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Host–Guest Complexation. 20. Chiral Recognition in Transport as a Molecular Basis for a Catalytic Resolving Machine[1,2]

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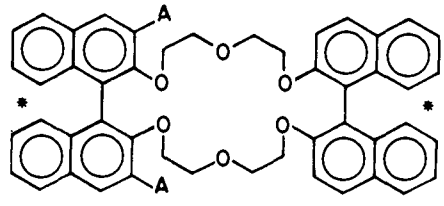
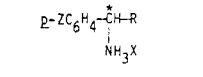
Abstract: Enantiomer differentiation (chiral recognition) occurred when designed, chiral hosts complexed and carried racemic amine salt guests from one aqueous solution through chloroform to a second aqueous solution where the guests were released. Optically pure hosts examined were 22-membered ring systems containing six roughly coplanar ether oxygens regularly spaced by attachment to one another through four ethylene (E) units. Two 1,1′-dinaphthyl (D) units of identical configuration, attached to oxygens at their 2,2′ positions, provided chiral barriers in the cycles. Besides the parent host, $D(OEOEO)_2D$ (**1**), two others were examined in which one of the dinaphthyl units was substituted in its 3,3′ positions to give $(CH_3)_2D(OEOEO)_2D$ (**2**) and $(ClCH_2)_2D(OEOEO)_2D$ (**3**). Chloroform solutions of these hosts (0.027 M), stirred at 24 °C in the bottom of a U-tube, contacted aqueous layers in the two arms. The solution in the α arm was 0.80 M in $LiPF_6$, 0.08 M in HCl, and 0.05–0.28 M in guest $*RNH_3Cl$ or $*RNH_3Br$ salt. The aqueous solution in the β arm was 0.10 M in HCl. Guests examined were $C_6H_5CH(CH_3)NH_3Br$ (**4**), $C_6H_5CH(CO_2CH_3)NH_3Cl$ (**5**), and p-$HOC_6H_4(CO_2CH_3)NH_3Cl$ (**6**). Rate constants for transport were measured for the faster moving A enantiomer (k_A*) and the slower moving B enantiomer (k_B*). Values of k_A^*/k_B^* varied from 1.45 (host **1** and guest **4**) to 10 (host **2** and guest **5**) and correlated roughly with D_A/D_B values, where D_A was the distribution coefficient of the more and D_B that of the less complexed enantiomer drawn from the aqueous into chloroform phases in one-plate extraction experiments. Hosts **2** and **3**, with their chiral barriers extended with CH_3 or $ClCH_2$ substituents, and the amino ester guests (**5** and **6**) gave the greatest chiral recognition in transport. The direction of the configurational bias in complexation corresponded to expectations based on scale molecular model examination of the diastereomeric complexes. A W-tube was designed for continuous and simultaneous removal of each enantiomer of racemic **5** from a central aqueous solution contacting two separate chloroform pools, one containing (*S,S*)-**2** and the second (*R,R*)-**2**. The enantiomeric guests were delivered to separate aqueous solutions, one in the left- and the other in the right-hand arm of the W-tube. Depending on experimental details, the *S,S* host delivered L-**5** to the left-hand aqueous pool in optical purities that ranged from 70 to 86%, and the *R,R* host delivered D-**5** to the right-hand aqueous pool in optical purities that ranged from 77 to 90%.

Biological transport of amino acids and their derivatives through lipophilic cell walls, up concentration gradients, is driven by linked H^+, Na^+, or K^+ transport down concentration gradients.[3] Metal cation transport, made possible by complexation with natural or synthetic host carriers through thin, synthetic membranes and organic bulk liquid membranes, has been studied extensively.[4] Lipophilic anions or cations in bulk toluene have been found to ion pair and transport amino acids and dipeptides from one aqueous solution to another.[5] The first example of chiral recognition in the differential transport (factors of 1.5 to >10) of enantiomeric guests through lipophilic media by complexation with chiral lipophilic hosts was reported in 1974.[2] The complexes were structured by hydrogen bonding of amine or amino ester salts to optically active macrocyclic ethers. A second example, communicated in 1975,[6] made use of optically active *N*-(1-naphthyl)methyl-α-phenylethylammonium ion paired differentially with the enantiomers of mandelic acid anion (factors of 1.22–1.42).[7]

The present paper[2] reports the results of experiments in which optically pure host compounds **1–3** selectively transport the enantiomers of guest salts **4–6** from one aqueous solution



1, A = H, or $O(OEOEO)_2O$
2, A = CH_3, or $(CH_3)_2O(OEOEO)_2O$
3, A = $ClCH_2$, or $(ClCH_2)_2O(OEOEO)_2O$



4, Z = H, R = CH_3
5, Z = H, R = CO_2CH_3
6, Z = HO, R = CO_2CH_3

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Table I. Differential Transport in U-Tube of Enantiomers A (Faster Moving) and B (Slower Moving) by 0.027 M Hosts in $CHCl_3$ at 24 °C

run no.	method	time, h	host	guest: initial α phase compd	guest: initial α phase concn, M	final β phase: % transferred	final β phase: isomer A	final β phase: % opt purity	k_A^*/k_B^* or (k_A^*/k_B^*)	EDC (K_A^*/K_B^*)
1a	A	20.5	(*S,S*)-**1**	(*R*)-**4**·HBr	0.05	14	*R*		1.5	1.5[a]
1b	A	23	(*S,S*)-**1**	(*S*)-**4**·HBr	0.05	10				
2a	A	15	(*S,S*)-**1**	(*R*)-**4**·HBr	0.10	10	*R*		1.45	1.5[e]
2b	A	4.6	(*S,S*)-**1**	(*S*)-**4**·HBr	0.10	2.4				
3a	A	11	(*R,R*)-**2**	(*R*)-**4**·HBr	0.05	11	*S*		1.7	1.9[b]
3b	A	9	(*R,R*)-**2**	(*S*)-**4**·HBr	0.05	12				
4	B	133	none	(*R*)(*S*)-**4**·HBr	0.05	2				
5	B	45	(*S,S*)-**1**	(*R*)(*S*)-**5**·HCl	0.21	17	*S*	35	2.1 (2.4)[c]	2.5[a]
6a	A	3	(*R,R*)-**2**	(*R*)-**5**·HCl	0.05	18	*R*		10	12[b]
6b	A	18	(*R,R*)-**2**	(*S*)-**5**·HCl	0.05	10				
7	B	19	(*R,R*)-**2**	(*R*)(*S*)-**5**·HCl	0.28	12	*R*	78	8 (10)[c]	12[b]
8	B	12	(*R,R*)-**3**	(*R*)(*S*)-**5**·HCl	0.28	8	*R*	82	10 (11.5)[c]	*d*
9	B	32	(*R,R*)-**3**	(*R*)(*S*)-**5**·HCl	0.28	12	*R*	77	8 (9.4)[c]	*d*
10	B	67	none	(*R*)(*S*)-**5**·HCl	0.18	3				
11	B	182	(*R,R*)-**2**	(*R*)(*S*)-**6**·HCl	0.28	10	*R*	74	6.7 (8)[c]	9[b]
12	B	182	none	(*R*)(*S*)-**6**·HCl	0.28	0.4				

[a] Reference 8c. [b] Reference 8. [c] Corrected for depletion of α phase of A relative to B enantiomer (see text). [d] Not determined.

through a chloroform solution to a second aqueous solution. The preparations, maximum rotations, optical stabilities, and absolute configurations of **1–3** have been reported.[8a,b] The chiral recognition in complexation, which hosts **1** and **2** exhibited toward the enantiomers of guest salts **4–6** in one-plate chloroform–water extraction experiments, has also been reported.[8c,d]

Results

Transport Experiments in a U-Tube. Two types of transport experiments were conducted in a 14 mm i.d. U-tube of about 30-mL capacity. Both types of runs involved a 0.027 M solution (10 mL) of host in $CHCl_3$ magnetically stirred at a constant (nonturbulent) rate in the bottom of the tube. In the β arm of the tube, floating on the $CHCl_3$ pool, was 5 mL of water, 0.10 M in hydrochloric acid. In method A, floating on the $CHCl_3$ pool in the α arm, was 5 mL of water, 0.05 or 0.10 M in *S* or *R* guest salt, 0.08 M in hydrochloric acid, and 0.80 M in $LiPF_6$. In paired experiments in which conditions differed only in time and the use of enantiomeric guests, the rates of transport of each guest from the α to the β arms were measured by monitoring the increase in absorbance (with time) of the UV spectrum of the solutions in the β arm. Plots of at least ten points of absorbance vs. time for each separate enantiomer gave straight lines from which were calculated zero-order rate constants for transport. The faster moving enantiomer was labeled A, the slower, B, and k_A^*/k_B^* was the ratio of rate constants observed for the transport of from ~3 to 18% of the total guest originally in the α arm. Table I reports values for k_A^*/k_B^*, the times employed, the percent of guest transported, the configuration of the host, and the configurations of enantiomers A and B. In control runs involving each of the three hosts in the absence of the guests, the H_2O and $CHCl_3$ layers were stirred for 50 h. No host could be detected by UV spectroscopy in the aqueous layers at the end of this time.

Method B differed from method A only in being a competition experiment between enantiomers of racemic guest placed in the α arm. The appearance of guest in the β arm was monitored by UV spectroscopy. After 8–17% of the total guest had been transported, the guest in the β arm was isolated, and its optical purity was determined polarimetrically. From the optical purities, k_A^*/k_B^* values were estimated. The faster moving enantiomer (A) was identified by the sign of its rotation and its established absolute configuration. Table I reports the results. In control runs 4, 10, and 12, the hosts were absent from the $CHCl_3$ layers, and longer times were usually employed. The results indicate that only 1–6% of the guest transported in the presence of host was uncomplexed.

Transport Experiments in W-Tubes. Two W-tubes were constructed of the general type shown in Figure 1. In the right-hand bend of the first of these (W-tube I) was introduced 10 mL of $CHCl_3$ that was 0.02 M in (*R,R*)-**2**.[8b] In the left hand bend of tube I was placed 10 mL of $CHCl_3$ that was 0.02 M in (*S,S*)-**2**.[8b] Each pool contained a small magnetic stirrer and was separated from the other by a glass barrier that extended upward in the central reservoir about 2 cm above the levels of the two pools. Into the central reservoir was introduced 15 mL of an aqueous solution (pH 4), which was about 3.5 M in $LiPF_6$ and 0.22 M in racemic $C_6H_5CH(CO_2CH_3)NH_3Cl$. This solution floated on each of the two $CHCl_3$ pools. Aqueous solutions (5 mL), which were 0.001 M in HCl, were introduced into both the left- and right-hand arms of the W-tube and floated on the $CHCl_3$ pools. At time zero, the two stirrers in the organic pools were started, with the rates being kept as nearly equal as possible. Great care was taken to avoid turbulence leading to bubbles of $CHCl_3$ climbing the barrier between the pools containing the enantiomeric hosts. The transport of guest salts to their respective destinations in the right- and left-hand aqueous solutions was monitored by periodic examination of their UV spectra at 270 nm. Between 5 and 10% of the guest was transported per run, at the end of which the aqueous solutions were withdrawn from the left- and right-hand arms. From these solutions, the esters were isolated, their optical rotations taken, and optical purities determined. The two arms were rinsed with 0.001 M HCl solution, and for run 2 fresh 5-mL portions of 0.001 M HCl were added to each arm without disturbing the slightly depleted central reservoir. After run 2, guest was isolated from the aqueous solution in the two arms and from the central reservoir, and was examined. The latter was 1% optically pure in the L-$C_6H_5CH(CO_2CH_3)NH_3X$ enantiomer. Thus the rates of transport of the two enantiomers from the central reservoirs through the two arms were not quite balanced, probably because the stirring rates were slightly different in the two $CHCl_3$ pools.

Runs 3 and 4 were carried out in W-tube II (Figure 1), which was designed to minimize forming concentration gradients of salts in the aqueous solutions and mixing the two chloroform solutions. When W-tube II was operating, three aqueous solutions were mixed with four helical stirrers activated through a gear arrangement by a single small motor. The

Table II. W-Tube Resolution by Differential, Simultaneous Transport of Both Enantiomers of Racemic $C_6H_5CH(CO_2CH_3)NH_3Cl$

run no.	T, °C	time, h	host (in arms) right	host (in arms) left	guest delivered to H_2O in arms: right % deliv	right % opt purity	right $(R)/(S)$	left % deliv	left % opt purity	left $(S)/(R)$
1[a]	23	25	(R,R)-**2**[b]	(S,S)-**2**[b]	8.8	77[c]	7.8	10	70[c]	5.6
2[a]	23	25	(R,R)-**2**[b]	(S,S)-**2**[b]	5.7	77[c]	7.5	5.4	79[c]	8.5
3[d]	23	14.5	(R,R)-**2**[e]	(S,S)-**2**[f]	1.1	84[g]	11[g]	0.7	81[g]	9.4[g]
4[d]	0	22	(R,R)-**2**[e]	(S,S)-**2**[f]	1.2	90[g]	19[g]	0.6	86[g]	13[g]

[a] W-Tube I. [b] Optically pure. [c] Determined by isolation. [d] W-Tube II. [e] 97% optically pure, 98% optically pure. [f] Determined by rotations of aqueous solutions in arms. The guest concentrations were determined by UV absorbance, and their optical purities were corrected for the slightly optically impure hosts used.

gears rested on a Teflon block, which also served as a top for the four openings to the cell. Dye-mixing tests with rose bengal in water revealed that at 60–120 rpm the helical stirrers completely mixed all aqueous solutions in 1 min. Magnetic stirrers were placed in each of the two $CHCl_3$ pools. The bends of the tube contained 15 mL of $CHCl_3$ solution each, the right-hand solution being 0.027 M in (R,R)-**2**, and the left-hand solution being 0.027 M in (S,S)-**2**. The average $CHCl_3$ path length in each bend was ~10 cm. The central aqueous reservoir was of 125-mL capacity and contained 100 mL of water at pH 4 that was 0.8 M in $LiPF_6$ and 0.28 M in $C_6H_5CH(CO_2CH_3)NH_3Cl$. A barrier about 3.7 cm in height separated the two centrally located $CHCl_3$–H_2O interfaces (~3.1 cm^2 area) from one another. Each of the right and left arms contained 15 mL of water that was 0.10 M in HCl. The interfaces in the two arms were 2.8 cm^2 in area. The cell and solutions were equilibrated in rooms held at 23 or 0 °C for 14 h before each run.

In runs 3 and 4, the transport was monitored by periodically withdrawing about 0.2 mL from the aqueous solutions in the right and left arms and determining their UV absorbances directly at 270 nm. At the end of each run, ~2 mL of each aqueous solution was withdrawn from each arm and allowed to equilibrate at ambient temperature. The concentrations of $C_6H_5CH(CO_2CH_3)NH_3Cl$ were determined from comparisons of UV absorbances of these solutions with those of standard aqueous solutions saturated with $CHCl_3$. The optical rotations of the solutions were determined at three wavelengths (λ 578, 546, and 436 nm), and ranged in magnitude from 0.233 to 2.723°. These optical rotations were compared to those of synthetic mixtures of the same concentrations of $C_6H_5CH(CO_2CH_3)NH_3Cl$ of known optical purity in 0.1 N aqueous HCl saturated with $CHCl_3$. From the results, the optical purities of the transported guests were calculated. Table II reports the results.

At the beginning of run 3, host (R,R)-**2** was 97.2% optically pure, and (S,S)-**2** was 98.2%. At the end of run 4, after 75 h in solution, the two hosts were rechromatographed to remove air oxidation products to give (85%) (R,R)-**2** of 96.2% and (S,S)-**2** of 98% optical purity. Thus the enantiomeric hosts underwent little mixing during these runs. At the end of run 3, the aqueous solutions in the two arms were removed. The two arms were rinsed thoroughly with 0.1 N HCl in water, and for run 4 fresh 15-mL portions of 0.10 N HCl in water were added to each arm. At the end of run 3 the rotation of the central reservoir indicated it to be 0.7% enriched in the L-amine salt, and at the end of run 4 it was still 0.7% enriched in the L-amine salt.

Equations That Relate Transport Rate, Distribution, and Association Constants for Complexes. Equations 1–3 define the equilibria involved when guest salt ($G^+ + X^-$) in water is equilibrated with host in $CHCl_3$ (H*).[9] Control experiments demonstrated that, with the guests and hosts studied, essentially no host (either complexed or uncomplexed) entered the

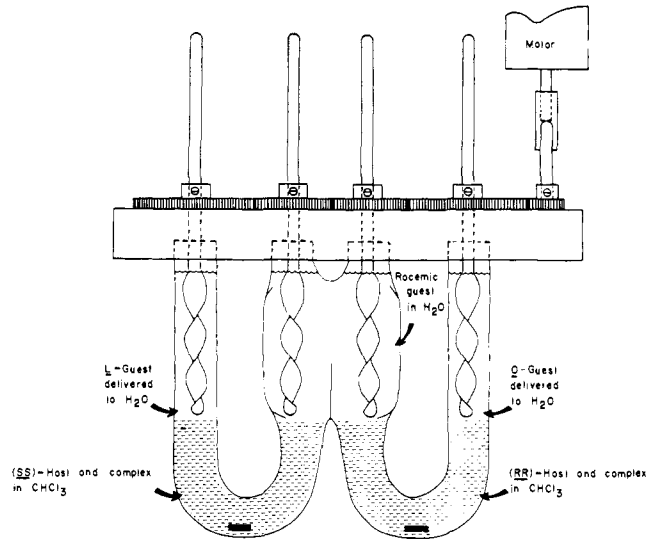


Figure 1. Resolving machine.

aqueous phase, and that most of the guest entering the $CHCl_3$ phase was complexed. The reasonable assumptions are made that the salt in water was dissociated and the salt entering the organic phase was ion paired. In addition, only 1:1 complexes formed in the organic phase. Starred terms apply to the organic phase only, and nonstarred terms to the aqueous phase or to constants involving both phases. For example, GX*·H* is the guest ion pair complexed with host in the $CHCl_3$ phase. Equation 4 relates K_d, K_e, and K_a*, as defined by eq 1–3.[8c,d]

$$G^+ + X^- \overset{K_d}{\rightleftharpoons} GX^* \quad (1)$$

$$G^+ + X^- + H^* \overset{K_e}{\rightleftharpoons} GX^*{\cdot}H^* \quad (2)$$

$$GX^* + H^* \overset{K_a^*}{\rightleftharpoons} GX^*{\cdot}H^* \quad (3)$$

$$K_e = K_d K_a^* = \frac{[GX^*{\cdot}H^*]}{[G^+][X^-][H^*]} \quad (4)$$

Equation 5 accounts for the total guest in the $CHCl_3$ phase in terms of uncomplexed and complexed salt concentrations or uncomplexed guest and host concentrations combined with the association constant between host and guest (K_a*). Equation 6 applies to one-plate experiments where guest is distributed between H_2O and $CHCl_3$ phases containing host in which D is the distribution constant. When guest is racemic amine salt and host is optically active, A is defined as the more and B as the less complexed enantiomer, and D_A and D_B are the distribution constants for the two enantiomers. Equation

7 defines EDC (the observed enantiomer distribution constant) in terms of measurable quantities of each enantiomer in each phase. The observed chiral recognition factor (CRF*) is the ratio of enantiomer A to enantiomer B in $CHCl_3$ at equilibrium, and the chiral storage factor (CSF) is the ratio of enantiomer B to enantiomer A in the H_2O layer at equilibrium. Since the distribution experiments involve enantiomers, K_d^A equals K_d^B, and each enantiomer competes for the same X^- during the extraction. Thus EDC can be expressed in terms of K_a^{*A}, K_a^{*B}, and [H*], as in eq 8. If complexation constants are reasonably high valued and [H*] is not too low, then $K_a^*[H^*] \gg 1$, and eq 9 applies. Under these conditions, essentially all guest in the $CHCl_3$ layer is complexed.

$$[GX^*]_{total} = [GX^*] + [GX^* \cdot H^*] = [GX^*](1 + K_a^*[H^*]) \quad (5)$$

$$D = \frac{[GX^*]_{total}}{[G^+]} = \frac{[GX^*](1 + K_a^*[H^*])}{[G^+]} = K_d[X^-](1 + K_a^*[H^*]) \quad (6)$$

$$EDC = \frac{D_A}{D_B} = \frac{[G_AX^*]_{total}}{[G_BX^*]_{total}} \frac{[G_B]}{[G_A]} = CRF^* \cdot CSF \quad (7)$$

$$EDC = \frac{K_d^A[X^-](1 + K_a^{*A}[H^*])}{K_d^B[X^-](1 + K_a^{*B}[H^*])} = \frac{1 + K_a^{*A}[H^*]}{1 + K_a^{*B}[H^*]} \quad (8)$$

$$EDC = \frac{K_a^{*A}}{K_a^{*B}} \quad (9)$$

In the U-tube transport experiments, we make the reasonable assumption that the equilibria described by eq 1-3 are established much faster across each $CHCl_3$-H_2O interface than guest is transported from the α to the β interface. Since diffusion of all solutes through the $CHCl_3$ phase is undoubtedly much slower than physical transport associated with stirring, constant stirring rates in uniform reaction vessels should give identical transport rates for all species present.

When these conditions apply, eq 10 is the rate expression (where k^* is the transport rate constant) for the approach to equilibrium for a system originally containing guest only in the α arm of the U-tube. A similar equation applies to back transport. Equation 11 can also be written, which expresses the rate as a function of $[G^+]^\alpha$ only. If conditions in the U-tube experiment are so arranged that $[X^-]^\alpha > [G^+]^\alpha$ and $[H^*]^\alpha > [GX^*\cdot H^*]^\alpha$, then all the terms on the right-hand side of eq 11 are close to being constant, and k_α^* is the rate constant for transport of guest from the α to the β phase. During transport of the first few percent of the guest, during which back transport is insignificant, $[G^+]_0^\alpha$ is essentially constant, and therefore eq 12 describes a zero-order process in which $k_0^* = k_\alpha^*[G]_0^\alpha$.

$$\text{rate} = k^*[GX^*]^\alpha{}_{total} = k^*K_d[G^+]^\alpha[X^-]^\alpha(1 + K_a^*[H^*]^\alpha) \quad (10)$$

$$\text{rate} = k_\alpha^*[G^+] \quad \text{where } k_\alpha^* = k^*K_d[X^-]^\alpha(1 + K_a^*[H^*]^\alpha) \quad (11)$$

$$\frac{d[G^+]^\beta}{dt} = k_\alpha^*[G^+]_0^\alpha \quad [G^+]_t^\beta = k_\alpha^*[G^+]_0^\alpha t = k_0^* t \quad (12)$$

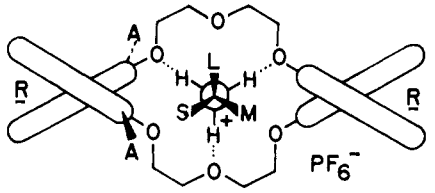
In the paired runs involving method A of Table I, linear plots of time vs. absorbance of the aqueous layer in the β arm of the U-tube were obtained from which the k_A^*/k_B^* values reported in Table I were calculated. Also recorded are the EDC values obtained previously from one-plate extraction experiments involving the same hosts, guests, solvent, and temperature.

In the enantiomer competition experiments of method B of Table I, the k_A^*/k_B^* values are the ratios of one point (zero-order) rate constants calculated from the optical purities of the guest isolated from the β arm after 1-17% of the total guest had been transported. Since the A enantiomer was selectively removed from the α aqueous solution during transport, that solution became enriched in the B enantiomer by a calculable, and usually significant, amount. The k_A^*/k_B^* parameters in these transport experiments resemble the CRF* parameters of eq 7. If the k_A^*/k_B^* values are multiplied by the values of $[G_B]/[G_A]$ calculated for the α aqueous phase at the time transport was interrupted, higher values of k_A^*/k_B^* are obtained that should equal those obtained at zero time, or in experiments conducted in which the α aqueous solution contained an infinite amount of racemic guest. The corrected k_A^*/k_B^* values symbolized by (k_A^*/k_B^*) are entered parenthetically in Table I beside the uncorrected values in those runs involving method B. Satisfactory agreement between methods A and B is shown by the results of runs 6 and 7, which involved the same host-guest combination. Method A gave $k_A/k_B^* = 10$, and method B gave $(k_A^*/k_B^*) = 10$.

Discussion

Rate Ratios as a Measure of Enantiomer Differentiation in Transport. Various combinations of the three hosts and three guests examined in the U-tube experiments produced k_A^*/k_B^* or (k_A^*/k_B^*) values ranged from a low of 1.45 (run 2) to a high of 11.5 (run 8) (see Table I). Thus, chiral recognition in transport by factors as high as ~12 has been realized by a rational design of host-guest structural relationships. The differential transport depends on lipophilization of the enantiomeric guest salts by complexation with a chiral host. The k_A^*/k_B^* values provide minimum measures of chiral recognition, since in their calculation no account is taken of the small amount of amine salt transported which is uncomplexed (see runs, 4, 10, and 12).

The configurations of the more rapidly transported A enantiomer were predicted a priori by examination of Corey-Pauling-Koltun molecular models of the diastereomeric complexes of assumed general structure **7** in which L, M, and



7

S stand for large, medium, and small groups attached to the chiral center of the guest. The three hosts all contain C_2 axes, so the same complexes are formed by attachment of guest to either face of the macrocycle. Diastereomer **7** (or its enantiomer) on steric grounds would appear to be the more stable. In **7**, the S group rests against one naphthalene wall of the chiral barrier, the M group extends alongside a second naphthalene wall, and the L group occupies a large cavity by itself. Structures diastereomeric or conformeric to **7** appear in models to be more crowded.

The degree of chiral recognition in transport varied widely with variation in the structures of both host and guest. Thus, $C_6H_5CH(CH_3)NH_3PF_6$ gave a k_A^*/k_B^* factor of 1.5 with $D(OEOEO)_2D$ and of 1.7 with $(CH_3)_2D(OEOEO)_2D$ as host. The amino ester $C_6H_5CH(CO_2CH_3)NH_3PF_6$ gave (k_A^*/k_B^*) of 2.4 with $D(OEOEO)_2D$, of 10 with $(CH_3)_2$-$D(OEOEO)_2D$, and of ~10.7 (average of 11.5 and 9.4) with $(ClCH_2)_2D(OEOEO)_2D$. Consequently, substitution of CO_2CH_3 for CH_3 as a medium-sized group in the guest considerably enhanced chiral recognition. This effect is attributed to π-acid to π-base attractive interactions between the

CO_2CH_3 group and a naphthalene group which in **7** lie against each other in parallel planes. This binding supplements $NH^+ \cdots O$ and $N^+ \cdots O$ attractions in structuring the complexes. Substitution of two $ClCH_2$ groups in host $(ClCH_2)_2D(OEOEO)_2D$ for the two CH_3 groups in $(CH_3)_2$-$D(OEOEO)_2D$ had essentially no effect on the chiral recognition. The enhanced chiral recognition associated with the hosts bearing CH_3 or $ClCH_2$ groups in the 3,3′ positions of one of the dinaphthyl units is attributed to two factors. First, these groups act as an extension of the chiral barrier. Second, they enforce a conformation on the $ArOCH_2$ units in which the electron pairs of the oxygens are turned inward and are favorably situated for binding NH^+ or N^+.[8d] With host $(CH_3)_2D(OEOEO)_2D$, the higher chiral recognition ($(k_A^*/k_B^*) = 8$) observed with guest *p*-$HOC_6H_4CH(CO_2CH_3)$-NH_3PF_6 as compared with $C_6H_5CH(CO_2CH_3)NH_3PF_6$ ($(k_A^*/k_B^*) = 10$) indicates that electronic factors slightly affect the relative free energies of the diastereomeric complexes.[8c-e]

The EDC values, based on one-plate distribution experiments,[8c,d] correspond well with the values for k_A^*/k_B^* (method A) or (k_A^*/k_B^*) (method B; see Table I). This correlation supports the assumption that mechanical mixing rather than diffusion across interfaces mainly controls the rate of passage of diastereomeric complexes through $CHCl_3$ in our experiments. The assumption indicates that the microscopic rate constants for mixing of the diastereomeric complexes of A and B, k^{*A} and k^{*B}, are equal. Since A and B are enantiomers, k_d^A equals k_d^B. From eq 11, eq 13 can be written, which reduces to eq 14. From eq 8 and 14, eq 15 follows, which is subject to all the limitations and assumptions used in obtaining eq 1-12.

$$\frac{k_A^*}{k_B^*} = \frac{k^{*A}K_d^A[X^-](1 + K_A^{*A}[H^*])}{k^{*B}K_d^B[X^-](1 + K_a^{*B}[H^*])} \quad (13)$$

$$\frac{k_A^*}{k_B^*} = \frac{1 + K_a^{*A}[H^*]}{1 + K_a^{*B}[H^*]} \quad (14)$$

$$EDC = k_A^*/k_B^* = K_a^{*A}/K_a^{*B} \quad (15)$$

In the EDC experiments, both the guest salt concentration in the aqueous phase and the host concentration in the organic phase were high so that large amounts of cation were present in the organic phase, and much of the host was complexed.[8c,d] In the transport experiments the concentration of complexed cation had to be low relative to the host concentration to justify the approximations made in the derivations. These approximations were as follows: (1) the mixing in the organic layer was the slow step in the transport, and it provided a uniform concentration of host and a concentration gradient of complexed guest through the medium; (2) at the H_2O–$CHCl_3$ interfaces, the enantiomeric organic salts rapidly equilibrated between the two phases; (3) the stirring in the two aqueous layers was good enough to provide uniform concentrations of all salts present throughout that phase. We make no claim that our model for transport applies to systems dissimilar to those described herein.

These experiments demonstrate that transport experiments of this kind can be used to determine approximate EDC values. The method is particularly valuable in cases involving very hydrophilic guests which are difficult to distribute into $CHCl_3$ solutions containing hosts (D_A and D_B values are low). In transport experiments, longer times can be exchanged for low D values.

W-Tube Transport Experiments. The W-tube experiments were devised to test the feasibility of building a catalytic resolving machine for simultaneously and continuously removing two enantiomers from a renewable central reservoir of racemic amine salt. Two enantiomeric hosts catalyzed the separation of the enantiomers of the racemic guest. Although the cell pictured in Figure 1 could be adapted to continuous operation, it was tested only in batch experiments. Runs 1-2 of Table II made at 23 °C were preliminary and were conducted in a cell similar to that of Figure 1, but which had poorer mixing of the central reservoir. Consequently, local concentration gradients of enantiomeric guest probably developed in the two halves of the central reservoir. A second negative feature of these runs was that the guest and $LiPF_6$ concentrations in the central reservoir were high enough so that $[H^*] \sim [GX^*{\cdot}H^*]$, whereas eq 15 should apply only when $[H^*] > [GX^*{\cdot}H^*]$. Even with these handicaps, the *R* enantiomer of the amino ester delivered by the *R,R* host to the right-hand aqueous solution was 77% optically pure, and the *S* enantiomer delivered by the *S,S* host to the left-hand aqueous solution varied from 70 to 79%.

Runs 3 and 4 were made at 23 and 0 °C, respectively, in the more carefully designed cell of Figure 1 with freshly purified (*R,R*)-**2** and (*S,S*)-**2**[8b] as host. At 23 °C in run 3 the (*R*)-$C_6H_5CH(CO_2CH_3)NH_3PF_6$ delivered was 84% optically pure and the (*S*)-$C_6H_5CH(CO_2CH_3)NH_3PF_6$ was 81% optically pure, which provided k_A^*/k_B^* values of 11 and 9.4, respectively. At 24 °C, the EDC value for the same host-guest combination was 12.[8d] At 0 °C in run 4, the *R* salt delivered was 90% optically pure and the *S* salt delivered was 86% optically pure, providing k_A^*/k_B^* values of 19 and 13, respectively. The EDC value obtained at 0 °C for the same host-guest combination was ~30,[8d] which corresponds to ~94% optically pure guests which ideally should have been delivered in the W-tube experiment at 0 °C. This ideal value was approached without fine tuning the machine. At the end of run 4, the (*R,R*)-**2** and (*S,S*)-**2** hosts isolated possessed essentially unchanged rotations and therefore had remained unmixed during the time employed in run 4.

Entropy of dilution in the overall process and inorganic salt "salting out" of the organic salt from the first aqueous phase provided the thermodynamic driving force for transport.

The limiting feature of a continuously operating resolving machine based on a W-cell or some modification is the rate of mixing of the enantiomeric hosts employed. Given enough time, mixing would ultimately occur through dissolution of host in the aqueous central reservoir, or by turbulence causing bubbles of host-containing $CHCl_3$ to be transferred from arm to arm.

A more practical resolving machine might be designed utilizing host of a single configuration continuously withdrawing a single desired enantiomeric guest from a central reservoir in which guest was catalytically racemizing at a rate more rapid than enantiomeric enrichment occurred. Such a system would, in effect, provide an infinite reservoir of racemic material at all times and would lead to a conversion of racemate to the desired enantiomer whose efficiency was limited only by the EDC values. The search for a suitable catalyzing system has been undertaken.

Experimental Section

General. Hosts of maximum rotation were used,[8a,b] unless otherwise noted, and before reuse were purified by chromatography[8b,c] to remove small amounts of oxidation products. Spectroscopic grade $CHCl_3$ was filtered through alumina before use to remove ethanol. In the runs of Table I involving method A, the guests used were of 98% or more maximum rotation. Maximum rotations of guests used in our calculations have been recorded and referenced elsewhere.[8d] Preparations of aqueous solutions of $LiPF_6$ have also been described.[8c,d] All UV readings were recorded utilizing a Beckman DU spectrophotometer.

U-Tube Transport. At 24 ± 1 °C in a U-tube of 14 mm i.d. was placed 10 mL of $CHCl_3$ that was 0.027 M in host. Water, 0.80 M in $LiPF_6$ and 0.08 M in HCl (5.0 mL) containing the guest amine hydrochloride or hydrobromide salt, was placed in the α arm. The β arm contained 5.0 mL of 0.10 M HCl in water. The α and β interfaces were about 1.5 cm^2 each, and the average $CHCl_3$ path length was about

6.5 cm. The $CHCl_3$ layer was mixed at a constant rate by a small magnetic stirrer which also mixed the aqueous layers, but less efficiently, by drag. Transport rates of the guest salts were followed by measuring the absorbance of the β phases in the UV spectrum at 256 nm for α-phenylethylamine salt (**4**), at 272 nm for phenylglycine methyl ester salt (**5**), and at 291 nm for *p*-hydroxyphenylglycine methyl ester salt (**6**). Host was undetectable in the UV spectrum of the β phase.

Method A of Table I. Individual transport rates for each enantiomer of the guest salts were measured in separate runs in tandem experiments from 2 to 18% transport. Plots of ten or more points of absorbance vs. time for the β phase were essentially linear through about 10% transport, and were used to calculate zero-order constants (k_A^*/k_B^*) in absorbance/min units. Identical stirring rates of host solutions were used for the paired runs.

Runs 1a and 1b provide examples of method A. A solution of 10 mL of $CHCl_3$ containing 191 mg of (*S,S*)-**1** at 24 ± 1 °C was released by syringe into the U-tube with stirring bar in place without wetting the upper part of the arms. Into the α arm was introduced by syringe 5.0 mL of an aqueous solution 0.08 M in HCl and 0.80 M in $LiPF_6$ containing 50 mg of (*R*)-$C_6H_5CH(CH_3)NH_3Br$ (run 1a) and 50 mg of (*S*)-$C_6H_5CH(CH_3)NH_3Br$ (run 1b). A solution of 5.0 mL of 0.10 M HCl was similarly introduced into the β arm. At periodic intervals the aqueous solution in the β arm was manually stirred and ca. 2 mL was withdrawn with a pipet and transferred to a UV cell. The UV absorbance of the solution in the β arm was monitored periodically by withdrawing with a pipet about 2 mL of the aqueous solution, which was thoroughly stirred (manually) prior to the sampling. After the direct and rapid measurement of the absorbance of this solution at 256 nm, it was returned to the β arm. The stirring was continued during the sampling and absorbance measurement. The ϵ of the guest at 256 nm is about 180. For run 1a, the following absorbances (time in h) were obtained: 0.02 (0), 0.24 (223), 0.30 (280), 0.52 (518), 0.57 (555), 0.63 (627), 0.69 (681), 0.75 (744), 0.79 (780), 1.22 (1232). From the slope of the linear plot of absorbance vs. time was obtained k_A^* of 9.83×10^{-4} absorbance units/h. For run 1b, the following absorbances (time in h) were observed: 0.00 (0), 0.05 (74), 0.09 (122), 0.14 (187), 0.17 (217), 0.23 (318), 0.25 (359), 0.29 (420), 0.32 (450), 0.46 (691), 0.50 (746), 0.54 (809), 0.57 (847), 0.59 (875), 0.88 (1409). These data produced k_B^* of 6.64×10^{-4} absorbance units/h. The two runs gave $k_A^*/k_B^* = 1.48$.

Method B of Table I. Run 5 illustrates the procedure. The same U-tube, solution volumes, host configuration and concentration, temperature, transfer, UV monitoring techniques, and stirring rates were used as in runs 1a and 1b. The 5 mL of aqueous solution in the α arm at zero time contained 204 mg of racemic $C_6H_5CH(CO_2CH_3)NH_3Cl$ and was 0.08 M in HCl and 0.80 M in $LiPF_6$. The 5 mL of aqueous solution in the β arm was 0.10 M in HCl. At zero time, the UV absorbance of the α arm was 2.2 at 272 nm. The absorbance in the β arm at 272 nm as a function of time (h) gave 0.00 (0), 0.00 (1), 0.08 (9.2), 0.28 (34), and 0.37 (45). After 45 h, the α aqueous solution was removed with a pipet, the arm was washed with 5 mL of water, and the combined aqueous solutions were made basic with excess 3% aqueous ammonia. This solution was extracted with 10 mL of CH_2Cl_2, the layers were separated, and the aqueous solution was washed with 10 mL of additional CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, evaporated to a small volume which was transferred to a tared vial, evaporated, and dried at 0.1 mm at ambient temperature for 10 min to give 18.7 mg of amino ester as an oil. This total sample was transferred with CH_2Cl_2 to a 1-mL volumetric flask, and its rotations were determined in a jacketed tube: $[\alpha]_{578}^{25}$ 57.2°, $[\alpha]_{546}^{25}$ 65°, $[\alpha]_{436}^{25}$ 119° (*c* 1.9, CH_2Cl_2), which provided calculated optical purities of 35.5, 35.1, and 35.1%, respectively. Thus, this material was 67.6% L ester and 32.4% *R* ester, and $k_A^*/k_B^* = 2.09$. Based on 17% transport of total salt from the α to the β aqueous solution and the above values, the α phase was enriched in the *R* ester by a factor of 1.16. Multiplication of 1.16 by 2.09 provides (k_A^*/k_B^*) = (2.4).

Two control experiments were conducted on the isolation procedure for runs 5 and 7–9. In the first, 30.4 mg of (*R*)-$C_6H_5CH(CO_2CH_3)NH_3Cl$ of 98% optical purity was dissolved in 10 mL of 0.1 M HCl and submitted to the isolation procedure used in run 5. Ester (21.4 mg, 70%) was recovered which gave $[\alpha]_{578}^{25}$ −157°, $[\alpha]_{546}^{25}$ −181°, and $[\alpha]_{436}^{25}$ −334° (*c* 2.1, CH_2Cl_2), which provided 97.5, 97.8, and 98.2% values for the optical purity of the recovered material. In the second control, 29.9 mg of 82% optically pure (*R*)-$C_6H_5CH(CO_2CH_3)NH_3Cl$ was submitted to the same procedure to give 21.3 mg of recovered ester (71%), which gave $[\alpha]_{578}^{25}$ −125°, $[\alpha]_{546}^{25}$ −145°, and $[\alpha]_{436}^{25}$ −264° (*c* 2.1, CH_2Cl_2), yielding values of 77.6, 78.4, and 77.6% for the optical purity of the recovered material.

Run 11, which involved racemic *p*-$HOC_6H_4CH(CO_2CH_3)NH_3Cl$ as guest, required a different extraction procedure for isolation of the transported salt. The basified (NH_3) aqueous phase was extracted six times with 3-mL portions of ethyl acetate. The combined extracts were dried with $MgSO_4$ and filtered, and the solvent was evaporated. The residual oil was dissolved in 5 mL of absolute CH_3OH into which was bubbled dry HCl gas for 5 min. The solvent was evaporated, transferred to a tared vial, and dried under a stream of dry nitrogen. The residue was dried at 25 °C for 16 h at 0.1 mm to constant weight to give 16.3 mg of salt (54%), whose rotation was taken in CH_3OH (1.70 mL) to give $[\alpha]_{578}^{25}$ −111° and $[\alpha]_{436}^{25}$ −239° (*c* 0.96, CH_3OH), which provide optical purities[8f] of 74 and 74%, respectively. Thus $k_A^*/k_B^* = 6.7$. Based on 10% transport of total salt, the α phase was enriched in the *S* isomer by a factor of 1.18, and (k_A^*/k_B^*) = 8.

W-Tube I Design. Runs 1–2 of Table II were conducted in W-tube I, whose total volume was 60 mL. The two arms were constructed of glass of 1.3 cm i.d. When loaded (see Results), the average $CHCl_3$ path was 9.0 cm long, and all four H_2O–$CHCl_3$ interfaces were 1.3 cm^2 in area. The aqueous layer of the *central* reservoir extended downward into the two arms 3.0 cm, and above the point of attachment of the two arms by 2.0 cm. These dimensions made it difficult to stir the central reservoir well enough to prevent concentration gradients of the two guest enantiomers from developing in the two arms immediately above the $CHCl_3$–H_2O interfaces. The following experiment provided this conclusion. The cell was loaded as in run 2 except that host and guest were absent. About 0.2 mL of rose bengal in water was added via syringe just above the $CHCl_3$–H_2O interface in one arm of the central reservoir. The stirrers in the $CHCl_3$ layers were started. The color of the dye took about 24 h to spread uniformly throughout the central reservoir.

Control Runs to Determine Extent of Mixing of the Two Organic Layers in W-Tube I. Limits were set on the rates of mixing of hosts (*R,R*)-**2** and (*S,S*)-**2** in the $CHCl_3$ solutions of the W-tube used in runs 1 and 2 of Table II. A 0.0148 M $CHCl_3$ solution of (*S,S*)-**2** (10 mL) was placed in the left arm, and 10 mL of $CHCl_3$ was placed in the right arm. Distilled water was floated on the $CHCl_3$ in the two arms (5 mL) and in the central reservoir (15 mL). The stirrers were turned at the same rate used in runs 1 and 2 at 23 °C for 31 h, and an aliquot was removed from the right-hand $CHCl_3$ solution which at 300 nm gave a UV absorbance equal to a host concentration of 2.5×10^{-6} M. Thus 0.017% of the host was transferred from the left to the right arm of the cell under the conditions of runs 1 and 2. A second control was run similar to the first except that the $CHCl_3$ solution in the left arm was 0.04 M in (*S,S*)-**2.** After 72 h of stirring at 4 °C, no host could be detected by UV absorption in the $CHCl_3$ solution in the right arm.

W-Tube II Runs 3 and 4. The W-tube of Figure 1 was used, whose dimensions and stirring arrangements were described in the Results section. Unless the cell and the solutions were thermally equilibrated in constant-temperature rooms (14 h) before each run, the $CHCl_3$ layers became turbid and deposited water droplets. The appearance of guest in the aqueous solutions of the outer arms was monitored by periodically stopping the stirrers and transferring 2 mL of each solution to a UV cuvette. The absorbance was determined at 270 nm at about 24 °C. The blank used was 0.1 N aqueous HCl solution.

The extinction coefficients and specific optical rotations of optically pure D-phenylglycine methyl ester hydrochloride twice recrystallized from MeOH–Et_2O was determined in 0.1 N aqueous HCl saturated with $CHCl_3$ for the range of concentrations of ester used for runs 3 and 4 of Table II. The four concentrations used were 1.008, 0.6000, 0.4110, and 0.1980 [*c*(dg)/(mL)]. The respective absorbances (A) at 270 nm were 2.490, 1.480, 1.009, and 0.498, which gave ϵ values ((cm)^2/(dg)) of 2.470, 2.467, 2.455, and 2.515. The respective specific rotations follow: at $[\alpha]_{578}^{25}$, −126.7, −126.7, −127.0, and −126.8°; at $[\alpha]_{546}^{25}$, −145.3, −145.2, −145.5, and −146.0°; at $[\alpha]_{436}^{25}$, −260.6, −260.3, −260.6, and −260.1°. Thus both the extinction coefficients and specific rotations were essentially concentration independent over the concentration range of runs 3 and 4 of Table II.

The rotations in $CHCl_3$ of the hosts used in runs 3 and 4 were as follows: (*R,R*)-**2**, $[\alpha]_{578}^{25}$ 142.0°, $[\alpha]_{546}^{25}$ 167.9°, $[\alpha]_{436}^{25}$ 374.2° at *c* 1.022, 97.1% ee; (*S,S*)-**2**, $[\alpha]_{578}^{25}$ −143.6°, $[\alpha]_{546}^{25}$ −170.2°, $[\alpha]_{436}^{25}$ −379.2° at *c* 1.04, 98.2% ee. The rotations of the hosts recovered from runs 3

and 4 after extraction and chromatographic purification (85%) follow: (*R,R*)-**2**, $[\alpha]_{578}^{25}$ 140.9°, $[\alpha]_{546}^{25}$ 166.8°, $[\alpha]_{436}^{25}$ 370.9° at *c* 1.09, 96.2% ee; (*S,S*)-**2**, $[\alpha]_{578}^{25}$ −143.3°, $[\alpha]_{546}^{25}$ −169.7°, $[\alpha]_{436}^{25}$ −377.9° at *c* 1.08, 98.0% ee.

For runs 3 and 4, 5.6 g of racemic phenylglycine methyl ester hydrochloride was dissolved in 100 mL of 0.8 M $LiPF_6$ solution which was 0.08 M in HCl to give a 0.28 M solution of guest used in the central reservoir. Chloroform solutions were prepared, one containing 300 mg of (*R,R*)-**2** in 15 mL (0.027 M) and the other 300 mg of (*S,S*)-**2** in 15 mL (0.027 M). These respective solutions were used in the right and left arms of W-tube II in runs 3 and 4. The respective absorbances and rotations observed (1 dm) for the guests delivered to the two arms at the ends of runs 3 and 4 were as follows: run 3, right arm, $A = 1.030$, α_{578}^{25} −0.431°, α_{546}^{25} −0.491°, α_{436}^{25} −0.885°, *R* guest; run 3, left arm, $A = 0.683$, $[\alpha]_{578}^{25}$ 0.274°, $[\alpha]_{546}^{25}$ 0.318°, $[\alpha]_{436}^{25}$ 0.574°, *S* guest; run 4, right arm, $A = 1.085$, $[\alpha]_{578}^{25}$ −0.485°, $[\alpha]_{546}^{25}$ −0.559°, $[\alpha]_{436}^{25}$ −1.001°, *R* guest; run 4, left arm, $A = 0.538$, $[\alpha]_{578}^{25}$ 0.233°, $[\alpha]_{546}^{25}$ 0.266°, $[\alpha]_{436}^{25}$ 0.477°, *S* guest. The percent of guest transported and the optical purity of the guests delivered to the arms corrected for the slightly impure host used in their transport are recorded in Table II.

References and Notes

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