maintained at 25-30 °C with an ice-water bath. The mixture was stirred for 15 min, the solvent was siphoned off into a suction flask, and the remaining resin was washed four times with 300 mL of CH_3OH, each time removing the methanol with a siphon and suction flask. The resin was drained free of interstitial liquid and dried in a vacuum oven for 20 h at 90 °C to give 109.6 g of chloromethylated resin. The starting resin, Amberlite XAD-2, gave the following elementary analysis. Found: C, 91.77; H, 8.07. Elemental analysis of the chloromethylated resin follows. Found: C, 86.58; H, 7.98; Cl, 3.97. Thus 1.12 mequiv of CH_2Cl groups/g of resin was introduced. Hence the equivalent weight of the chlorinated polymer is 893. If the resin is assumed to be 20 mol % divinylbenzene and 80 mol % styrene, then the equivalent weight (per C_6H_5 group) of the original resin is ~137, or ~15% of the C_6H_5 groups present in the resin were chloromethylated.

Grafting of (*R,R*)-8 to Resin to Give (*R,R*)-10 and Its Methoxylation to Give (*R,R*)-12. To 2.63 g (3.35 mmol) of (*R,R*)-**8** dissolved in 300 mL of pure, dry THF was added 2.50 g of NaH (50% dispersion in mineral oil), and the solution was heated at reflux for 30 min under N_2, after which 29.0 g of dry (deoxygenated) chloromethylated resin was added under N_2. The heating at reflux was continued for 7 days. The reaction mixture was cooled and filtered, and the solid was washed successively with CH_3OH (exothermic), water (containing a few drops of 6 N HCl solution), CH_2Cl_2, and again with CH_3OH. The solid was then dried at 90 °C in a vacuum oven (0.1 mm of Hg) for 12 h to give 30.3 g of cycle grafted to resin, (*R,R*)-**10**, which contained, on elemental analysis, 3.71% chlorine. The filtrate and washings were combined; the organic layer was separated, washed with water, brine and dried ($MgSO_4$). The mixture was filtered and evaporated, and the residual solid was washed with pentane to remove the mineral oil. It was then dissolved in CH_2Cl_2, evaporation of which left 1.8 g of crude solid. This material was chromatographed on 300 g of alumina and eluted successively with 25% pentane-CH_2Cl_2 (1 L), pure CH_2Cl_2 (1 L), and CH_2Cl_2-CH_3OH (98:2 v:v) to give 1.30 g of (*R,R*)-**8**. Thus, of the 2.63 g of (*R,R*)-**8** introduced into the reaction mixture, 1.33 g disappeared during the reaction and is assumed to have become attached to the resin. This assumption is supported by the fact that the resin gained 1.3 g in weight during the reaction, while, from the chlorine analysis, 0.03 g of chlorine was being lost. Hence 1.33 g of other material, presumably the host, was added to the resin. If 1.33 g of (*R,R*)-**8** became attached to polymer to give 30.3 g of (*R,R*)-**10**, then 1.70 mmol of host sites was present on 30.3 g of resin, or (*R,R*)-**10** contained 0.056 mmol of host/g.

To 30.3 g of (*R,R*)-**10** mixed with 250 mL of absolute methanol was added 15.4 g (0.29 mol) of $NaOCH_3$. The mixture was refluxed for 15 h, cooled, acidified carefully with aqueous HCl (exothermic) to pH 5, and filtered. The polymer was thoroughly washed with water and then absolute methanol and was dried at 90 °C at 0.1 mm of Hg for 12 h in a vacuum oven to give 30.0 g of (*R,R*)-**12**. Elemental analysis of this material showed 0.65% of chlorine. Thus, by difference, ~0.87 mequiv/g of CH_3O was calculated to be present in (*R,R*)-**12**, along with 0.18 mequiv/g of Cl and 0.056 mmol of host/g. Thus the equivalent weight of host sites in (*R,R*)-**12** is ~17 800. If XAD-2 is assumed to be 20 mol % divinylbenzene and 80 mol % styrene, then ~0.8% of the original C_6H_5 groups of the resin are attached to host sites in (*R,R*)-**12**.

Grafting of (*R,R*)-7 to Resin to Give (*R,R*)-9, and Its Methoxylation to Give (*R,R*)-11. By a procedure similar to that described above, 2.53 g of (*R,R*)-**7** and 29.0 g of chloromethylated resin were converted into 29.5 g of (*R,R*)-**9**, containing 3.80% of chlorine by elemental analysis, and 0.048 mmol of host/g, which with $NaOCH_3$ was converted into (*R,R*)-**11** containing 0.60% chlorine. Thus (*R,R*)-**11** contained 0.17 mequiv of Cl/g, 0.90 mequiv of CH_3O groups/g, and 0.048 mmol of host/g.

Preparation of Chromatographic Columns. Host-bound resins (*R,R*)-**11** and (*R,R*)-**12** were sieved to give (*R,R*)-**12** of 250-325 mesh used in column A and (*R,R*)-**12** and (*R,R*)-**11** of 325-400 mesh used in columns B and C, respectively. The resin was suspended in $CHCl_3$-CH_3CN (1:1 v:v) and transferred into a "cartridge" stainless steel column of about twice the length of, but the same bore as, the final chromatographic column. No swelling of the resin was noted when mixed with solvent. The cartridge column was connected to the stainless steel precision bore chromatographic column containing the same solvent mixture. The slurry in the cartridge was pumped at 3 mL/min at 800-900 psi into the chromatographic column fitted with a porous plug at the outlet. A Milton Roy Mini-Pump with a maximum capacity of 16 mL/min was used in both loadings of the columns. The columns were jacketed and insulated for constant temperature control. Pure, dry, degassed solvents were used in loading, washing, storing, or running the chromatographic columns. The resin particles were rapidly filtered out of the slurry onto the porous plug at the bottom of the column, leaving a stable bed. After loading, the columns were conditioned by washing with 1 L of CH_3OH, 1 L of $CHCl_3$, and 1 L of the desired mobile phase.

The columns were fitted for sample introduction with injection loops from a Waters Associate chromatograph, Model 202. The bottoms of the columns led to conductivity cells of 0.10-mL capacity made of two brass plates held apart by a Teflon gasket. The cells had a constant of ~0.017 cm^{-1}. The cells were electrically attached to a Phillips PR 9501 direct-reading conductivity bridge attached to a recorder. The dead volume of each column was determined by injecting the nonretained compounds, methanol, benzene, hexane, and pentane, as samples onto the columns and determining their retention volumes. Column A was 60 by 0.75 (i.d.) cm in dimension and was loaded with 9.5 g of (*R,R*)-**12**. With fittings and packed with resin, it was found to possess a nonoccupied volume of 23.76 ± 0.04 mL. When corrected for the volumes of the connecting tubes and injection loop, and dead volume (that not occupied by resin) of the column itself was 18.36 ± 0.04 mL. Columns B and C were 60 by 0.40 (i.d.) cm and were packed with 4.0 g of (*R,R*)-**12** and (*R,R*)-**11**, respectively. With fittings and packed with resin, they were found to possess a nonoccupied volume of 9.50 ± 0.50 mL, which, when corrected for the volumes of tubings and injection loop, was 7.50 ± 0.50 mL. At the end of the runs, the columns were washed with methanol and then with the solvent used for the next run. The columns were stored under pure methanol and did not deteriorate with time or use if kept wet and out of contact with air.

Perchlorate and Hexafluorophosphate Salts of the Amino Acids. The perchlorate salts were prepared as follows. A weighed amount of the racemic amino acid was suspended in absolute methanol. One equivalent of 70% perchloric acid in water was added with constant stirring. Suspended solid dissolved when the acid was added. The solvent was evaporated at reduced pressure to leave a solid wet with water. The water was removed as a binary azeotrope with benzene. The final dry solid salt was recrystallized from CH_3CN-$CHCl_3$. This method worked well for the preparation of the perchlorate salts of phenylglycine (mp 238-239.5 °C) (Anal. ($C_8H_{10}ClNO_6$) C, H), tyrosine (mp 151-153 °C) (Anal. ($C_9H_{12}ClNO_7$) C, H), tryptophan (mp 100-101 °C) (Anal. ($C_{11}H_{13}ClN_2O_6$) C, H), hydroxyphenylglycine (mp 2(7-219 °C) (Anal. ($C_8H_{10}ClNO_7$) C, H), valine (mp 143-145 °C) (Anal. ($C_5H_{12}ClNO_6$) C, H), phenylalanine (mp 207-209 °C) (Anal. ($C_9H_{12}ClNO_6$) C, H), isoleucine (mp 150-152 °C) (Anal. ($C_6H_{14}ClNO_6$) C, H), and *tert*-leucine (mp 242-244 °C) (Anal. ($C_6H_{14}ClNO_6$) C, H). The perchlorate salts of methionine and alanine were used directly.

The perchlorate salts of the amino methyl esters were prepared from their corresponding hydrochlorides[16a] as follows. A weighed amount of the ester hydrochloride salt was suspended in $CHCl_3$-CH_3CN (1:1 v/v). To this suspension was added 1 equiv of anhydrous NH_4ClO_4 ($LiClO_4$ could also be used) under nitrogen with constant stirring (10 h). The solution was filtered and the filtrate evaporated at reduced pressure to produce a white solid, which was recrystallized from $CHCl_3$-CH_3CN (95:5 v/v). This procedure was applied to the preparation of the methyl ester perchlorate salts of phenylglycine (mp 154-156 °C) (Anal. ($C_9H_{12}ClNO_6$) C, H), *p*-hydroxyphenylglycine (mp 185-188 °C) (Anal. ($C_9H_{12}ClNO_7$) C, H), *p*-chlorophenylglycine (mp 173-174 °C) (Anal. ($C_9H_{11}Cl_2NO_6$) C, H), *p*-carbomethoxyphenylglycine (mp 161-163 °C) (Anal. ($C_{11}H_{14}ClNO_8$) C, H), phenylalanine (mp 157-159 °C) (Anal. ($C_{10}H_{14}ClNO_6$) C, H), and tyrosine (mp 172-174 °C) (Anal. ($C_{10}H_{14}ClNO_7$) C, H).

The hexafluorophosphate salt of racemic phenylglycine methyl ester was prepared as follows. In 10 mL of CH_2Cl_2 was dissolved 1.0 g (6.1 mmol) of methyl phenylglycinate. To this was added 1.3 g (6.1 mmol) of $(C_2H_5)_2O{\cdot}HPF_6$ (Aldrich Chemical Co.). White crystals (needles) separated from this solution at 0 °C to produce 1.8 g (95%) of salt, mp 87-89 °C. This salt was soluble in $CHCl_3$ and hygroscopic. Its ^1H NMR spectrum in D_2O gave δ 3.64 (s, CH_3, 3 H), 4.59 (s, NH_3, 3 H), 5.20 (s, CH, 1 H), 7.40 (s, ArH, 5 H). Anal. ($C_9H_{12}O_2NPF_6$) C, H.

Application of this procedure to the methyl esters of racemic *p*-chlorophenylglycine hydrochloride,[10b] *p*-carbomethoxyphenylglycine hydrochloride,[10b] and phenylalanine hydrochloride[16a] gave >75% yields of the corresponding salts.

Optical Resolution of the Methyl Esters of *p*-Chlorophenylglycine, *p*-Carbomethoxyphenylglycine, and Phenylglycine Perchlorates and of Alanine Perchlorate (Free Acid). For all resolutions, column A was filled with a 6-mL injection loop. The resolution of p-$ClC_6H_4CH(CO_2CH_3)NH_3ClO_4$ is illustrated first. In three runs, 58.1, 75.0, and 57.2 mg (190.3 mg) of racemic salt were each dissolved in 6 mL of $CHCl_3$-CH_3CN (90:10 v/v) and injected onto the column, which was run at a flow rate of 0.5 mL/min and a pressure of 680 psi. Each run produced a well-defined minimum between the two maxima for the enantiomers. Three fractions were cut, enantiomer B (just after the first maximum), a middle fraction containing B and A, and enantiomer A (just before the second maximum). The middle fractions from the three runs were combined and reinjected, and fractions were similarly cut. All B fractions from the four injections were combined and reinjected to give one peak of V_B = 25 mL, wt 63 mg, $[\alpha]^{25}_{578}$ +73.7°, $[\alpha]^{25}_{546}$ +84.3° (c 0.83, CH_3OH). All A fractions from the four injections were combined and reinjected to give one peak of V_A = 40 mL, wt 75 mg $[\alpha]^{25}_{578}$ −69.5°, $[\alpha]^{25}_{546}$ −80.3° (c 0.77, CH_3OH).

Similar runs produced the less-retained enantiomer B of the methyl ester perchlorate of *p*-carbomethoxyphenylglycine, $[\alpha]^{25}_{578}$ +75.9°, and the more-retained enantiomer A, $[\alpha]^{25}_{578}$ −76.0° (c 0.80, CH_3OH).

Two runs of 25 mg each of the methyl ester of phenylglycine perchlorate were similarly made. The final, more-retained A band (V_{RA} = 39 mL) gave 20 mg of the D isomer, $[\alpha]^{25}_{589}$ −129° (c 1.2, 6 N HCl). The final, less-retained, B band (V_{RB} = 20 mL) gave 18 mg of the L isomer, $[\alpha]^{25}_{589}$ +132° (c 1.0, 6 N HCl). These rotations were corrected to what would have been obtained had the hydrochloride rather than the perchlorate salts been weighed. The literature value for L-phenylglycine methyl ester hydrochloride is $[\alpha]^{25}_{589}$ +133.1° (c 1.0, 6 N HCl).[16c]

In the resolution of alanine perchlorate, five runs of 5 mg each in $CHCl_3$-CH_3CN (96:4 v/v) were made initially, the first half of the first band, the last half of the second band, and the middle fractions being collected separately. The respective middle fractions from the five runs were combined, concentrated, and reinjected, and the process repeated twice more. The combined first fractions (less-retained B enantiomer) were concentrated and reinjected, and the first band judiciously separated from the second. The process was repeated five more times, at which point no second band was detected. The final first band had V_{RB} = 40 mL and gave 6.1 mg of the L enantiomer as a viscous oil, $[\alpha]^{25}_{589}$ +13.2° (c 0.61, 6 N HCl), lit.[16d] $[\alpha]^{25}_{589}$ +14.7° (c 1.3, 6 N HCl). The second (more retained) bands were similarly treated to give a final less-retained band free of its enantiomer, V_{RA} = 55 mL, which yielded 5.0 mg of the D enantiomer, $[\alpha]^{25}_{589}$ −14.0° (c 0.50, 6 N HCl). These rotations were corrected to what would have been obtained had the hydrochloride rather than the perchlorate salts been weighed.

Circular Dichroism Spectra of the Methyl Ester Salts of Phenylglycine, Phenylalanine, and Their Para-Substituted Derivatives. The CD spectra of six salts were taken in CH_3OH (c 0.9 ± 0.1), each of which gave two Cotton effects, one at 215-220 nm ($\pi \rightarrow \pi^*$), whose sign was configuration dependent, and one at 250-260 nm, whose sign was configurationally independent and negative. The methyl ester hydrochloride salts of known absolution configuration[16] correlated with their molecular ellipticities at the wavelengths indicated as follows: L-phenylglycine, $[\theta]$ +1260° at ~220 nm; D-*p*-hydroxyphenylglycine,[16b] $[\theta]$ −950° at ~215 nm; L-phenylalanine, $[\theta]$ +800° at ~220 nm; L-tyrosine, $[\theta]$ +1100° at ~220 nm. For the two methyl ester perchlorate salts of unknown configuration, the assignments were made as follows: less-bound (+)-*p*-chlorophenylglycine (isomer B), $[\theta]$ +240° at ~215 nm (thus L configuration), and more-bound (−)-*p*-chlorophenylglycine (isomer A), $[\theta]$ −240° at 215 nm (thus, D configuration); less-bound (+)-*p*-carbomethoxyphenylglycine (isomer B), $[\theta]$ +300° at ~220 nm (thus L configuration), and more-bound (−)-*p*-carbomethoxyphenylglycine (isomer A), $[\theta]$ −310° (thus D configuration).

References and Notes

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