

kept at 37 °C in a thermostat. At appropriate time intervals the UV spectrum was recorded (1-cm quartz cells) during approximately 7 half-lives, until the extinction at 311 nm remained constant. The exact half-life values were determined graphically by plotting the extinction values at 311 nm against the reaction time. First-order kinetics were usually observed during the first 3 half-lives. All calculations were based on the experimentally determined (after 7 half-lives) value at infinite time.

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### References and Notes

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- (8) Throughout the synthetic scheme the three compounds show larger coupling constants than their erythro isomers. The threeo and erythro assignment has been confirmed, since the submission of this publication, by an X-ray structure determination on a crystal of the threeo-hydroxyethylpenem ester **14t** (coupling constant 5.8 Hz compared to 3.5 Hz for the erythro isomer **14e**). The X-ray analysis, performed by Mrs. G. Rihs, Physical Research Laboratories, Ciba-Geigy Ltd., Basel, will be published elsewhere.
- (9) The KBr spectra of **3t** and **3e** show OH absorptions at ca. 3500 cm<sup>-1</sup>, consistent with intermolecular but not with intramolecular hydrogen bonding. The solution spectra in CH<sub>2</sub>Cl<sub>2</sub> of both esters **14t** and **14e** (erythro isomer) show absorptions of free OH at 3610 cm<sup>-1</sup> and associated OH at 3520 cm<sup>-1</sup> at high (10%) concentrations. In dilute (1%) solutions the broad band at 3520 cm<sup>-1</sup> disappears completely. This feature, which is observed with **14t** and **14e**, is incompatible with intramolecular hydrogen bonding: L. J. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd ed., Wiley, New York, 1958, p 96. The X-ray structure analysis of **14t** also confirmed the absence of any intramolecular hydrogen bonding in the crystalline state.

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## Host-Guest Complexation. 22. Reciprocal Chiral Recognition between Amino Acids and Dilocular Systems

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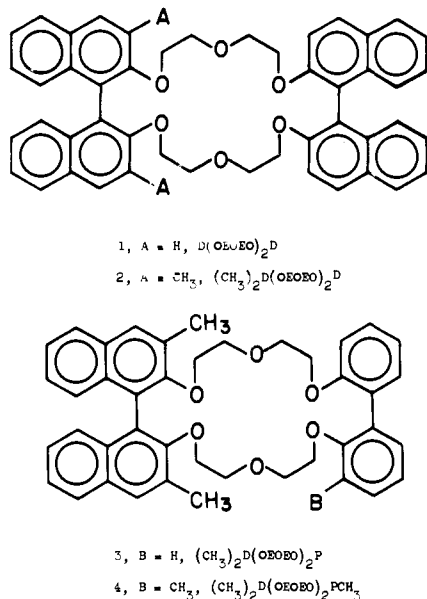
**Abstract:** The direction of configurational bias and the extent of chiral recognition have been determined for complexation between seven amino acid perchlorate guests and four macrocyclic polyether hosts containing chiral elements. In solution experiments, racemic guest in D<sub>2</sub>O was extracted by optically pure host in 0.45 mole fraction CD<sub>3</sub>CN in CDCl<sub>3</sub>. From the signs and magnitudes of the rotations of the guests recovered from each layer, the directions of the configurational bias and differences in free energies between the diastereomeric complexes ( $\Delta(\Delta G^\circ)$  values) were estimated. The hosts were 22-membered ring systems containing six ether oxygens attached to one another through four ethylene units (E) and two chiral 1,1'-binaphthyl (D) units of the same configuration attached to oxygens at their 2,2' positions, or one D unit and one 1,1'-diphenyl (P) unit attached to oxygens at its 2,2' positions. Methyl groups, when attached at the 3,3' positions of the D units or one of the 3 positions of the P unit, extended the steric barriers. With D,L-C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub> as the standard guest, hosts (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D, (S)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>P, (RR)-D(OEOEO)<sub>2</sub>D, and (S)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>PCH<sub>3</sub> at 0 °C gave complexes favoring the (SS)(L), (S)(L), (RR)(D), and (S)(L) configurations by  $-\Delta(\Delta G^\circ)$  values of 1.4, 0.8, 0.4, and 0.3 kcal/mol, respectively. The fraction of the total free energy of complexation which represents chiral recognition is termed the chiral efficiency. The chiral efficiencies of these hosts binding the standard chiral guest decreased in the same order from 0.33 to 0.17. With (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D as the standard host at 0 °C, (SS)(L) complexes with RCH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub> of different R groups were favored by these respective  $-\Delta(\Delta G^\circ)$  values (kcal/mol): C<sub>6</sub>H<sub>5</sub>, 1.4; *p*-HOC<sub>6</sub>H<sub>4</sub>, 1.3; C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, 0.7; (CH<sub>3</sub>)<sub>2</sub>CH, 0.5; C<sub>8</sub>H<sub>6</sub>NCH<sub>2</sub>( $\beta$ -indolylmethyl), 0.4; CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>, 0.45; CH<sub>3</sub>, 0.45. Chemical-shift differences in the <sup>1</sup>H NMR spectra of the (SS)(L) and (SS)(D) complexes of (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D with C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub> were compatible with structural predictions based on CPK molecular model comparisons. The diphenyl unit of (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>P was found by <sup>1</sup>H NMR temperature-dependent spectra to be conformationally equilibrating with an activation energy of about 19.4 kcal/mol at 89 °C. The direction of the chiral bias observed in solution was also observed in the crystalline state. The efficient and total enantiomeric resolution of (RR)(SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D was realized by crystallizing the (RR)(D) and (SS)(L) complexes prepared with D- and L-C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub>, respectively. The other diastereomeric complexes composed from these components failed to crystallize. A new synthesis of (RR)- and (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D is reported.

Parts 7<sup>3a</sup> and 8<sup>3b</sup> of this series reported the syntheses, optical stabilities, absolute configurations, and maximum rotations, of host compounds **1** and **2**, each of which contained two chiral elements (dilocular systems). Host compound **2** exhibited the highest chiral recognition in complexation of amino esters of a number of dilocular systems studied.<sup>3c,d</sup> Thus (RR)- or

(SS)-**2** in CDCl<sub>3</sub> at 0 °C were found to extract preferentially the respective R or S enantiomers of amino esters, RCH(CO<sub>2</sub>CH<sub>3</sub>)NH<sub>3</sub>PF<sub>6</sub>, from D<sub>2</sub>O by factors that ranged from 30 with R = C<sub>6</sub>H<sub>5</sub> to 2.2 with R = CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>. The diastereomeric complexes, (RR)(D) and (RR)(L), differed from one another in CDCl<sub>3</sub> at 0 °C by  $-\Delta(\Delta G^\circ)$  values that

ranged from 1.9 to 0.42 kcal/mol. A catalytic resolving machine was designed based on stereoselective transport of the two enantiomers of  $C_6H_5CH(CO_2CH_3)NH_3PF_6$  in  $D_2O$  in contact with separate  $CDCl_3$  layers, one containing (*RR*)- and the other (*SS*)- $(CH_3)_2D(OEOEO)_2D$ . The enantiomeric amino ester salts were delivered to separate water layers in about 90% optical purities.<sup>3e</sup> Host **2** attached at one of its 6 positions of the naphthyl unit through a  $CH_2CH_2OCH_2$  spacer unit to para positions of a macroreticular polystyrene resin was used to resolve chromatographically a variety of racemic amino acids and esters.<sup>3f</sup>

The overall objective of the present study was to further investigate those structural factors which provide complementary and differential complexation between organic partners. Chiral hosts **1–4** and the enantiomers of  $\alpha$ -amino acid

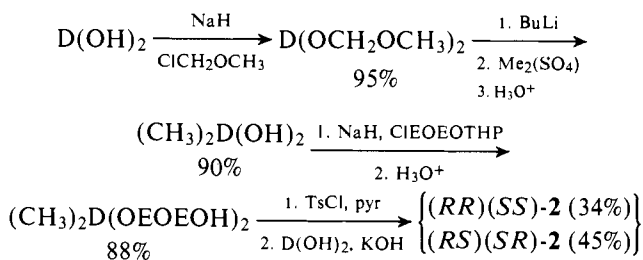


perchlorate salts were the complexing partners. Because of the complexity of the systematic names of **1–4**, line formulas are used whose parts are defined as follows: E is  $CH_2CH_2$ ; D is the 1,1'-dinaphthyl unit attached at its 2,2' positions to oxygens (O) and to the H or  $CH_3$  at its 3,3' positions; P is the 1,1'-diphenyl unit attached in its 2,2' positions to oxygens, and one  $CH_3$  is attached at one 3 position in **4**.

## Results

**Synthesis of Hosts.** Host  $(CH_3)_2D(OEOEO)_2D$  (**2**) of maximum rotation provided the highest chiral recognition in complexing enantiomeric primary amine salts of those studied in the past.<sup>3d</sup> Its synthesis involved different starting materials for preparations and enantiomeric resolutions of the chiral units,  $(CH_3)_2D(OH)_2$  and  $D(OH)_2$ .<sup>3a,b</sup> A new and simpler synthetic scheme is reported here in which either racemic or enantiomeric  $D(OH)_2$  is converted to  $(CH_3)_2D(OH)_2$ . In the latter case, the appropriate enantiomers of the two units were coupled as in Chart I to give (*RR*)- or (*SS*)- $(CH_3)_2D(OEOEO)_2D$ . When racemic  $D(OH)_2$  and  $(CH_3)_2D(OH)_2$  were coupled, the diastereomeric racemates were separated chromatographically. Subsequently, the desired (*RR*)-(*SS*)- $(CH_3)_2D(OEOEO)_2D$  was easily resolved by crystallizing the (*RR*)(D) or (*SS*)(L) enantiomers of the host complexed with the appropriate and available D or L enantiomers of  $C_6H_5CH(CO_2H)NH_3ClO_4$  from EtOAc in 78 and 52% yields, respectively. The absolute configurations, maximum rotations, and optical stabilities of **1** and **2** ( $D(OH)_2$  and  $(CH_3)_2D(OH)_2$ ) have been reported previously.<sup>3a,b</sup> Coupling of (*S*)- $(CH_3)_2D(OEOEOH)_2$  of maximum rotation with

Chart I



$P(OH)_2$  gave (*S*)- $(CH_3)_2D(OEOEO)_2P$  (44%) and with  $CH_3P(OH)_2$  gave (*S*)- $(CH_3)_2D(OEOEO)_2PCH_3$  (33%).

Attempts to obtain crystalline complexes of  $D-C_6H_5CH(CO_2H)NH_3ClO_4$  and (*SS*)-**2**, or of that guest and (*RS*)(*SR*)-**2**, failed. Attempts to epimerize (*RS*)(*SR*)-**2** to (*RR*)(*SS*)-**2** either thermally or photochemically also failed.

Introduction of the diphenyl unit (P) into **3** and **4** poses the interesting question of whether the two phenyl groups rotate fast enough at the complexation temperatures of 0 °C to equilibrate the two possible diastereomeric hosts and their complexes. At ~50 °C, two  $^1H$  NMR methyl peaks of equal intensity were observed in the spectrum of  $(CH_3)_2D(OEOEO)_2P$  with  $\Delta\nu = 6$  Hz. At 89 °C these peaks coalesced. Since both (*SS*)- $(CH_3)_2D(OEOEO)_2P$  and (*SR*)- $(CH_3)_2D(OEOEO)_2P$  contain  $C_2$  axes, each should exhibit singlet methyl peaks of potentially different chemical shifts if rotations about the phenyl-phenyl bonds are slow on the  $^1H$  NMR time scale. The results indicate that at 89 °C rotation is fast, and that  $\Delta G^\ddagger$  for this rotation is ~19 kcal/mol<sup>4</sup> at this temperature. This energy barrier suggests that at 0 °C the half-life for phenyl-phenyl rotation is on the order of seconds. The rates of complexation-decomplexation are very fast on the  $^1H$  NMR and human time scales, and uncomplexed host was always present in excess. Probably the diastereomers and their complexes equilibrated at the 0 °C used for complexation.

**Extraction and Distribution Experiments.** Standard extraction experiments were made as follows. To solutions of 0.45 mole fraction of purified  $CD_3CN$  in purified  $CDCl_3$  was added 1.0 mmol of hosts of maximum rotations to give 5 mL of 0.20 M solutions. Solutions (3 mL) were prepared of purified racemic  $RCH(CO_2H)NH_3ClO_4$ <sup>3f</sup> (3.0 mmol) in  $D_2O$  that was 1.0 M in guest and 1.5–4.0 M in  $LiClO_4$ . The pH was adjusted to 1.0 with  $HClO_4$ . The organic and aqueous solutions were combined in a centrifuge tube, cooled to 0 °C, thoroughly mixed, and centrifuged, and the layers *very carefully* separated. These operations were carried out in a cold room at 0 °C. The amino acids were isolated from each of the two layers, and their enantiomeric purities<sup>3d</sup> were determined by methods A, B, C, or D (see Experimental Section).<sup>5</sup> Appropriate control experiments were run with synthetic mixtures of known composition to demonstrate that no racemization or enantiomer fractionation occurred during the isolation and analytical procedures.

The values of G/H in the organic layer were adjusted to lie between 0.2 and 0.8 by varying two parameters. Addition of  $LiClO_4$  to the aqueous phase "salted out"  $RCH(CO_2H)NH_3ClO_4$  into the organic phase, and concentrations of 0–4.0 M  $LiClO_4$  were needed to obtain workable amounts of guest in the organic phase. Host in  $CDCl_3$  alone as the organic phase failed to extract workable quantities of guest, so  $CD_3CN$  was added to the organic phase to increase the amount of complex formed at equilibrium. In runs 1–9 and 15–22 of Table I the organic phase was 0.45 mole fraction  $CD_3CN$ . In runs 10–14 the mole fraction of  $CD_3CN$  in  $CDCl_3$  was varied incrementally from 0.35 to 0.58.

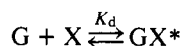
**Table I.** Enantiomer Distribution Constants (EDC) and  $-\Delta(\Delta G^\circ)$  Values for Extraction of Racemic  $RCH(CO_2H)NH_3ClO_4$  from  $D_2O$  into  $CDCl_3$ - $CD_3CN$  Solutions of Optically Pure Hosts (H) at 0 °C

run no.	mol fract $CD_3CN$	$LiClO_4$ , M	anal. meth <sup>a</sup>	host formula	R of amino acid	org sol at equil			EDC <sup>c</sup>	$(K_a^A/K_a^B)^d$	$-\Delta(\Delta G^\circ)$ , kcal/mol <sup>e</sup>
						$G^*/H^*$ by wt	calcd <sup>b</sup>	dom complex			
1 <sup>f</sup>	0.45	4.0	A	D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>		0.3	(RR)(D)	1.7	1.8	.3
2	0.45	2.0	A	D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>		0.2	(RR)(D)	2.1	2.25	.4
3	0.45	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> P	C <sub>6</sub> H <sub>5</sub>	0.4	0.4	(S)(L)	4.1	4.3	0.8
4	0.45	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> PCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>		0.2	(S)(L)	1.7	1.7	0.3
5	0.45	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.5	0.7	(SS)(L)	9.8	10.4	1.2
6	0.45	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.7	0.6	(SS)(L)	10.7	11.7	1.3
7	0.45	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.5	0.6	(SS)(L)	10.3	11.0	1.3
8	0.45	2.0	B	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.6	0.6	(SS)(L)	13.9	15.3	1.4
9	0.45	2.0	C	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.6	0.6	(SS)(L)	12.2	14.6	1.4
10	0.35	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.6	0.6	(SS)(L)	12.9	13.6	1.4
11	0.40	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.6	0.6	(SS)(L)	12.4	13.0	1.4
12	0.45	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.7	0.7	(SS)(L)	10.5	11.4	1.3
13	0.52	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.8	0.7	(SS)(L)	8.8	10.0	1.2
14	0.58	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub>	0.8	0.7	(SS)(L)	7.1	8.2	1.1
15	0.45	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	<i>p</i> -HOC <sub>6</sub> H <sub>4</sub>		0.5	(SS)(L)	9.4		1.2
16	0.45	2.0	B	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	<i>p</i> -HOC <sub>6</sub> H <sub>4</sub>		0.5	(SS)(L)	10.5		1.3
17	0.45	3.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		0.5	(SS)(L)	3.8		0.7
18	0.45	1.5	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	(CH <sub>3</sub> ) <sub>2</sub> CH		0.2	(SS)(L)	2.61		0.5
19	0.45	1.5	B	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	(CH <sub>3</sub> ) <sub>2</sub> CH		0.2	(SS)(L)	2.65		0.5
20	0.45	2.0	A	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	C <sub>8</sub> H <sub>6</sub> NCH <sub>2</sub>		0.3	(SS)(L)	2.13		0.4
21	0.45	4.0	D	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	CH <sub>3</sub> S(CH <sub>2</sub> ) <sub>2</sub>		0.8*	(SS)(L)	2.3		0.45
22	0.45	4.0	D	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	CH <sub>3</sub>		0.4*	(SS)(L)	2.3		0.45

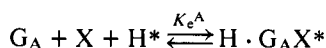
<sup>a</sup> See Experimental Section. <sup>b</sup> Equation 27. <sup>c</sup> Calculated assuming no uncomplexed guest in organic layer at equilibrium. <sup>d</sup> Calculated taking into account uncomplexed guest in the organic layer at equilibrium. <sup>e</sup> Equation 28. <sup>f</sup> Run at 25 °C. \* Calculated from <sup>1</sup>H NMR integrations of CH<sub>3</sub> groups of diastereomeric complexed guests in organic phase at equilibrium.

Gravimetric experiments were conducted to determine the distribution constants ( $K_d$ ) for racemic  $C_6H_5CH(CO_2H)NH_3ClO_4$  between the aqueous and organic phases whose compositions simulated those of runs 10–14 of Table I. In these runs, noncomplexing racemic 2,2'-dimethoxy-1,1'-dinaphthyl was substituted for host at a concentration (0.472 M) in the organic layer, which provided a weight of material per unit volume equal to that of host used in runs 10–14. Table II reports the results. A control extraction demonstrated that, at 0.45 mole fraction  $CD_3CN$  in  $CDCl_3$  carried out in the absence of guest, a trivial amount of  $LiClO_4$  entered the organic layer.

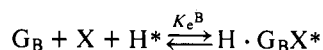
**Definitions, Equations, and Assumptions.** Equations 1–5 define  $K_d$ ,  $K_e$ , and  $K_a$ , the distribution, extraction, and association constants, respectively. In these equations, H is host, G is guest cation, X is guest anion, GX is guest salt, H·GX is complex and  $V$  stands for volumes. The letter A as subscript or superscript refers to the enantiomer *more complexed* and B to the enantiomer *less complexed* in the organic phase, the subscript i means initial, the superscript asterisk means organic phase, and the absence of it means aqueous phase. Equations 6 follow from eq 1–5.



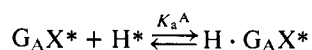
$$K_d = [GX^*]/[G][X] \quad (1)$$



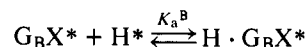
$$K_e^A = [H \cdot G_A X^*]/[G_A][X][H^*] \quad (2)$$



$$K_e^B = [H \cdot G_B X^*]/[G_B][X][H^*] \quad (3)$$



$$K_a^A = [H \cdot G_A X^*]/[G_A X^*][H^*] \quad (4)$$



$$K_a^B = [H \cdot G_B X^*]/[G_B X^*][H^*] \quad (5)$$

$$K_a^A = K_e^A/K_d \quad K_a^B = K_e^B/K_d \quad (6)$$

Application of eq 1–5 to the foregoing extraction and distribution experiments involves the following assumptions: (1) the solutions are perfect; (2) complexes formed in the organic phase are one-to-one and are ion paired; (3) noncomplexed guest salts in the organic phase are ion paired; (4) values of  $K_d$  for racemic guest equal those for the enantiomeric guests; (5) neither host nor complex is distributed in the aqueous phase at equilibrium.

Equation 7 defines the *chiral storage factor* (CSF), eq 8, the *chiral recognition factor* (CRF\*), and eq 9, the *enantiomer distribution constant* (EDC). Equations 10 and 11 describe the mass balance of the enantiomeric guests at equilibrium. Equations 7–11 contain the four unknowns ( $[H \cdot G_A X^*] + [G_A X^*]$ ), ( $[H \cdot G_B X^*] + [G_B X^*]$ ),  $[G_A]$ , and  $[G_B]$ , which, when solved in terms of the measurable parameters, CSF, CRF\*,  $G_i$ ,  $V$ , and  $V^*$ , give eq 12–15.

$$CSF = G_B/G_A = [G_B]/[G_A] \quad (7)$$

$$CRF^* = \frac{H \cdot G_A X^* + G_A X^*}{H \cdot G_B X^* + G_B X^*} = \frac{[H \cdot G_A X^*] + [G_A X^*]}{[H \cdot G_B X^*] + [G_B X^*]} \quad (8)$$

$$EDC = CSF \cdot CRF^* \quad (9)$$

$$[G_A] = \frac{[G_i]}{2} - \frac{V^*}{V} ([H \cdot G_A X^*] + [G_A X^*]) \quad (10)$$

$$[G_B] = \frac{[G_i]}{2} - \frac{V^*}{V} ([H \cdot G_B X^*] + [G_B X^*]) \quad (11)$$

$$[G_A] = \frac{G_i(1 - CRF^*)}{2V(1 - EDC)} \quad (12)$$

$$[G_B] = \frac{G_i(CSF - EDC)}{2V(1 - EDC)} \quad (13)$$

$$[H \cdot G_A X^*] + [G_A X^*] = \frac{G_i(CRF^* - EDC)}{2V^*(1 - EDC)} \quad (14)$$

$$[H \cdot G_B X^*] + [G_B X^*] = \frac{G_i(1 - CSF)}{2V^*(1 - EDC)} \quad (15)$$

Equation 16 comes from mass balance at equilibrium. Equations 17 and 18 follow from eq 1, rearrangement of eq 14 gives eq 19, and of eq 15 gives eq 20. Equation 21 comes from mass balance at equilibrium.

$$[X] = [G_A] + [G_B] + [LiX] \quad (16)$$

$$[G_A X^*] = K_d[G_A][X] \quad (17)$$

**Table II.** Distribution Constants ( $K_d$ ) of Racemic  $C_6H_5CH(CO_2H)NH_3ClO_4$  between  $D_2O$  (2–4 M  $LiClO_4^a$  and 1.2 M in Guest) and  $CDCl_3$ – $CD_3CN$  Mixtures 0.472 M in Racemic 2,2'-Dimethoxy-1,1'-dinaphthyl

run no.	mol fract $CD_3CN$ in $CDCl_3$	$t, ^\circ C$	$K_d^b \times 10^3, M^{-1}$	run no.	mol fract $CD_3CN$ in $CDCl_3$	$t, ^\circ C$	$K_d \times 10^3, M^{-1}$
1	0	0	0.076	7	0	25	0.051
2	0.22	0	0.17	8	0.22	25	0.16
3	0.36	0	0.52	9	0.36	25	0.50
4	0.45	0	0.86	10	0.45	25	0.98
5	0.52	0	1.6	11	0.52	25	1.6
6	0.58	0	2.3	12	0.58	25	2.1

<sup>a</sup> 2.0 M in runs 1–6 and 4.0 M in runs 7–12. <sup>b</sup> Equation 1.

$$[G_B X^*] = K_d [G_B] [X] \quad (18)$$

$$[H \cdot G_A X^*] = \frac{G_i(CRF^* - EDC)}{2V^*(1 - EDC)} - [G_A X^*] \quad (19)$$

$$[H \cdot G_B X^*] = \frac{G_i(1 - CSF)}{2V^*(1 - EDC)} - [G_B X^*] \quad (20)$$

$$[H^*] = [H_i^*] - [H \cdot G_A X^*] - [H \cdot G_B X^*] \quad (21)$$

Equations 17–21, coupled with the experimental data, provide the values of  $[H \cdot G_A X^*]$ ,  $[G_A X^*]$ , and  $[H^*]$  needed to solve eq 4 for  $K_a^A$ , and those of  $[H \cdot G_B X^*]$ ,  $[G_B X^*]$ , and  $[H^*]$  needed to solve eq 5 for  $K_a^B$ . Values of the ratio of  $K_a^A/K_a^B$  for  $C_6H_5CH(CO_2H)NH_3ClO_4$  as guest are listed in Table I.

If it is assumed that  $[H \cdot G_A X^*] \gg [G_A X^*]$  and  $[H \cdot G_B X^*] \gg [G_B X^*]$ , then eq 8 reduces to eq 22, eq 14 to eq 23, and eq 15 to eq 24. Equations 23, 12, 16, and 21, coupled with the experimental data, supply values of  $[H \cdot G_A X^*]$ ,  $[G_A]$ ,  $[X]$ , and  $[H^*]$  needed to calculate  $K_e^A$  of eq 2. Similarly, eq 24, 13, 16, and 21 and the data provide values of  $[H \cdot G_B X^*]$ ,  $[G_B]$ ,  $[X]$ , and  $[H^*]$  needed to calculate  $K_e^B$  of eq 3. Equations 6, when combined, provide eq 25. When substituted with eq 2, 3, 7, 22, and 9, eq 25 gives eq 26. Table I records the EDC values calculated based on this assumption for all the guests studied. Table I also records  $K_a^A/K_a^B$  values taking into account the amount of uncomplexed  $C_6H_5CH(CO_2H)NH_3ClO_4$  distributed in the organic layer at equilibrium.

$$CRF^* = [H \cdot G_A X^*] / [H \cdot G_B X^*] \quad (22)$$

$$[H \cdot G_A X^*] = \frac{G_i(CRF^* - EDC)}{2V^*(1 - EDC)} \quad (23)$$

$$[H \cdot G_B X^*] = \frac{G_i(1 - CSF)}{2V^*(1 - EDC)} \quad (24)$$

$$K_a^A/K_a^B = K_e^A/K_e^B \quad (25)$$

$$\frac{K_a^A}{K_a^B} = \frac{[H \cdot G_A X^*] [G_B]}{[H \cdot G_B X^*] [G_A]} = CRF^* \cdot CSF = EDC \quad (26)$$

Comparisons of the  $K_a^A/K_a^B$  and EDC values listed in Table I calculated for  $C_6H_5CH(CO_2H)NH_3ClO_4$  as guest measure the size of the error introduced by the assumption that the organic phase contains a negligible amount of uncomplexed guest. The  $K_a^A/K_a^B$  values are usually about 5–10% higher than the EDC values. Corrections were not applied to the other guests examined in this investigation. Thus the EDC values reported represent minimum  $K_a^A/K_a^B$  values which are probably less than 10% low.

The relative amounts of guest and host ( $G^*/H^*$ ) at equilibrium were determined roughly either by direct measurement (weights of isolated materials or  $^1H$  NMR integrations) or by calculation utilizing eq 27, or by both the first and third methods. Equation 27 is derived from eq 23 and 24 in which it has been assumed that uncomplexed guest in the organic phase is negligible. Within experimental error, this parameter is not sensitive to the small amount of uncomplexed guest in the organic layer. When available from both sources, the

$G^*/H^*$  values obtained are in good agreement (see Table I).

$$G^*/H^* = \frac{G_i(CRF^* + 1)(CSF - 1)}{2H_i(EDC - 1)} \quad (27)$$

## Discussion

**Effect of Host Structure on Chiral Recognition of Enantiomers of Standard Guest.** The perchlorate salt of phenylglycine was chosen as the standard guest acid for evaluating chiral recognition of various hosts for the following reasons: (1) the ester of this salt had exhibited the highest enantiomer distribution constants (EDC), and thus provided the most sensitive probe for chiral recognition of any esters examined;<sup>3d</sup> (2) the benzyl and ortho protons of the guest modified by the aryl groups of the host provide  $^1H$  NMR spectral information for structures of the complexes in solution; (3) both enantiomers of this guest acid are available commercially; (4) the hydrophilic-lipophilic properties of this acid salt allowed convenient quantities to be extracted from  $D_2O$  into  $CDCl_3$  0.45 mole fraction in  $CD_3CN$  in the presence of hosts with widely differing complexing properties at 0  $^\circ C$ .

$$\Delta(\Delta G^\circ) = -RT \ln EDC \quad (28)$$

The chiral recognition (kcal/mol) is measured by the differences in free energies of formation on the diastereomeric complexes in the organic layer ( $-\Delta(\Delta G^\circ)$  values), as expressed in eq 28. Runs 1–7 of Table I provide the following decreasing order of  $-\Delta(\Delta G^\circ)$  values (kcal/mol) as the structure of the host changed:  $(CH_3)_2D(OEOEO)_2D$ , 1.3;  $(CH_3)_2D(OEOEO)_2P$ , 0.8;  $D(OEOEO)_2D$ , 0.4;  $(CH_3)_2D(OEOEO)_2PCH_3$ , 0.3. The direction of the configuration bias was the same for all complexes, the more stable complexes possessing the  $(SS)(L)$ ,  $(S)(L)$ , or  $(RR)(D)$  configurations. Runs 2–7 were carried out under identical conditions, and the values of  $G^*/H^*$  at equilibrium provide a rough measure of the complexing strength of the hosts. These values decrease in the following order as the host structure is changed:  $(CH_3)_2D(OEOEO)_2D$ , 0.6;  $(CH_3)_2D(OEOEO)_2P$ , 0.4;  $D(OEOEO)_2D$ , 0.2;  $(CH_3)_2D(OEOEO)_2PCH_3$ , 0.2. Thus, the more strongly binding the host, the higher the chiral recognition in this series.

Of the four hosts,  $(CH_3)_2D(OEOEO)_2D$  (**2**) is the most organized for complexation prior to the approach of the guest. Molecular models (CPK) of the substance indicate that the methyl groups in the 3,3' positions of the 1,1'-dinaphthyl unit enforce a conformation on the  $OCH_2$  groups attached at the 2,2' positions, which directs the electron pairs of the oxygens toward the center of the cavity. In potential alternative conformations, the attached  $CH_2$  group runs into methyl, aryl, or oxygen. The enforced conformation coupled with the extension of the chiral barrier by the methyl groups provides  $(CH_3)_2D(OEOEO)_2D$  with about 0.9 kcal/mol more chiral recognition than is observed with  $D(OEOEO)_2D$ .

In the next best host,  $(CH_3)_2D(OEOEO)_2P$  (**3**), a diphenyl unit (P) is substituted for the dinaphthyl unit (D). At the

**Table III.** Association Constants ( $K_a$ ) and Free Energies of Association of Diastereomeric Complexes Involving  $C_6H_5CH(CO_2H)NH_3ClO_4$  in  $CDCl_3$ - $CD_3CN$  at 0 °C

run no.	mol fract $CD_3CN^a$	host	$K_a^A, M^{-1} b$	$K_a^B, M^{-1} c$	$-\Delta G_A^\circ, kcal/mol^d$	$-\Delta G_B^\circ, kcal/mol^d$	$-\Delta(\Delta G^\circ), kcal/mol^e$	$-\Delta(\Delta G^\circ)/-\Delta G_A^\circ$
1 <sup>f</sup>	0.45	D(OEOEO) <sub>2</sub> D	82	46	2.61	2.27	0.34	0.13
2	0.45	D(OEOEO) <sub>2</sub> D	138	61	2.68	2.23	0.45	0.17
3	0.45	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> P	458	106	3.33	2.53	0.80	0.24
6	0.45	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	1376	118	3.93	2.59	1.30	0.33
7	0.45	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	2085	189	4.15	2.85	1.30	0.31
8	0.45	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	1800	117	4.07	2.59	1.48	0.36
9	0.45	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	1879	129	4.09	2.64	1.45	0.35
10	0.35	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	3238	239	4.39	2.98	1.41	0.32
11	0.40	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	2530	200	4.26	2.88	1.38	0.32
12	0.45	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	1721	152	4.05	2.73	1.32	0.33
13	0.52	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	1081	109	3.80	2.55	1.25	0.33
14	0.58	(CH <sub>3</sub> ) <sub>2</sub> D(OEOEO) <sub>2</sub> D	836	103	3.66	2.52	1.14	0.31

<sup>a</sup> In  $CDCl_3$ . <sup>b</sup> From eq 4. <sup>c</sup> From eq 5. <sup>d</sup> From eq 29. <sup>e</sup> From eq 30. <sup>f</sup> 25 °C.

temperature used in the extractions (0 °C), the diphenyl unit of the host probably equilibrates between an *S* and an *R* configuration. Molecular models of the complexes indicate that this degree of freedom is undoubtedly frozen out. However, in the extracted mixture in run 3, (*SS*)(*L*) and (*SR*)(*L*) complexes were probably in equilibrium with one another, as were the alternative (*SS*)(*D*) and (*SR*)(*D*) complexes. Of these four, the results suggest that the complex of the (*SS*)(*L*) configuration was the most stable. Had this not been true, the chiral recognition would have been lower than the observed 0.8 kcal/mol, and the direction of the chiral bias might even have been inverted. The practical advantage to host (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>P (**3**) is that in its synthesis only one chiral element needs to be introduced. However, substitution of a P for a D unit results in a loss of over a third of its chiral recognition (0.5 kcal/mol) as compared to (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D, whose two chiral units provide a higher degree of enforced structure.

Introduction of one methyl group on the diphenyl unit of (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>P(CH<sub>3</sub>) (**4**) lowers the chiral recognition by 0.5 kcal/mol over what is observed for the host without this methyl group (**3**). The extra methyl group in **4** destroys the *C*<sub>2</sub> axis found in the other three hosts, makes the host "sided", and increases to eight the possible number of diastereomeric complexes formed in the extraction. Although the overall direction of the chiral bias is the same as that of the other three hosts, the many complexes formed from this one host and the enantiomeric guests undoubtedly led to averaging and cancellation of much of the net advantage in stability that one complex had over the others.

The effect of temperature on chiral recognition was examined only with D(OEOEO)<sub>2</sub>D (runs 1 and 2, Table I). As was observed in complexation of the amino acid ester salts,<sup>3c,d</sup> the lower temperature (0 °C) provided about 0.1 kcal/mol more chiral recognition.

**Relationships between Host-Guest Structure and Free Energies of Binding of Diastereomeric Complexes.** The guest distribution constants in the absence of host for  $C_6H_5CH(CO_2H)NH_3ClO_4$  of Table II ( $K_d$ ) allowed association constants to be calculated in the organic phase for host binding each enantiomeric guest (eq 4 and 5). Table III lists the values of  $K_a^A$  (the constant for the more associated guest enantiomer A) and of  $K_a^B$  (the constant for the less associated guest enantiomer B). Values of  $-\Delta G_A^\circ$ ,  $-\Delta G_B^\circ$ , and  $-\Delta(\Delta G^\circ)$  are also listed. The free energies were calculated from eq 29 and 30.

$$\Delta G_A^\circ = -RT \ln K_a^A$$

$$\Delta G_B^\circ = -RT \ln K_a^B \quad (29)$$

$$\Delta(\Delta G^\circ) = -RT \ln (K_a^A/K_a^B) \quad (30)$$

As host is changed in the order of increasing binding ability in runs 2, 3, 6, and 7,  $-\Delta G_A^\circ$  and  $-\Delta G_B^\circ$  values (kcal/mol) increase respectively as follows: D(OEOEO)<sub>2</sub>D, 2.6 and 2.3; (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>P, 3.3 and 2.5; (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D, 4.0 and ~2.7. The hosts become better complexing agents for *both enantiomers* in the same order, but the  $-\Delta G_A^\circ$  values increase more than the  $-\Delta G_B^\circ$  values as the general binding power of the hosts increases. Thus the chiral recognition increases as the binding power of the host increases.

For host (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D binding enantiomer A, the  $-\Delta G_A^\circ$  values (kcal/mol) decreased in the following order with increasing mole fraction of  $CD_3CN$  in  $CDCl_3$ : 4.4 at 0.35; 4.3 at 0.40; 4.05 at 0.45; 3.8 at 0.52; 3.7 at 0.58. The same order is observed for (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D binding enantiomer B, but the  $-\Delta G_B^\circ$  values fall off less rapidly with increasing mole fraction (respectively): 3.0 at 0.35; 2.9 at 0.40; 2.7 at 0.45; 2.55 at 0.52; 2.5 at 0.58. Thus, as the medium becomes more polar, the free energies of complex formation for both enantiomers decrease. However, the decrease is more marked for the more bound enantiomer. As a result, chiral recognition decreases with increasing solvent polarity.

The interesting question arises as to what fraction of the free energy of binding of the more bound enantiomer represents chiral recognition. The parameter  $[-\Delta(\Delta G^\circ)]/[-G_A^\circ]$  measures this fraction, which might be termed *chiral efficiency*. Table III lists the chiral efficiencies for those runs that involve  $C_6H_5CH(CO_2H)NH_3ClO_4$  as guest. In passing from hosts D(OEOEO)<sub>2</sub>D to (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>P to (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D in runs 2, 3, 6, and 7, the chiral efficiency increases from 0.17 to 0.24 to 0.32. Thus the best host is only about 32% efficient in its chiral recognition. The improved analytical technique represented by run 8 raised this value to only 36%. Interestingly, the chiral efficiency remained at  $0.32 \pm 0.01$  kcal/mol as the solvent composition was changed from 0.35 to 0.58 mole fraction  $CD_3CN$  in  $CDCl_3$  (runs 10–14).

These trends suggest that, if chiral recognition with  $-\Delta(\Delta G^\circ)$  values as high as 5 kcal/mol is to be observed, more powerfully binding hosts will have to be designed. For example, with a chiral efficiency factor of 0.36, a  $-\Delta G_A^\circ$  value of ~14 kcal/mol would be required to produce  $-\Delta(\Delta G^\circ) = 5$  kcal/mol.

**Effect of Guest Structure on Chiral Recognition with a Standard Host.** Since (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D was the strongest binder and exhibited the highest chiral recognition toward  $C_6H_5CH(CO_2H)NH_3ClO_4$  of any of the hosts examined, it was chosen as the standard host for examination of other guest salts. The chiral recognition was measured in terms of the differences in free energy of the diastereomeric complexes in the organic layer [ $-\Delta(\Delta G^\circ)$  values of Table 1]. Runs 6, 15, 17, 18, and 20–22 of Table 1 provide the following decreasing

order of  $-\Delta(\Delta G^\circ)$  values (kcal/mol) as the structure of the guest changed:  $C_6H_5CH(CO_2H)NH_3ClO_4$ , 1.3; *p*- $HOC_6H_4CH(CO_2H)NH_3ClO_4$ , 1.2;  $C_6H_5CH_2CH(CO_2H)NH_3ClO_4$ , 0.7;  $(CH_3)_2CHCH(CO_2H)NH_3ClO_4$ , 0.5;  $CH_3SCH_2CH_2CH(CO_2H)NH_3ClO_4$ , 0.45;  $CH_3CH(CO_2H)NH_3ClO_4$ , 0.45;  $C_8H_8NCH_2CH(CO_2H)NH_3ClO_4$  (tryptophane salt), 0.4. For all seven amino acid salts, the configurational direction of the chiral bias was the same and the (SS)(L) diastereomer was the more stable.

With one exception, this order conforms to the character of the R group of  $RCH(CO_2H)NH_3ClO_4$  in the following sense: the greater the steric requirements of this group in the vicinity of the chiral center of the guest, the higher the chiral recognition. Thus  $C_6H_5 \sim p\text{-}HOC_6H_4 > C_6H_5CH_2 \sim (CH_3)_2CH > CH_3SCH_2CH_2 \sim CH_3$  in steric requirements when adapted to those of the chiral barrier of the host. The exception is provided by tryptophane salt. This is the most lipophilic of the guests examined, and conceivably the unexpectedly low EDC value observed (2.1) is due to more than the usual small amount of uncomplexed guest distributing into the organic layer at equilibrium. With the more hydrophilic  $C_6H_5CH(CO_2H)NH_3ClO_4$  as guest using the same solvent system, correction for this uncomplexed material in the organic phase (e.g., run 6) amounted to only about 0.07 kcal/mol.

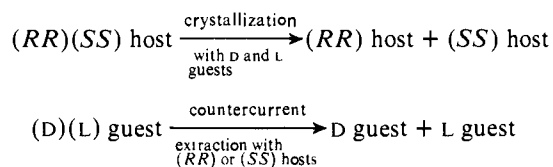
**Effect of Organic Solvent Composition on Chiral Recognition Involving  $(CH_3)_2D(OEOEO)_2D$  and  $C_6H_5CH(CO_2H)NH_3ClO_4$ .** Runs 10–14 of Table I record the EDC,  $K_a^A/K_a^B$ , and  $-\Delta(\Delta G^\circ)$  values for the (SS) host complexing the D and L guests in  $CDCl_3$ – $CD_3CN$  mixtures that range from 0.35 to 0.58 mole fraction in  $CD_3CN$ . As shown by the results of Table II, the distribution constants of racemic guest between the aqueous and organic layers ( $K_d$ ) changed at 0 °C from  $0.076 \times 10^{-3}$  to  $2.3 \times 10^{-3} M^{-1}$  when the organic phase was changed from  $CDCl_3$  to 0.58 mole fraction  $CD_3CN$  in  $CDCl_3$ , respectively. When  $CDCl_3$  alone was used as the organic phase in the complexation experiments, too little guest was drawn into the organic phase for EDC determinations. For the other solvent compositions it was observed that both the EDC and  $K_a^A/K_a^B$  values decreased as the organic layer became enriched in  $CD_3CN$ . The EDC values are directly measured, and do not take into account the uncomplexed guest in the organic phase, whereas the  $K_a^A/K_a^B$  values are corrected for this uncomplexed guest (see Results section). Extrapolation of plots of solvent composition against either EDC or  $K_a^A/K_a^B$  values to  $CDCl_3$  free of  $CD_3CN$  suggests that EDC or  $K_a^A/K_a^B$  values of about 20 would probably be observed in  $CDCl_3$ , which provides a  $-\Delta(\Delta G^\circ)$  of about 1.6 kcal/mol difference between the diastereomeric complexes. As observed previously with esters<sup>3c,d</sup> and acids,<sup>3f</sup> the composition of the solvent plays an important role in the observed chiral recognition between host and guest. This conclusion is not surprising in view of the fact that host and solvent are competing with one another in binding to a very polar guest salt.

In a preliminary communication,<sup>2</sup> we reported that at 0.45 mole fraction of  $CD_3CN$ – $CDCl_3$  at 0 °C with  $(CH_3)_2D(OEOEO)_2D$  as host and  $C_6H_5CH(CO_2H)NH_3ClO_4$  as guest, EDC values of 52 were observed in two separate experiments. At either higher or lower concentrations of  $CD_3CN$  in  $CDCl_3$ , the preliminary EDC values observed were comparable to those reported here. Four different investigators applying three different isolation methods have been unable to duplicate these preliminary values of 52, and we conclude that they were spurious. The greatest care must be taken not to subject the optically active guest isolated from the two layers to any kind of enantiomeric fractionation. When chiral recognition becomes high, very small amounts of fractionation have a large effect on EDC values. Because of this potential source of error, three different isolation techniques were developed (referred to in Table I as methods A, B, and

C). Of these, method C is the most refined and tends to give the highest  $-\Delta(\Delta G)$  values.<sup>5</sup>

**A Chiral Breeding Cycle That Involves Complexation both in the Liquid and Solid Phases.** Classical resolution methods were originally used to prepare (RR)- and (SS)- $(CH_3)_2D(OEOEO)_2D$  (**2**) of maximum rotation.<sup>3a,b</sup> We now report that (RR)(SS)- $(CH_3)_2D(OEOEO)_2D$  can be very simply resolved into its enantiomers by crystallization of the more stable diastereomeric complex between (RR)- $(CH_3)_2D(OEOEO)_2D$  and  $D\text{-}C_6H_5CH(CO_2H)NH_3ClO_4$ , or (SS)- $(CH_3)_2D(OEOEO)_2D$  and  $L\text{-}C_6H_5CH(CO_2H)NH_3ClO_4$  in practical yields. When racemic host was treated in ethyl acetate with 0.5 equiv of D guest, essentially diastereomerically pure complex (RR)(D)-**5** crystallized. The (SS) host remaining in solution was purified through crystallization of complex (SS)(L)-**5**. Thus chiral recognition in solution and in the crystalline state involves the same configurational bias. Attempts to crystallize the (SS)(D) diastereomer failed, even when enantiomerically pure components were mixed. Unfortunately, the crystals of the (SS)(L) complex obtained were found unsuitable for X-ray structure determination.

Enantiomeric resolution of (RR)(SS)-**2** by crystallization of its diastereomeric complexes with D or L guest completes the chiral breeding cycle formulated. Host is resolved with guest by crystallization, and guest is resolved with host by extraction.



**Structures of Diastereomeric Complexes in Solution.** The 100-MHz <sup>1</sup>H NMR spectra of the diastereomerically pure complexes formed between (SS)- $(CH_3)_2D(OEOEO)_2D$  and L- and D- $C_6H_5CH(CO_2H)NH_3ClO_4$  were determined in 0.45 mole fraction  $CD_3CN$  in  $CDCl_3$ . The complexes were formed by the standard extraction procedure exemplified by runs 5–9 of Table I except that enantiomerically pure guests were substituted for racemic material. Although the extractions were carried out at 0 °C, the spectra were taken at probe temperature. Chart II records the chemical shifts of the diastereomeric complexes, and parenthetically the corresponding chemical shifts in  $CDCl_3$  of similar complexes between  $(CH_3)_2D(OEOEO)_2D$  and ester  $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ ,<sup>3d</sup> and between  $D(OEOEO)_2D$  and ester  $C_6H_5CH(CO_2CH_3)NH_3PF_6$ .<sup>3c</sup> The corresponding chemical shifts of  $(CH_3)_2D(OEOEO)_2D$  alone in 0.45 mole fraction  $CD_3CN$  in  $CDCl_3$  are also recorded parenthetically.

The patterns of chemical shifts for the three sets of diastereomeric complexes compared in Chart II are similar enough to one another to suggest that those of the same configuration possess similar structures, although the hosts and guests differ somewhat. Thus in complexes of the more stable (SS)(L) configurations, the NCH (methine) proton singlets of the phenylglycine guests are 0.71–0.55 ppm upfield of those observed for the (SS)(D) isomers. The ortho proton multiplets of the phenyl group of the phenylglycine guests in complexes of the (SS)(L) configuration are 1.3–0.34 ppm upfield of those observed in complexes of the (SS)(D) configuration. The  $CH_3Ar$  proton singlets of the host in the complexes of the (SS)(L) configuration are 0.09–0.08 ppm upfield of those of the (SS)(D) configuration. The sets of multiplets associated with the  $CH_2OCH_2$  protons of the hosts in the complexes of the (SS)(L) configuration are 0.06–0.4 ppm upfield of those observed for those of the (SS)(D) configuration. The sets of multiplets of the  $ArOCH_2$  protons of the hosts in the complexes of the (SS)(L) and (SS)(D) configurations are generally closer

Chart II

<sup>1</sup> H NMR δ	(SS)(L)-5	(SS)(D)-5
NCH	4.29 (4.42)* (4.42)†	5.00 (4.97)* (4.97)†
	6.08 (6.31)* (6.56)†	6.9-7.4 (6.9-7.4)* (6.9-7.4)†
CH <sub>3</sub> Ar	2.27 (2.26)* (2.38)*	2.36 (2.34)* (2.38)*
CH <sub>2</sub> OCH <sub>2</sub>	2.94; 3.14 (2.82; 3.10)* (2.90)† (3.28)‡	3.00; 3.30 (3.02; 3.50)* (3.22)† (3.28)‡
ArOCH <sub>2</sub>	3.64; 4.17 (3.64; 4.18)† (3.50; 3.98)† (3.04; 3.70)‡	3.74; 4.02 (3.70; 4.00)* (3.54; 3.98)† (3.04; 3.70)‡

\* Corresponding chemical shifts of complex of host with C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>CH<sub>3</sub>)NH<sub>3</sub>ClO<sub>4</sub>.† Corresponding chemical shifts of complex of ester with D(OEOEO)<sub>2</sub>D.‡ Corresponding chemical shifts of (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D uncomplexed in some medium.

to one another than are the other protons, and no patterns are visible in their chemical-shift differences.

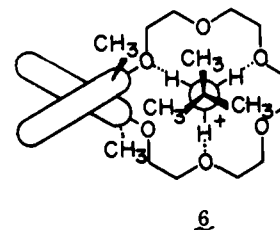
The effects of CD<sub>3</sub>CN concentration in CDCl<sub>3</sub> on the <sup>1</sup>H NMR spectra of the diastereomeric complexes were examined on solutions formed by extracting aqueous solutions of L-C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub> and of D-C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub> with organic solutions of (SS)(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D. Too little complex was formed for spectral examination with organic solutions lower than 0.11 mole fraction CD<sub>3</sub>CN in CDCl<sub>3</sub>. From 0.11 to 0.52 mole fraction CD<sub>3</sub>CN in CDCl<sub>3</sub>, the spectra of the diastereomeric complexes were essentially unchanged.

Since (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D contains a C<sub>2</sub> axis, the same potential structures are generated by binding the guest enantiomers to either of the two faces of the macroring. The formula of (SS)(R)-5 in Chart II resembles the X-ray structure for the (SS)(D) complex between (SS)-1 and C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>CH<sub>3</sub>)NH<sub>3</sub>PF<sub>6</sub>.<sup>6</sup> The (SS)(L)-5 structure correlates the <sup>1</sup>H NMR spectrum observed for the complex with expectations derived from examination of CPK molecular models of the complex. In (SS)(L)-5, three NH...O hydrogen bonds in a tripod arrangement are envisioned as holding the two partners together. The dihedral angle between the three hydrogens attached to N and the three substituents attached to the chiral center is presumed to be 60°, as in the X-ray structure of the complex between (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>E and (CH<sub>3</sub>)<sub>3</sub>CNH<sub>3</sub>ClO<sub>4</sub>,<sup>7</sup> which also has the hydrogen-bonded tripod binding (see structure 6).

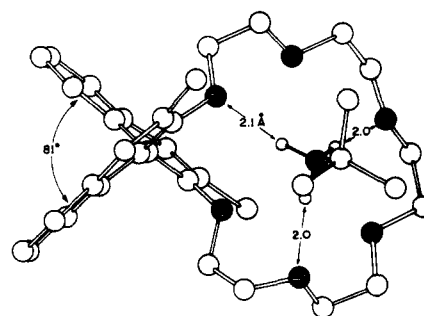
In (SS)(L)-5, the phenyl is the largest group attached to the chiral center of the guest, and is placed in the largest cavity of the host in between and roughly perpendicular to the two naphthalene "walls" which define the cavities. This arrangement places one of the ortho hydrogens of the phenyl in the shielding region of one of the naphthalene rings, which accounts for its upfield chemical shift. This phenyl lies over and contacts two of the CH<sub>2</sub>OCH<sub>2</sub> hydrogens of the host, which explains the upfield chemical shift of these protons. The hydrogen as the smallest group attached to the chiral center of the guest of (SS)(L)-5 contacts the same naphthalene ring and likewise is moved upfield. The carboxyl group in (SS)(L)-5 is aligned in a plane parallel to the opposite naphthalene "wall", with its hydroxyl group hydrogen bonded to one of the ArO oxygens of the host. The naphthalene and carboxyl group may also bind each other by π-acid-π-base interactions. This structure accounts for the <sup>1</sup>H NMR spectrum of the (SS)(L) complex, and was envisioned prior to experiment. The (SS)(D)

complex was designed "not to form", and hence we have less confidence in the structure (SS)(D)-5 formulated for it.

Host (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D shows about 1 kcal/mol more chiral recognition toward C<sub>6</sub>H<sub>5</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub> than (RR)-D(OEOEO)<sub>2</sub>D (compare runs 2 and 7 of Table I). Thus the two methyl groups play an important role in the chiral recognition. In the X-ray structure of the complex between (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>E and (CH<sub>3</sub>)<sub>3</sub>CNH<sub>3</sub>ClO<sub>4</sub> (6),<sup>7</sup> the best



6

Structure of (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>E-t-BuNH<sub>3</sub><sup>+</sup> complex derived from CPK models

X-ray structure

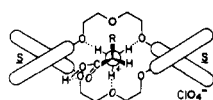
plane of the oxygens of the macroring is not perpendicular to the planes of the naphthalene rings, but is displaced in such a way as to relieve repulsions between the methyl groups of the host and guest. Molecular models of (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D indicate that one of the important roles played by the methyl groups in the host is to resist similar splaying displacements in complexes of this host. The methyl group of the host on the side remote from the face binding the guest contacts the other naphthalene on the same side when the cavities on the binding side are enlarged by the splaying motion. Thus the chiral center of the guest and the chiral barriers of the host are held closer together in the complexes of (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D than in those of either (RR)-D(OEOEO)<sub>2</sub>D or (S)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>P.

Markedly different <sup>1</sup>H NMR spectra also were observed for the pure diastereomeric complexes of (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D and the enantiomers of *p*-HOC<sub>6</sub>H<sub>4</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub>, CH<sub>3</sub>SCH<sub>2</sub>CH<sub>2</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub>, and CH<sub>3</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub>. Since many of the peaks overlap, a complete analysis is not possible. However, the more stable (SS)(L) diastereomers do exhibit <sup>1</sup>H NMR spectra consistent with the general structure (SS)(L)-7 of Chart III for the more stable diastereomers. The more visible chemical shifts for the diastereomeric complexes in 0.45 mole fraction CD<sub>3</sub>CN in CDCl<sub>3</sub> are listed in Chart III.

### Experimental Section

**General.** All <sup>1</sup>H NMR spectra were taken on a Varian HA-100 spectrometer operated at ambient temperature with Me<sub>4</sub>Si as internal standard. Rotations were taken in a 1-dm thermostated cell on a Perkin-Elmer polarimeter 141. Reagent-grade CH<sub>2</sub>Cl<sub>2</sub> was fractionally distilled before use. Tetrahydrofuran was distilled from sodium benzophenone ketyl before use. Chloroform was washed five

Chart III



(SS)(L)-2

R of guest	protons	$\delta$ of protons (ppm)	
		(SS)(L)-isomer	(SS)(D)-isomer
$p$ -HOC <sub>6</sub> H <sub>4</sub>	NCH <sub>2</sub>	4.42	4.97
$p$ -HOC <sub>6</sub> H <sub>4</sub>	<i>o</i> -phenyl	6.28 and 6.54*	6.9-7.4
CH <sub>3</sub>	CH <sub>3</sub> -CHN	1.35	1.39
CH <sub>3</sub> SCH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub> S	1.64	1.52

\*Centers of two AB patterns.

times with equal volumes of water, dried over MgSO<sub>4</sub>, distilled, and deoxygenated with N<sub>2</sub> before use. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were taken on an AEI model MS-9 double-focusing mass spectrometer at 70 eV.

**Known Hosts and Guests.** Hosts (*RR*)-D(OEOEO)<sub>2</sub>D (**1**)<sup>3a</sup> and (*SS*)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D (**2**)<sup>3b</sup> of maximum rotation were employed. The amino acid perchlorates were examined.<sup>3f</sup> Their esters and ester salts<sup>3c,3d</sup> have been previously reported, as has racemic 2,2'-dimethoxy-1,1'-dinaphthyl.<sup>8</sup> In the following section a new synthesis of (CH<sub>3</sub>)<sub>2</sub>D(OH)<sub>2</sub> is reported. The compound was converted to the stereoisomers of (CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D.

**3,3'-Dimethyl-2,2'-dihydroxy-1,1'-dinaphthyl.** The mineral oil of 20.0 g of NaH (0.417 mol) was washed out with THF. To the NaH stirred under nitrogen in 1.0 L of dry THF was added in portions 50.0 g (0.175 mol) of 2,2'-dihydroxy-1,1'-dinaphthyl. After H<sub>2</sub> evolution stopped, 85 g (1.1 mol) of ClCH<sub>2</sub>OCH<sub>3</sub> was added to the stirred heavy precipitate, and the resulting mixture was stirred for 12 h and then filtered through a pad of Celite. The filtrate was shaken with 500 mL of H<sub>2</sub>O and 1 L of CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were washed with water saturated with KHCO<sub>3</sub>. The organic layer was dried and filtered through a squat column of alumina, and the column filtrate was evaporated until crystals appeared. Petroleum ether was added, and, after standing, 2,2'-bis(methoxymethoxy)-1,1'-dinaphthyl was collected, weight 62 g (95%), mp 93-94 °C, M<sup>+</sup> 374. Anal. (C<sub>24</sub>H<sub>22</sub>O<sub>4</sub>) C, H.<sup>9</sup>

To a mixture of 15 g (40.1 mmol) of the above bisacetal in 250 mL of THF stirred under N<sub>2</sub> at 0 °C was added 160.3 mL of 1.6 M BuLi (100.2 mmol) in hexane. The mixture was stirred at 0 °C for 45 min, and a tan precipitate appeared. The reaction mixture was allowed to warm to 25 °C and to the stirred suspension was added 12.6 g (9.5 mL, 100.2 mmol) of (CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>. The mixture was stirred for 12 h, 10 mL of water saturated with Na<sub>2</sub>CO<sub>3</sub> was added, and the solvent was evaporated under reduced pressure at 50 °C. The residue in 150 mL of CH<sub>2</sub>Cl<sub>2</sub> was washed twice with water, and to the organic solution were added 150 mL of CH<sub>3</sub>OH and 10 mL of concentrated hydrochloric acid. The solution was stirred for 3 h and the solvent was evaporated. The yellow product was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-hexane to give 11.3 g (90%) of 3,3'-dimethyl-2,2'-dihydroxy-1,1'-dinaphthyl, mp 204-206 °C. The spectroscopic properties were identical with those of the literature.<sup>3b</sup>

**(RR)(SS)- and (RS)(SR)-2,3,4,5-Di-1,2-(3-methylnaphtho)-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((RR)(SS)-2) and ((RS)(SR)-2).** The syntheses of the diastereomeric mixture of racemates followed reported procedures<sup>3b</sup> applied to the scheme indicated in the Results section and involved 9.8 g of (CH<sub>3</sub>)<sub>2</sub>D(OH)<sub>2</sub> as starting material. The remaining steps always involved 10-20 g of material, and each intermediate possessed the expected physical properties.<sup>3b</sup> The tosylation of (CH<sub>3</sub>)<sub>2</sub>D(OEOEOH)<sub>2</sub> went in 91% yield. The ring closure to give the diastereomeric isomers of **2** involved procedure II,<sup>3b</sup> and gave an 87% yield of a mixture of (*RR*)(*SS*)- and (*RS*)(*SR*)-**2** after filtration chromatography on alumina. The relative amounts of the two diastereomeric racemates were determined by the relative intensities of their CH<sub>3</sub>Ar absorptions in the <sup>1</sup>H NMR spectrum of the final mixture. That of (*RR*)(*SS*)-**2** absorbs at  $\delta$  2.40 ppm and that of (*RS*)(*SR*)-**2** at 2.50 ppm,<sup>3b</sup> and the former represented about 40% and the latter about 60% of the mixture. This material (10.7 g) was submitted

to medium-pressure chromatography (30-90 psi) on 40-60  $\mu$ m silica gel with 4% (v) EtOAc in CH<sub>2</sub>Cl<sub>2</sub> as solvent. From the column were recovered 6.1 g (*R<sub>f</sub>* ~0.20 in CH<sub>2</sub>Cl<sub>2</sub>) of (*RS*)(*SR*)-**2** as the faster and 3.9 g (*R<sub>f</sub>* ~0.15 in CH<sub>2</sub>Cl<sub>2</sub>) of (*RR*)(*SS*)-**2** as the slower moving stereoisomer. The physical properties were identical with those reported.<sup>3b</sup>

**Enantiomeric Resolution of (RR)(SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D ((RR)(SS)-2) through Complexation.** To a solution of 2.0 g (2.7 mmol) of (*RR*)(*SS*)-**2** in 2.0 mL of CHCl<sub>3</sub> was added a solution of L-phenylglycinium perchlorate (0.34 g, 1.35 mmol) in 4.0 mL of ethyl acetate. The (*SS*)(*L*) complex crystallized at 25 °C during 48 h, the mother liquor was decanted, and the crystals were washed and filtered from CHCl<sub>3</sub> to give after drying 0.70 g (52%) of material, mp 206-208.5 °C dec (gas evolution). Anal. (C<sub>58</sub>H<sub>54</sub>ClNO<sub>12</sub>) C, H. This complex was shaken with 0.1 N aqueous HCl (20 mL) and 50 mL of CH<sub>2</sub>Cl<sub>2</sub>, the phases were separated, and the aqueous layer was washed with two 25-mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, the solvent was evaporated, and the residue was chromatographed through 50 g of neutral alumina, activity III with 50% hexane-50% CH<sub>2</sub>Cl<sub>2</sub> to give 0.506 g (97% recovery) of (*SS*)-**2** (50% overall) as a dried foam, [ $\alpha$ ]<sub>578</sub><sup>25</sup> - 146.3°, [ $\alpha$ ]<sub>546</sub><sup>25</sup> - 173.8°, [ $\alpha$ ]<sub>436</sub><sup>25</sup> - 387° (c 1.3, CHCl<sub>3</sub>).

The mother liquors from crystallization of the above complex were evaporated, the residue was decomplexed by the above procedure, and the free host was recovered. This material was dissolved in 2.0 mL of CHCl<sub>3</sub> and mixed with 4 mL of EtOAc containing 0.35 g (1.39 mmol) of D(-)-phenylglycinium perchlorate. The crystals that separated were washed with CHCl<sub>3</sub> and dried to give 1.07 g (80%) of (*RR*)(*D*) complex, mp 206.5-207.5 °C dec (gas evolution). This material was converted by the above procedure to 0.783 g (93%) of (*RR*)-**2** (78% overall) as a dried foam, [ $\alpha$ ]<sub>578</sub><sup>25</sup> + 146.4°, [ $\alpha$ ]<sub>546</sub><sup>25</sup> + 173, [ $\alpha$ ]<sub>436</sub><sup>25</sup> + 386° (c 1.25, CHCl<sub>3</sub>).

A sample of 3.75 g (5.06 mmol) of (*SS*)-**2** of maximum rotation prepared from (*S*)-(CH<sub>3</sub>)<sub>2</sub>D(OH)<sub>2</sub> and (*S*)-D(OH)<sub>2</sub> was converted to its complex with 1.273 g (5.06 mmol) of L-phenylglycinium perchlorate. The complex gave mp 207.5-208.5 °C dec (gas evolution), and when converted back to (*SS*)-**2** gave 3.07 g of material, [ $\alpha$ ]<sub>578</sub><sup>25</sup> - 146.5°, [ $\alpha$ ]<sub>546</sub><sup>25</sup> = -173.1°, [ $\alpha$ ]<sub>436</sub><sup>25</sup> - 387° (c 1.25, CHCl<sub>3</sub>). The near identity of the magnitudes of rotations of samples of (*RR*)- and (*SS*)-**2** prepared in different ways indicates that the materials are essentially optically pure.

**Formation of the Complex between (SS)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub>D and L-p-HOC<sub>6</sub>H<sub>4</sub>CH(CO<sub>2</sub>H)NH<sub>3</sub>ClO<sub>4</sub>.** To a solution of 0.300 g (0.405 mmol) of (*SS*)-**2** in 6 mL of EtOAc was added a solution of 0.108 g (0.405 mmol) of L-*p*-hydroxyphenylglycinium perchlorate in 2 mL of EtOAc. Crystals separated from the homogeneous solution, and after 3 h they were collected, washed with CH<sub>2</sub>Cl<sub>2</sub>, and dried, mp 207.5-220 °C dec (evolution of a gas), weight 0.370 g (91%). Anal. (C<sub>58</sub>H<sub>54</sub>ClNO<sub>13</sub>) C, H, N. The host was recovered by the extraction procedure to give 0.266 g (89%) for the cycle of reactions.

Preliminary experiments demonstrated that (*SS*)-2,3,4,5-di-1,2-(3-methyl-5,6,7,8-tetrahydronaphtho)-13,14,15,16-di-1,2-(5,6,7,8-tetrahydronaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((*SS*)-**2** with the outer aryl rings reduced) also formed a nicely crystalline complex with L-phenylglycinium perchlorate.

**(S)-2,3,4,5-Di-1,2-(3-methylnaphtho)-13,14,15,16-di(1,2-benzo)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((S)-3).** To a mixture stirred under N<sub>2</sub> of 1.26 g (6.76 mmol) of *o,o'*-dihydroxybiphenyl (Aldrich) in 300 mL of refluxing THF were added 1.0 g (15 mmol) of 85% KOH pellets and 1.26 mL of water. To the resulting homogeneous solution was added dropwise (15 min) a solution of 5.40 g (6.76 mmol) of (*S*)-(CH<sub>3</sub>)<sub>2</sub>D(OEOEO)<sub>2</sub> of maximum rotation<sup>3b</sup> in 120 mL of dry THF. After 40 h at reflux, no tosylate remained (<sup>1</sup>H NMR of aliquot). The reaction mixture was cooled and neutralized with concentrated aqueous HCl, and the solvent was removed under vacuum. The residue was shaken with 150 mL of CH<sub>2</sub>Cl<sub>2</sub> and 300 mL of 2 N HCl in water. The phases were separated, and the aqueous phase was extracted with two additional 150-mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>-K<sub>2</sub>CO<sub>3</sub>, and the solvent was evaporated. The residue was filtered through about 20 g of activity III neutral alumina and washed thoroughly with 40% hexane in CH<sub>2</sub>Cl<sub>2</sub>. The solvent was evaporated, and the residue was submitted to gel permeation chromatography on an 18-ft. 100-Å styragel column in CH<sub>2</sub>Cl<sub>2</sub> to give a single peak at 187-mL retention volume containing (*S*)-**3**, 2.36 g (55%), as a glass. This material was



chromatographed through 250 g of activity III neutral alumina in 40% hexane in  $\text{CH}_2\text{Cl}_2$ , 10-mL fractions being cut. Fractions 24–44 contained only product with  $R_f$  0.28 (40% hexane in  $\text{CH}_2\text{Cl}_2$ ). When evaporated, they gave a colorless foam which when dried at 70 °C (0.1 mm) gave 1.88 g (44%) of (S)-3;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.43 (s, 3,  $\text{ArCH}_3$ ), 2.50 (s, 3,  $\text{ArCH}_3$ ), 3.0–4.2 (m, 16,  $\text{OCH}_2$ ), 6.8–8.0 (m, 18,  $\text{ArH}$ ),  $M^+ m/e$  640. Anal. ( $\text{C}_{42}\text{H}_{40}\text{O}_6$ ), C, H.

The temperature-dependent  $^1\text{H NMR}$  spectrum of (R)(S)-3 was examined in diphenyl ether solution, and the coalescence temperature of the  $\text{ArCH}_3$  resonances was found to be 89 °C.

(S)-2,3,4,5-Di-1,2-(3-methylnaphtho)-13,14-(1,2-benzo)-15,16-(3-methyl-1,2-benzo)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((S)-4). The same procedure for ring closure was applied to 5.829 g (7.295 mmol) of (S)- $(\text{CH}_3)_2\text{D}(\text{OEOEO})_2$  of maximum rotation<sup>3b</sup> and 2,2'-dihydroxy-3-methyl-1,1'-diphenyl<sup>10</sup> to give 2.58 g (54%) of material of 187-mL retention volume on an 18-ft, 100-Å styragel gel permeation column in  $\text{CH}_2\text{Cl}_2$ . Further chromatographic purification gave 1.57 g (33%) of pure (S)-4 as a colorless foam after drying at 70 °C for 12 h;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.22, 2.27, 2.38, 2.50 (4 s, 1.5 H each,  $\text{ArCH}_3$ ), 2.47 (s, 3,  $\text{ArCH}_3$ ), 3.0–4.4 (m, 16,  $\text{OCH}_2$ ), 7.0–8.0 (m, 17,  $\text{ArH}$ );  $M^+ m/e$  654. Anal. ( $\text{C}_{43}\text{H}_{42}\text{O}_6$ ), C, H.

**Determination of  $K_d$  Values.** For the experiments conducted at 0 °C, 20-mL solutions were prepared which varied between 0 and 0.58 mole fraction of  $\text{CD}_3\text{CN}$  in  $\text{CDCl}_3$  containing 2.964 g of 2,2'-dimethoxy-1,1'-dinaphthyl. This amount of "host substitute" was equal on a weight basis to the amount of host used in the EDC determinations that involved  $(\text{CH}_3)_2\text{D}(\text{OEOEO})_2$  (see below). Solutions (10 mL) of  $\text{D}_2\text{O}$  that were 1.2 M in  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{H})\text{NH}_3\text{ClO}_4$  and 2.0 M in  $\text{LiClO}_4$  and whose pH was adjusted to 1.0 with  $\text{HClO}_4$  were also prepared. The two solutions were placed in a cold room at 0 °C, shaken together at 0 °C for 1 h, and centrifuged in the cold room, and the aqueous solution was carefully withdrawn with a capillary pipet, leaving a small meniscus at the interface. The small meniscus, the interface, and a small amount of the organic phase were carefully removed with a new pipet. Finally a 15.0-mL aliquot of the organic phase was withdrawn into a syringe, the needle was removed, and the contents were placed in a tared round-bottomed flask. The solvent was removed under reduced pressure (<40 °C), and the solid obtained was dried to constant weight at 0.1 mm at 25 °C. The weights of salt extracted were calculated by the difference between the weights obtained and the weights of 2,2'-dimethoxy-1,1'-dinaphthyl present in 15 mL of the organic layer (2.223 g). The amount of salt extracted varied between 0.8 mg in the absence of  $\text{CD}_3\text{CN}$  to 32.7 mg in the presence of 0.58 mole fraction of  $\text{CD}_3\text{CN}$  in  $\text{CDCl}_3$ . The results were duplicatable within 1% at the highest and 25% at the lowest amount of  $\text{CD}_3\text{CN}$ . Table II reports the  $K_d$  values. The determinations made at 25 °C were conducted the same way except for the following: the temperature change; 15 mL of the organic layers was shaken with 7.5 mL of the  $\text{D}_2\text{O}$  layers that were 4 M in  $\text{LiClO}_4$ ; and a 10-mL aliquot of the organic layer was evaporated. The weights of salt extract varied between 0.8 mg at 0 mole fraction  $\text{CD}_3\text{CN}$  and 32.7 mg at 0.58 mole fraction  $\text{CD}_3\text{CN}$  in  $\text{CDCl}_3$ .

Experiments conducted similarly to those at 0 °C described above were carried out in the absence of "host substitute", and provided the following weights (mg) of salt extracted at the corresponding mole fractions of  $\text{CD}_3\text{CN}$  in  $\text{CDCl}_3$ : 1.1 at 0; 20.3 at 0.22; 52.0 at 0.36; 108.2 at 0.45; 169.9 at 0.52; 213.0 at 0.58. Thus, addition of the "host substitute" to the organic phase *substantially depressed* the amounts of  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{H})\text{NH}_3\text{ClO}_4$  extracted into the organic layer at equilibrium. At 0.45 mole fraction of  $\text{CD}_3\text{CN}$  in  $\text{CDCl}_3$ , a control experiment was run in which the organic salt was omitted from the  $\text{D}_2\text{O}$  phase, but the 2.0 M  $\text{LiClO}_4$  salt was retained. The amount of  $\text{LiClO}_4$  extracted into the organic phase was 1.2 mg.

**Procedure A for Determination of Enantiomer Distribution Constants (EDC).** The procedure is exemplified by run 10 of Table I. To a 10-mL graduated cylinder were added 0.74 g (1.0 mmol) of (SS)- $(\text{CH}_3)_2\text{D}(\text{OEOEO})_2$  (2) of rotation  $[\alpha]_{578}^{25} -146.5^\circ$ ,  $[\alpha]_{546}^{25} -173.4^\circ$ ,  $[\alpha]_{436}^{25} -385.2^\circ$  (c 1.0,  $\text{CHCl}_3$ ) and 5.0 mL of 0.35 mole fraction of  $\text{CD}_3\text{CN}$  in  $\text{CDCl}_3$  (1.65 g of  $\text{CD}_3\text{CN}$  and 8.35 g of  $\text{CDCl}_3$ ) to give a final volume of 5.6 mL. To a 5-mL graduated cylinder were added 755 mg (3.0 mmol) of racemic  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{H})\text{NH}_3\text{ClO}_4$ , 2.5 mL of a 2.0 M solution of  $\text{LiClO}_4$  in  $\text{D}_2\text{O}$ , and 2 drops of 70% aqueous  $\text{HClO}_4$  to provide a final volume of 3.0 mL of pH ~0.5. The acid was required to complete dissolution of the salt. The two solutions were combined in a clean 25-mL centrifuge tube at 25 °C, capped with aluminum foil, and placed in a cold room at 0 °C. After thermal

equilibrium (~1 h), the mixture was shaken vigorously with a vortex mixer for 60 s and then centrifuged for 15 min in the cold room. The tube was carefully immersed in a mixture of ice and water and returned to a laboratory at 25 °C. Approximately 1.5 mL of the aqueous phase was withdrawn using a 5-mL glass syringe with a 6 by 20 in. gauge needle. This solution was transferred to a 20-mL test tube. The interface was then withdrawn with the same syringe and needle and saved. When most of the aqueous phase was withdrawn, the meniscus inverted leaving a ring of aqueous phase around the outside, as much of which as possible was removed. With a clean 5-mL syringe and needle, an aliquot of the organic phase was withdrawn as follows. The needle was inserted through the center of the organic meniscus while air was being slowly expelled. The needle was inserted until it nearly touched the bottom of the tube, and 3.3 mL of the organic phase was pulled into the syringe. The needle was detached from the syringe, and the organic solution was injected into a 100-mL round-bottomed flask.

To the 1.5 mL of the aqueous phase was added 5 mL of  $\text{CH}_2\text{Cl}_2$ . The tube was stoppered with a rubber septum, carefully shaken, and centrifuged (~1 min). The bulk of the aqueous phase was removed with a glass pipet and lyophilized (~12 h).

The organic phase was evaporated under reduced pressure, and the clear, colorless oil was dissolved in 25 mL of  $\text{CH}_2\text{Cl}_2$  and transferred to a 125-mL separatory funnel. The resulting homogeneous solution was extracted with three 10-mL portions of 0.1 N aqueous HCl. The combined aqueous extracts were washed with 10 mL of  $\text{CH}_2\text{Cl}_2$  and lyophilized in a tared flask (12 h) to give 90.7 mg of a white powder.

The white powder from the original aqueous phase was quantitatively transferred into a 50-mL pear-shaped flask with 12 mL of anhydrous MeOH. To the resulting colorless, homogeneous solution was added 13 mL of a 1.9 M methanolic HCl solution to produce a final HCl concentration of ~1 M. This solution was heated at reflux for 3.5 h and cooled, and the solvent and excess HCl were removed by rotatory evaporation at ~1 mm and <40 °C. After 30 min on the rotavap, the residue was dissolved in 10 mL of water, and the resulting colorless, homogeneous solution was filtered through a piece of glass wool into a 125-mL separatory funnel. The reaction flask and filter were washed twice with additional 5-mL portions of water, the combined aqueous solutions were neutralized to pH 9–10 with 3% aqueous  $\text{NH}_4\text{OH}$ , and the neutralized solution was extracted with five 10-mL portions of  $\text{CH}_2\text{Cl}_2$ , care being taken to completely eliminate the aqueous from the organic phases, which were combined in a 100-mL tared round-bottomed flask. The solvent was rotatory evaporated at <40 °C and reduced pressure and film dried at 0.1 mm for 30 min to give 168.6 mg of  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{CH}_3)\text{NH}_2$  as a clear, colorless oil. This oil was transferred quantitatively into a 10-mL volumetric flask with three 3-mL portions of pure  $\text{CH}_2\text{Cl}_2$ . The solution was brought to the mark with  $\text{CH}_2\text{Cl}_2$  and shaken, and an aliquot (c 1.686) transferred to a 1-dm thermostated polarimeter cell. The observed and specific rotations, the specific rotations of optically pure ester, and the percent enantiomeric excess (ee) and CSF values calculated for three wavelengths of the guest from the original aqueous phase are listed. The average CFS value is 1.51.

$\lambda$ , nm	$\alpha_{\text{obsd}}$	$[\alpha]^{25}$	$[\alpha]_{\text{max}}^{25}$	% ee	CSF
518	-0.548°	-32.5°	-161°	20.2	1.51
546	-0.632°	-37.5°	-185°	20.3	1.51
436	-1.154°	-68.4°	-340°	20.1	1.50

The white powder obtained from the original organic phase was esterified in exactly the same manner to give 58.6 mg (98%) of methyl ester as a colorless oil. This oil was transferred quantitatively into a 5-mL volumetric flask to give c 1.172 in  $\text{CH}_2\text{Cl}_2$ , whose rotations and calculated CRF\* values are listed. These provided an average CRF value of 8.57. Since  $\text{EDC} = \text{CRF} \cdot \text{CSF}$ , the EDC for the run was 12.9.

$\lambda$ , nm	$\alpha_{\text{obsd}}$	$[\alpha]^{25}$	% ee	CRF*
578	1.495°	127.6°	79.3	8.66
546	1.721°	146.8°	79.4	8.71
436	3.133°	267.3°	78.6	8.33

**Control Experiments.** When submitted to the above esterification procedure, 52.3 mg of 98% optically pure D- $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{H})$ -

$\text{NH}_3\text{ClO}_4$  gave 33.0 mg (96%) of 98% optically pure  $\text{D-C}_6\text{H}_5\text{CH}(\text{CO}_2\text{CH}_3)\text{NH}_2$ . When 2.4 M methanolic HCl solution was used, a 95% recovery of 96% optically pure ester was recovered. When 0.1 M methanolic HCl was employed, only a 27% recovery of ester was realized.

An extraction was carried out as in run 10 except that host was absent and the organic phase was 0.45 mole fraction in  $\text{CD}_3\text{CN}$ . The initially used 98% optically pure  $\text{D-C}_6\text{H}_5\text{CH}(\text{CO}_2\text{H})\text{NH}_3\text{ClO}_4$  was converted to its ester as in run 10 to give  $\text{D-C}_6\text{H}_5\text{CH}(\text{CO}_2\text{CH}_3)\text{NH}_2$  of 98% optically pure material. Esterification of 100 mg of 70% optically pure  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{H})\text{NH}_3\text{ClO}_4$  was carried out as in run 10 to give 62.0 mg (95%) of  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{CH}_3)\text{NH}_2$  of 68% optical purity. When further dried at 0.1 mm at 25 °C for 2, 3, and 12 h, the material volatilized to 59.5, 57.3, and 42.4 mg, respectively. The material finally obtained was 64% optically pure. This experiment suggests that optically active ester is slightly more volatile than racemic, and that the drying period should be minimized.

**Procedure B for Determination of Enantiomer Distribution Constants (EDC).** The procedure is exemplified by run 8 of Table I. The extraction involved 731.0 mg (0.987 mmol) of  $(S,S)$ - $(\text{CH}_3)_2\text{D}(\text{OEOEO})_2\text{D}$  of maximum rotation dissolved in 5.0 mL of 0.45 mole fraction  $\text{CD}_3\text{CN}$  in  $\text{CDCl}_3$  (0.2 M solution) and 753.5 mg of racemic  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{H})\text{NH}_3\text{ClO}_4$  dissolved in 3.0 mL of  $\text{D}_2\text{O}$ , 2.0 M in  $\text{LiClO}_4$ . The solutions were shaken at 0 °C and the layers separated as in procedure A. The organic layer aliquot (3.3 mL) was evaporated, and the residue was treated as in procedure A to separate the amino acid perchlorate from host. The final white solid from the lyophilized aqueous extract was dried at 40 °C for 1 h at 0.1 mm to give 135.5 mg of  $\text{C}_6\text{H}_5\text{CH}(\text{CO}_2\text{H})\text{NH}_3\text{ClO}_4$  (equivalent of 81.4 mg of free amino acid) which was transferred in its entirety into a 10.0-mL volumetric flask with 5 N aqueous HCl ( $c$  0.81) which gave the tabulated rotations and CRF\* values and an average CRF\* value of 9.3. The procedure for the aqueous layer was identical with procedure A and gave an average CSF value of 1.51 to provide an EDC of 13.9.

$\lambda$ , nm	$\alpha_{\text{obsd}}$	$[\alpha]^{25}$	$[\alpha]_{\text{max}}^{25}$	% ee	CRF*
589	1.100°	135°	168°	80.5	9.3
578	1.143°	140°	175°	80.1	9.1
546	1.317°	162°	201°	80.4	9.2
436	2.372°	291°	362°	80.5	9.3

When the material from the organic layer was recovered and esterified as in procedure A, the average CRF\* was 6.84, which gave an EDC of 10.3 (run 7 of Table I). Whenever compared, procedure B always provided a slightly higher EDC value.

## References and Notes

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## Catalysis of the Reversible Elimination Reactions of Substituted $N$ -( $\beta$ -Phenylethyl)quinuclidinium Ions in Aqueous Solution<sup>1</sup>

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**Abstract:** The rate constants for elimination reactions of substituted  $N$ -( $\beta$ - $p$ -nitrophenylethyl)quinuclidinium ions induced by hydroxide ion in water at 25 °C show only a small sensitivity to the  $\text{p}K_a$  of the leaving quinuclidine, with  $\beta_{\text{lg}} = -0.18$ . The primary isotope effect is  $k_{\text{H}}/k_{\text{D}} = 8.5$  and the secondary solvent isotope effect is  $k_{\text{OD}}/k_{\text{OH}} = 1.55$  for the quinuclidine derivative. The rates of these elimination reactions are comparable to or faster than that of 2- $p$ -nitrophenylethyl bromide. The reaction is readily reversible in quinuclidine buffers and the rate constants of the addition reaction to  $p$ -nitrostyrene show a large dependence on the  $\text{p}K_a$  of substituted quinuclidines with  $\beta_{\text{nuc}} = 0.69$ ; the equilibrium constants in the elimination direction follow  $\beta_{\text{eq}} = -0.89$ . The addition reaction shows general acid catalysis by protonated quinuclidines and the elimination reaction shows general base catalysis, with a Brønsted coefficient of  $\beta = 0.68$  for elimination from the diazabicyclooctane derivative. Elimination reactions from the corresponding phenyl compounds are  $\sim 10^3$  slower and show a more negative value of  $\beta_{\text{lg}} = -0.35$  in water at 40 °C; in  $\text{EtONa}/\text{EtOH}$  the value of  $\beta_{\text{lg}}$  is  $-0.28$ . The change in  $\beta_{\text{lg}}$  for the phenyl compounds corresponds to a negative structure-reactivity coefficient  $p_{\text{yy}'} = \partial\beta_{\text{lg}}/\partial\sigma = \partial\rho/\partial\text{p}K_{\text{lg}}$ , consistent with the expected E2 mechanism for the phenyl compounds. However, it is uncertain whether the  $p$ -nitrophenyl compounds react by an E2 or an irreversible E1cB mechanism.

We report here a study of the effects of changing structure of the leaving group and the base catalyst for elimination reactions of substituted  $\beta$ -phenylethylammonium salts in aqueous solution. There is evidence that the mechanisms of a number of carbonyl and imine-forming elimination reactions

are determined by the lifetimes of intermediates along the reaction coordinate and it would be of interest to know the extent to which this holds also for olefin-forming eliminations.<sup>2-5</sup> It has been shown that a concerted mechanism is enforced by the negligible lifetime of the carbanion "intermediate" in the decomposition of cyclopropanols through a carbonyl-forming elimination reaction<sup>6</sup> and it is likely that a

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