Host–Guest Complexation. 21. Catalysis and Chiral Recognition through Designed Complexation of Transition States in Transacylations of Amino Ester Salts[1,2]

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Abstract: The results are reported of a study of catalysis and chiral recognition by designed complexation of transition states in transacylations of amino ester salts. Four chiral hosts were prepared, (*S*)- and (*R*)-$(HSM)_2D(OEOEO)_2E$ (**1**), (*S*)-$(HSM)_2D(OEOEOCH_3)_2$ (**2**), (*R*)(*S*)-$(HSPhOM)_2D(OEOEO)_2E$ (**5**), and (*R*)(*S*)-$(HSPhOM)_2D(OEOEOCH_3)_2$ (**6**), in which M is CH_2, E is CH_2CH_2, and D is 1,1′-dinaphthyl substituted in its 2,2′ positions by O's and in its 3,3′ positions by M's, and Ph is ortho-substituted phenyl. The pseudo-first-order kinetics were studied for acylation of large excesses of these hosts by the *p*-nitrobenzoate ester salts of glycine, L-alanine, L-leucine, L-valine, L-proline, and L- and D-phenylalanine. Solvents buffered to pH (referred to water) of 4.3 to 7.0 ranged from 40% H_2O–CH_3CN (v) to 20% EtOH–CH_2Cl_2 to 20% MeOH–$CHCl_3$ to 0.2% H_2O–3% CH_3CN–$CHCl_3$ to 0.04% EtOH–3% CH_3CN–$CHCl_3$. The rates of appearance of *p*-nitrophenol were followed by UV spectroscopy at 25 °C. Evidence was obtained that the active nucleophile was RS^-. Cycles such as **1** and **5** were strong complexers of monoalkylammonium salts, and noncycles such as **2** and **6** were not. Therefore, $k_{cycle}/k_{noncycle}$ values were used to determine the effect of highly ordered complexation on reaction rates in 20% EtOH–CH_2Cl_2. Since proline is a secondary amine, its ester salt did not give highly ordered complexes, and as a result **1** and **2** gave $k_{cycle}/k_{noncycle} = 0.8$. The ester salt of glycine and the L-ester salts of alanine, valine, phenylalanine, and leucine gave $k_{cycle}/k_{noncycle}$ values derived from (*S*)-**1** and (*S*)-**2** of >130, ≳130, 160, 490, and >1170, respectively. The ester salt of glycine gave a $k_{cycle}/k_{noncycle}$ value of >230 with (*R*)(*S*)-**5** and (*R*)(*S*)-**6**. The rate enhancements are attributed to transition-state stabilization by complexation. In 20% EtOH in $CHCl_3$, *k* for L-phenylalanine ester salt reacting with (*S*)-**1** was 560 times *k* that was observed for the same reaction run in the presence of K^+ ion at concentrations $[K^+]/[RNH_3^+] \sim 120$. Thus K^+ acted as a competitive and dominant binder of **1**, and eliminated the acceleration caused by structured complexation. The effect of solvent on $k_{cycle}/k_{noncycle}$ values was determined for the reaction of L-phenylalanine ester salt with (*S*)-$(HSM)_2D(OEOEO)_2E$ and (*S*)-$(HSM)_2D(OEOEOCH_3)_2$. These values decreased as the solvent became more hydroxylic as follows: 1600, 0.04% EtOH–3% CH_3CN–$CHCl_3$; 960, 20% MeOH–$CHCl_3$; 490, 20% EtOH–$CHCl_3$; 8.2, 40% H_2O–CH_3CN (v). The hydroxylic solvents appear to be weak competitive inhibitors of complexation, and therefore are rate inhibiting. Comparison in 20% EtOH–CH_2Cl_2 of the *k*'s for reaction of (*R*)-$(HSM)_2D(OEOEO)_2E$ with L-$RCH(NH_3^+)CO_2Ar$ normalized to ester salt with R = $(CH_3)_2CH$ gave the following rate factors for the various R groups: CH_3, 290; $(CH_3)_2CHCH_2$, 46; $C_6H_5CH_2$, 17; $(CH_3)_2CH$, 1. Thus the reaction rates decreased with increasing steric requirements of the R groups at their points of attachment to the ester salts, and the thiol host showed high structural recognition in reacting with the various guests. In 20% EtOH–CH_2Cl_2, the *k* values for the reactions of (*S*)- and (*R*)-$(HSCH_2)_2D(OEOEO)_2E$ with L-$RCH(NH_3^+)CO_2Ar$ were determined. Values of $(k)_{S\cdot L}/(k)_{R\cdot L}$ (rate constants for formation of diastereomeric thiol ester products) correlated with the nature of the R groups of the amino ester salts as follows: CH_3, 1; $(CH_3)_2CHCH_2$, 6.4; $C_6H_5CH_2$, 8.2; $(CH_3)_2CH$, 9.2. Both the direction of the chiral bias and the relative values of these chiral recognition factors for complexation in the rate-limiting transition states correlate with expectations based on Corey–Pauling–Koltun molecular models of the diastereomeric ortho intermediates for the transacylation. Similarities and differences are noted between the transacylation reactions of this study and those catalyzed by enzyme systems.

An exciting challenge to organic chemists is the synthesis and study of organic catalysts of lowest possible molecular weight that possess some of the attributes of enzyme systems. The properties of enzymes the most worth copying in synthetic systems are as follows. (1) Enzymes induce fast reaction rates under mild reaction conditions. (2) Enzymes show high structural and chiral recognition in the substrates whose reactions they catalyze. (3) Each enzyme molecule causes the reactions of enormous numbers of substrate molecules per unit time. Those properties the least worth mimicking (unless the object is to understand enzyme mechanism) are their large molecular weights, vast numbers of chiral centers, and their limited solubilities in solvents other than water. They are also unstable to handling, to many reaction conditions, and to several inhibitors.

The information available on how and why the proteases catalyze transacylations is extensive enough to allow synthetic systems to be designed that will incorporate and organize those functional groups responsible for binding and catalysis. Ideally, a synthetic transacylating host should contain a binding site that exhibits the following features: (1) The binding site should be designed so that the rates of host–guest complexation–decomplexation should be very fast. (2) The binding site should locate the acyl group of the guest in a position favorable for reaction with a nucleophile attached to the host which is both a good entering group for an acyl carbonyl and a good leaving group for an acylated complex intermediate. Thus the complexation process should collect and orient the reactants, and thereby turn remote groups into neighboring groups. (3) The binding site should orient the complexed guest in such a way that steric and chiral barriers of host and guest are complementary. (4) The binding sites of the host should be arranged so that convergent proton-transfer catalysts attached to the host are able to contact with minimal conformational reorganization the heteroatoms of the acyl groups of the complexed starting guest, the acylated complex and the ortho intermediates for the acylation and deacylation processes. These proton-transfer catalysts should also hydrogen bond and orient the final solvent nucleophile. (5) The binding site and all other parts of the host should be as free as possible from equilibria that provide nonproductive conformations for binding and reaction. Hopefully, introduction of these structural features into a host would allow the free energies of the transition states of reactions of selected guests to be lowered by complexation and their reaction rates to be potentiated.

Other investigators (particularly Cramer, Bender, Kaiser, Breslow, Tabushi, and van Hooidonk) have used the lipophilic torus of the naturally occurring cyclodextrins as binding sites for organic guest compounds. The hydroxyl groups attached to the rim provided nucleophiles for reactions of the bound

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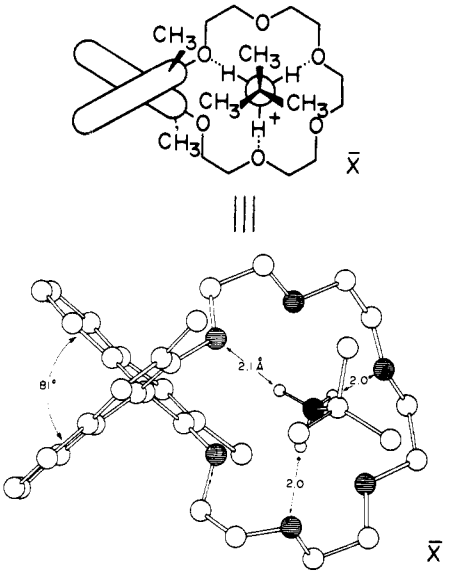
guest.[4] Proton transfer catalysts have also been attached to the hydroxyl groups.[5] Some stereospecificity was observed in acylations[6] of the cyclodextrin systems. A completely synthetic complexing carbomacrocyclic hydroxamic acid was used as host and nucleophile to give dramatic rate enhancements in a transacylation.[7]

Others have communicated that macrocyclic ethers with bound dihydropyridinium groups reduced complexed substrates.[8,9] Since our 1976 communications on the present work appeared, others have also found (communications) that macrocyclic polyethers attached to thiol groups catalyze by complexation the transacylation of the thiol groups by *p*-nitrobenzoate esters of primary amino acid salts.[10,11] One communication reported an example of very high chiral recognition in this acylation.[11]

In our studies of ground state organic-to-organic binding, complex I between $(CH_3)_2D(OEOEO)_2E$ and *t*-$BuNH_3$ picrate was found to form in $CHCl_3$ at 25 °C with $\Delta G° = -6.4$ kcal/mol, whereas the corresponding complex with NH_4^+ was −8.9 kcal/mol.[12] Molecular model (CPK) examination of complex I suggested that it should possess the structure formulated. This hypothesis was strengthened by the formation of I with X = ClO_4, whose analysis showed it to be 1:1. Its X-ray structure[13] confirmed the structural assignment arrived at by examination of CPK molecular models. In the X-ray structure, one methyl group of the host lies in between (and contacts) two of the methyl groups of the $(CH_3)_3CNH_3^+$ guest. Similarly, molecular model examination of a complex between (*S*)-**1** and L-RC*H(NH_3^+)CO_2Ar places the SH group of the host between the H and CO_2Ar groups attached to C* of the guest. The $ArCH_2SH$ group of the host is a good nucleophile, as is that of the protease, papain. The macrocyclic ether of the host is a strong binding and orienting site for NH_3^+, as is the binding site of the protease, trypsin. Furthermore, a molecular model of the complex between (*S*)-**1** and L-RCH(NH_3^+)CO_2Ar is visibly more complementary from a steric point of view than that between (*S*)-**1** and D guest. Finally, the fact that (*S*)-**1** possesses a C_2 axis means that the same complex is formed irrespective of which face of the macroring is complexed.

These facts taken in sum led us to make the following predictions. (1) The rate-limiting transition state for acylation of *S* host by L guests would be stabilized by complexation, and hence complexation would catalyze the transacylation. (2) The transacylation rates would depend on the steric requirements of the side chains of the amino ester salts; the faster the rates, the lower the steric requirements. (3) The transacylation rates would be more catalyzed when *S*-L or *R*-D complexes were formed than when *S*-D or *R*-L complexes were involved. (4) The chiral recognition in the catalysis would be greater, the greater the steric requirements of the R group close to its point of attachment to the chiral center of the guest.

Earlier work demonstrated that $\Delta G°$ of formation of the complex between cyclic host **3** and *t*-$BuNH_3^+$ picrate in $CDCl_3$ at 25 °C was 3 kcal/mol more negative than $\Delta G°$ of formation for the complex between noncyclic host **4** and the same guest.[12] This large difference suggested that comparisons between the rates of acylation of (*S*)-**1** and (*S*)-**2** by $RCH(NH_3^+)CO_2Ar$ under identical conditions should indicate the effect that highly ordered complexation has on the stability of the rate-controlling transition state for acylation. The study was extended to analogues **5** and **6**, in which the nucleophiles were thiophenols, and to diol **7**, which is identical with **1** except that two OH groups have replaced the two SH groups. The kinetics of acylation of 2-hydroxyethanethiol (**10**) also was investigated for mechanistic and comparison purposes. This simple thiol was chosen over others because of its high solubility and its low volatility in the solvents selected for study.



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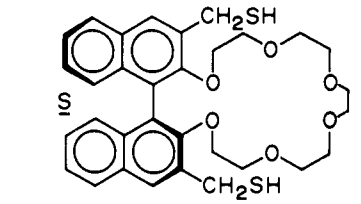
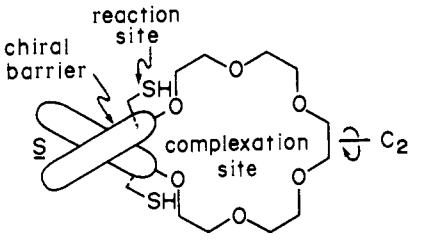
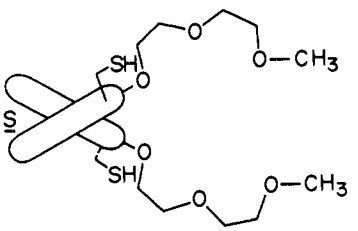




(S)-1

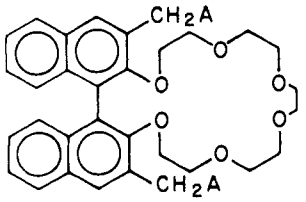


(S)-2

In the convenient line formulas for **1–9**, M stands for CH_2 substituted in the 3,3′ positions of a 1,1′-dinaphthyl (D) unit substituted in its 2,2′ positions with oxygens attached through CH_2CH_2 (E) units to other oxygens, and Ph stands for an ortho-substituted phenyl unit.

Results

Syntheses. Hosts $(HSM)_2D(OEOEO)_2E$ (**1**) and $(HSM)_2D(OEOEOCH_3)_2$ (**2**), both as racemates and enantiomers, were prepared by the respective treatment of $(ClM)_2D(OEOEO)_2E$ and $(ClM)_2D(OEOEOCH_3)_2$ with thiourea and hydrolysis of the corresponding thiouronium salts formed (29–36%). Cycle $(ClM)_2D(OEOEO)_2E$ of known



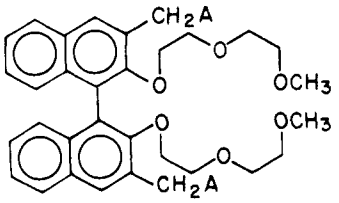
1, A = SH, $(HSM)_2O(OEOEO)_2E$

3, A = H, $(CH_3)_2O(OEOEO)_2E$

5, A = o-OC_6H_4SH, $(HSPhOM)_2O(OEOEO)_2E$

7, A = OH, $(HOM)_2D(OEOEO)_2E$

8, A = S-THP



2, A = SH, $(HSM)_2O(OEOEOCH_3)_2$

4, A = H, $(CH_3)_2O(OEOEOCH_3)_2$

6, A = o-OC_6H_4SH, $(HSPhOM)_2O(OEOEOCH_3)_2$

9, A = S-THP

10, $HOCH_2CH_2SH$

11, $E(OEOEO)_2E$

absolute configuration and maximum rotation has already been described,[14] and the open-chain analogue $(ClM)_2D(OEOEOCH_3)_2$ was synthesized by conventional reactions (Experimental Section). These same racemic dichlorides, when treated with the *S*-tetrahydropyranyl ether of thiocatechol sodium salt, gave the corresponding thioacetals **8** (99%) and **9** (51%). Hydrolysis of **8** with $HCl·H_2O$ gave $(HSPhOM)_2D(OEOEO)_2E$ (**5**, 30%) and hydrolysis of **9** produced $(HSPhOM)_2D(OEOEOCH_3)_2$ (**6**, 88%). Diol $(HOM)_2D(OEOEO)_2E$ (**7**) was already available.[14]

Dithiols **1**, **2**, **5**, and **6** were unstable to oxidative polymerization, but differed greatly from one another. Cycle $(HSPhOM)_2D(OEOEO)_2E$ (**5**) was by far the worst, and had to be prepared, purified, and handled in oxygen- and transition-metal-free media. Its open-chain analogue, $(HSPhOM)_2D(OEOEOCH_3)_2$ (**6**), was much less sensitive. Since cycle **5** is undoubtedly a better complexing agent for metal ions than **6**, **5** probably scavenges transition metals which catalyze the oxidative polymerization, $n(HS\text{-}host\text{-}SH) \rightarrow HS(hostS)_{n-1}$ ShostSH. Although more stable than **5** and **6**, **1** and **2** also (particularly the former) had to be handled and stored in an inert atmosphere at −10 °C.

Kinetics. Pseudo-first-order rates for liberation of *p*-nitrophenol from *p*-nitrophenyl esters (guests) were followed spectrophotometrically at 25 °C in solvents that ranged in polarity from 40% H_2O-CH_3CN to 0.04% EtOH-3% CH_3CN-$CHCl_3$ (v). The solutions contained different buffers which, when dissolved in water, gave pHs that ranged from 4.3 to 7.0. With buffers of less than pH 7, *p*-nitrophenol formation was followed at 345 nm, and with buffers of greater than pH 7 (see below), *p*-nitrophenoxide formation was followed at 425 nm. The first-order rates of reaction of the esters with buffer were first measured, and then the pseudo-first-order rate constants for the ester guests reacting in the presence of large excesses of host (usually a factor of 50 or more) were determined. Multiple determinations of rates (usually three or more) composed of at least 15 points each covering 4–5 half-lives were made for calculating the rate constants. Stable end points were observed. The first-order rate constants were determined graphically. Data from arbitrarily selected runs were subjected to least-squares analysis to give correlation coefficients of 0.999 or better. Rate constants calculated by the two methods agreed within 2% or better. Rate constants for reactions of the esters with the medium in the absence of host were subtracted from the average of those obtained in the presence of host. The resulting rate constants (k) are listed in Table I, along with the solvents, buffers, hosts, and guests. The percent of each solvent component and the buffer compositions and concentrations are listed in the footnotes of Table I.

With 2-hydroxyethanethiol (**10**) at 5.0×10^{-2} M and phenylalanine *p*-nitrophenyl ester at 1×10^{-4} M in 40% H_2O-CH_3CN (v) and an ionic strength of 0.5 (NaCl), the values of k were determined at pH 4.8 as NaOAc-HOAc buffer (equimolar amounts) concentration was varied. The values of $k \times 10^2$ (s^{-1}) obtained were as follows: at 0.075 M buffer, 1.0; at 0.15 M, 1.2; at 0.30 M, 1.1; at 0.46 M, 1.0. Thus k values for this buffer concentration range were constant. This fact indicates that the reaction is not subject to general acid or base catalysis. At the same temperature, in the same medium, at the same concentrations of thiol and ester, and the same ionic strength, the dependence of k on OH^- concentration was determined at a constant total buffer concentration of 0.20 M. The values of $k \times 10^2$ (s^{-1}) obtained were as follows: 0.24 at 0.3×10^{-9} M OH^-; 0.55 at 0.7×10^{-9}; 1.13 at 1.3×10^{-9}; 2.34 at 2.5×10^{-9}. A plot of these parameters gives a good straight line with a slope of 0.97, which passes through the origin. Thus, under these conditions, the thiolysis rate is first order in hydroxide ion concentration, or $k = k_2(RS^-)$ where k_2 is a second-order rate constant. Since 2-hydroxyethanethiol has a pK_a[15] of about 10, then $(RS^-) \sim 10^{-10}(RSH)/(H^+)$. From the experimental conditions, values of (RSH) and (H^+) were 5×10^{-2} and 10^{-5} M, respectively. Therefore, $(RS^-) = 5 \times 10^{-7}$ M. Since the measured value of k was about 10^{-2} s^{-1}, $k_2 = 2 \times 10^4$ M^{-1} s^{-1}.

This value for the bimolecular rate constant is reasonable. It is a factor of 10^6 below the normal diffusion-controlled rate constant so that the extremely low (RS^-) value does not require an abnormally high k_2 value to account for that of k. Furthermore, this k_2 value is close to that of 10^5 M^{-1} s^{-1} observed for the reaction between pivaldehyde and 2-hydroxyethanethiol.[16] This reaction was believed to proceed by the unassisted attack of thiolate anion on the carbonyl group.

Similar experiments were carried out with glycine *p*-nitrophenyl ester in 20% EtOH-CH_2Cl_2 (v), 0.5 M in $(CH_3)_4NCl$ at the same temperature and concentrations of reactants buffered with varying concentrations of a 1:1 molar ratio of AcOH-$(CH_3)_4NOAc$. The values of $k \times 10^2$ s^{-1} obtained with different total buffer concentrations (M) were as follows: 2.05 at 0.20; 2.58 at 0.4; 2.97 at 0.6; 3.25 at 0.8; 3.21 at 1.0. The change of k by a factor of 1.5 as total buffer concentration was changed fivefold is nonlinear, and is probably a bulk medium effect rather than a specific participation of buffer in the rate-determining step. In contrast, a strong linear dependence of k on the buffer ratio $[(CH_3)_4NOAc]/[AcOH]$ was observed for the same reaction under the same conditions. The values of $k \times 10^2$ s^{-1} obtained with different values of this buffer ratio were as follows: 0.91 at 0.4; 1.17 at 0.50; 1.54 at 0.67; 2.58 at 1.0; 4.35 at 1.5. In the absence of a meaningful method of measuring the pH in this solvent system, this buffer ratio is presumed to describe the relative acidity-basicity of the medium. Thus it seems likely that thiolate anion was the attacking nucleophile in 20% EtOH-CH_2Cl_2 (v), as well as in 40% H_2O-CH_3CN (v).

It seems very likely that thiol ester formation was the reaction whose rate was followed in the above experiments. The question arises as to the rate of solvolysis of thiol ester once formed. This reaction was followed polarimetrically at λ 546 nm in a 1-dm tube at 25.0 °C. The low observed rotations of

Table I. Rate Constants for Liberation of *p*-Nitrophenol from 10^{-4} M Solutions of $RCH(NH_3Br)CO_2C_6H_4NO_2$-*p* (Guest) in Presence of 5.0×10^{-3} M Hosts at 25 °C

run no.	solvent[a]	buffer[b]	host no.	guest, $RCH(NH_3Br)CO_2Ar$ R	guest, $RCH(NH_3Br)CO_2Ar$ confign	10^3k[c] s^{-1}
1	20% EtOH-CH_2Cl_2	A	none	H		2.6
2	20% EtOH-CH_2Cl_2	A	**11**	H		8.1
3	20% EtOH-CH_2Cl_2	A	(*R*)(*S*)-**7**	H		7.3
4	20% EtOH-CH_2Cl_2	A	(*S*)-**1**	prolyl	L	16
5	20% EtOH-CH_2Cl_2	A	(*S*)-**2**	prolyl	L	21
6	20% EtOH-CH_2Cl_2	A	(*S*)-**1**	H		>700
7	20% EtOH-CH_2Cl_2	A	(*S*)-**2**	H		5.4
8	20% EtOH-CH_2Cl_2	A	(*S*)-**1**	CH_3	L	≲700
9	20% EtOH-CH_2Cl_2	A	(*S*)-**2**	CH_3	L	5.4
10	20% EtOH-CH_2Cl_2	A	(*S*)-**1**	$(CH_3)_2CH$	L	13
11	20% EtOH-CH_2Cl_2	A	(*S*)-**2**	$(CH_3)_2CH$	L	0.08
12	20% EtOH-CH_2Cl_2	A	(*S*)-**1**	$C_6H_5CH_2$	L	200
13	20% EtOH-CH_2Cl_2	A	(*S*)-**2**	$C_6H_5CH_2$	L	0.41
14	20% EtOH-CH_2Cl_2	A	(*S*)-**1**	$(CH_3)_2CHCH_2$	L	≲700
15	20% EtOH-CH_2Cl_2	A	(*S*)-**2**	$(CH_3)_2CHCH_2$	L	0.6
16	20% EtOH-CH_2Cl_2	A	(*S*)-**1**	$C_6H_5CH_2$	D	25
17	20% EtOH-CH_2Cl_2	A	(*S*)-**2**	$C_6H_5CH_2$	D	0.36
18[d]	20% EtOH-CH_2Cl_2	A	**10**	$C_6H_5CH_2$	L	11
19[d]	20% EtOH-CH_2Cl_2	A	**10**	$C_6H_5CH_2$	D	11
20[e]	20% EtOH-CH_2Cl_2	A	(*R*)(*S*)-**5**	H		>970
21[e]	20% EtOH-CH_2Cl_2	A	(*R*)(*S*)-**6**	H		4.2
22[e]	20% EtOH-CH_2Cl_2	A	(*R*)(*S*)-**5**	CH_3	L	128
23	20% EtOH-CH_2Cl_2	A	(*R*)(*S*)-**5**	CH_3	D	129
24[f]	20% EtOH-$CHCl_3$	A	none	$C_6H_5CH_2$	L	0.013
25[f]	20% EtOH-$CHCl_3$	A	(*S*)-**1**	$C_6H_5CH_2$	L	130
26[f,g]	20% EtOH-$CHCl_3$	A	none	$C_6H_5CH_2$	L	0.016
27[f,g]	20% EtOH-$CHCl_3$	A	(*S*)-**1**	$C_6H_5CH_2$	L	0.23
28	20% EtOH-CH_2Cl_2	B	(*S*)-**1**	CH_3	L	700
29	20% EtOH-CH_2Cl_2	B	(*R*)-**1**	CH_3	L	700
30	20% EtOH-CH_2Cl_2	B	(*S*)-**1**	$(CH_3)_2CH$	L	22
31	20% EtOH-CH_2Cl_2	B	(*R*)-**1**	$(CH_3)_2CH$	L	2.4
32	20% EtOH-CH_2Cl_2	B	(*S*)-**1**	$(CH_3)_2CHCH_2$	L	700
33	20% EtOH-CH_2Cl_2	B	(*R*)-**1**	$(CH_3)_2CHCH_2$	L	110
34	20% EtOH-CH_2Cl_2	B	(*S*)-**1**	$C_6H_5CH_2$	L	340
35	20% EtOH-CH_2Cl_2	B	(*S*)-**1**	$C_6H_5CH_2$	L	340
36	20% EtOH-CH_2Cl_2	B	(*R*)-**1**	$C_6H_5CH_2$	L	41
37	20% EtOH-CH_2Cl_2	B	(*S*)-**1**	$C_6H_5CH_2$	D	42
38	20% EtOH-CH_2Cl_2	B	(*R*)-**1**	$C_6H_5CH_2$	D	340
39	20% MeOH-$CHCl_3$	C	none	H		0.03
40	20% MeOH-$CHCl_3$	C	(*R*)(*S*)-**1**	H		>970
41	20% MeOH-$CHCl_3$	C	(*R*)(*S*)-**2**	H		0.36
42	20% MeOH-$CHCl_3$	C	(*S*)-**1**	$C_6H_5CH_2$	L	110
43	20% MeOH-$CHCl_3$	C	(*S*)-**2**	$C_6H_5CH_2$	L	0.11
44	20% MeOH-$CHCl_3$	C	(*S*)-**1**	$C_6H_5CH_2$	D	16
45	40% H_2O-CH_3CN	D	(*S*)-**1**	H		110
46	40% H_2O-CH_3CN	D	(*S*)-**1**	H		110
47	40% H_2O-CH_3CN	D	(*S*)-**2**	H		5.4
48	40% H_2O-CH_3CN	D	(*S*)-**1**	$C_6H_5CH_2$	L	18
49	40% H_2O-CH_3CN	D	(*S*)-**2**	$C_6H_5CH_2$	L	2.2
50[h]	0.2% H_2O-3% CH_3CN-$CHCl_3$	E	none	$C_6H_5CH_2$	L	0.013
51[h]	0.2% H_2O-3% CH_3CN-$CHCl_3$	E	(*R*)-**1**	$C_6H_5CH_2$	D	263
52[h]	0.2% H_2O-3% CH_3CN-$CHCl_3$	E	(*R*)-**1**	$C_6H_5CH_2$	L	35.5
53[i]	0.04% EtOH-3% CH_3CN-$CHCl_3$	F	none	$C_6H_5CH_2$	L	0.011
54[i]	0.04% EtOH-3% CH_3CN-$CHCl_3$	F	(*R*)-**1**	$C_6H_5CH_2$	D	289
55[i]	0.04% EtOH-3% CH_3CN-$CHCl_3$	F	(*R*)-**1**	$C_6H_5CH_2$	L	36.5
56[i]	0.04% EtOH-3% CH_3CN-$CHCl_3$	F	(*S*)-**2**	$C_6H_5CH_2$	L	0.183
57[i]	0.04% EtOH-3% CH_3CN-$CHCl_3$	F	(*S*)-**2**	$C_6H_5CH_2$	D	0.178

[a] Solvent compositions by volume; last solvent listed brings percent to 100. [b] pHs of buffers refer to what they would be if in H_2O. Compositions of buffers follow: A, 0.2 M AcOH, 0.1 M $(Me)_4NOAc$, pH 4.5; B, 0.3 M AcOH, 0.1 M $(CH_3)_4NOAc$, pH 4.3; C, 0.10 M collidine-HCl, 0.01 M collidine, pH 6.4; D, 0.2 M AcOH, 0.2 M NaOAc, pH 4.8; E, 0.071 M CF_3CO_2H, 0.099 M collidine, 0.4 M $(Bu)_4NClO_4$, "pH" 7.0; F, 0.071 M CF_3CO_2H, 0.099 M collidine, 0.15 M $(Et)_4NClO_4$, pH 7.0. [c] Pseudo-first-order rate constants, corrected for solvent-buffer reaction, made in triplicate runs of at least 14 points each unless otherwise indicated. When host was absent, the *k* observed for the reactions with solvent-buffer are recorded. [d] Host concentration, 5×10^{-2} M. [e] Duplicate runs. [f] Host when present 2.57×10^{-3} M, guest 1.17×10^{-4} M, single runs. [g] Medium 0.0138 M in KOAc. [h] Host when present, 4.46×10^{-3} M, guest 6.71×10^{-5} M, single runs. [i] Host when present, 2.18×10^{-3} M, guest 6.58×10^{-5} M, single runs.

solutions of the amino ester salts and $HSCH_2CH_2OH$ required that optically active host be employed. A solution of 20% EtOH-CH_2Cl_2 (v) was prepared that was 0.01 M in L-phenylalanine *p*-nitrophenyl ester, 0.02 M in (*S*)-$(HSM)_2$-D$(OEOEO)_2$E, 0.20 M in AcOH, and 0.10 M in $(CH_3)_4$-NOAc. After the rapid initial burst of *p*-$NO_2C_6H_4OH$ release,

Table II. Rate Acceleration Factors and Activation Free Energy Differences for Thiolysis of RCO_2Ar by $(HSM)_2D(OEOEO)_2E$ (1) vs. $(HSM)_2D(OEOEOCH_3)_2$ (2), or by $(HSPhOM)_2D(OEOEO)_2E$ (5) vs. $(HSPhOM)_2D(OEOEOCH_3)_2$ (6) in 20% EtOH-$CHCl_2$ at 25 °C

guest, R of RCO_2Ar	host/ side chain	$k_{cycle}/k_{noncycle}$[a]	$-\Delta(\Delta G^{\ddagger})$,[b] kcal/mol	runs compared[c]
$(CH_2)_3\overline{CN}H_2^+$	HSM	0.8	−0.1	4 + 5
$CH_2(NH_3^+)$	HSM	>130	>2.9	6 + 7
$CH_2(NH_3^+)$	*o*-HSPhOM	>230	>3.2	20 + 21
$CH_3CH(NH_3^+)$	HSM	>130	>2.9	8 + 9
$(CH_3)_2CHCH(NH_3^+)$	HSM	160	3.0	10 + 11
$C_6H_5CH_2CH(NH_3^+)$	HSM	490	3.7	12 + 13
$(CH_3)_2CHCH_2CH(NH_3^+)$	HSM	>1170	>4.2	14 + 15

[a] Diastereomeric complexes, L-*S* configurations only. [b] $\Delta(\Delta G^{\ddagger}) = \Delta G^{\ddagger}_{cycle} - \Delta G^{\ddagger}_{noncycle}$. [c] See Table I.

the slow change in optical rotation was followed with 19 points until the rotation ceased to change. The initially observed rotation was 0.475° and the final was 0.305°. The reaction followed good first-order kinetics to a constant end point over an 80-h period to give $k_{cv} = 2.0 \times 10^{-5}\ s^{-1}$. The rotation was taken of a solution prepared identically with the above initial solution except that the ethyl ester of L-phenylalanine was substituted for the *p*-nitrophenyl ester. The rotation observed was within 7% of that produced as an end point in the kinetic run. These results show that an intermediate was produced in the initial fast reaction, which in turn underwent a slow reaction.

Discussion

Mechanistic Model for Reactions Studied. Two consecutive reactions have been kinetically characterized. The first is the thiolysis of *p*-nitrophenyl esters of amino acid salts. The second is the solvolysis of the thiol esters formed initially. When the first (thiolysis) reaction is slow, direct reaction of the aryl esters with solvent becomes competitive. The observed rate constants for the appearance of *p*-nitrophenol were corrected for the direct solvolysis reaction. The resulting thiolysis rate constants, *k*, are listed in the tables.

Equations 1–5 provide a mechanistic model for discussion of the results. Equation 1 formulates the thiolysis reaction with HSR as the nucleophile. Equation 2 involves the equilibrium of thiol with thiolate anion, whose forward and reverse reactions are presumed to be very fast compared to other processes. Equation 3 formulates the thiolysis reaction with ^-SR as nucleophile as a fast reaction. Equation 4 describes the very rapidly established equilibrium between *p*-nitrophenoxide and *p*-nitrophenol. The slow solvolysis of the initially formed thiol ester is written in eq 5.

$$HSR + RCH(NH_3^+)CO_2Ar \xrightarrow{?} RCH(NH_3^+)COSR + HOAr \quad (1)$$

$$HSR + B^- \underset{fast}{\overset{very}{\rightleftharpoons}} \bar{S}R + HB \quad (2)$$

$$^-SR + RCH(NH_3^+)CO_2Ar \xrightarrow{fast} RCH(NH_3^+)COSR + {}^-OAr \quad (3)$$

$$HB + {}^-OAr \underset{fast}{\overset{very}{\rightleftharpoons}} HOAr + {}^-B \quad (4)$$

$$HOR + RCH(NH_3^+)COSR \underset{}{\overset{slow}{\rightleftharpoons}} RCH(NH_3^+)CO_2R + HSR \quad (5)$$

Evidence presented in the Results section indicates that in 40% H_2O-CH_3CN (v) the thiolysis of $^+NH_3CH_2CO_2Ar$ by $HOCH_2CH_2SH$ is best described by eq 3. The rate of the thiolysis reaction was independent of buffer concentration, indicating the absence of any general acid or base catalysis. However, it was first order in OH^- concentration. The dominance of the reaction of eq 3 is also consistent with what was observed for the same reactants in 20% EtOH-CH_2Cl_2 (v), where the thiolysis reaction was first order in the buffer ratio $(OAc^-)/(HOAc)$, but was nearly independent of the total buffer concentration. Other solvent systems and reactants were not examined. Under some of the reaction conditions listed in Table I, it is possible that HSR serves as a competitive nucleophile, as described in eq 1.

Since RS^- at very low concentrations is the most probable nucleophile in the thiolysis reactions studied, the observed rate constants depend greatly on the pK_a values of the thiols examined. Thus comparisons of rate constants for reactions of $HSCH_2CH_2OH$ and host compounds such as $(HSM)_2D(OEOEO)_2E$ or $(HSM)_2D(OEOEOCH_3)_2$ are meaningless.

The solvolysis of the initially formed thiol ester (eq 5) was only studied (polarimetrically) in 20% EtOH-CH_2Cl_2 with (*S*)-$(HSM)_2D(OEOEO)_2E$ and L-$C_6H_5CH_2CH(NH_3^+)CO_2Ar$ as the initial reactants (burst kinetics). The first-order rate constant for this reaction (k_{cv}) was 10^4 lower valued than the pseudo-first-order rate constant (k) for formation of the thiol ester (run 12, Table I). Although this reaction was not studied in the other systems, it seems likely that, particularly in those cases where the thiolysis reactions were very fast, the thiolyses were much faster than the solvolyses of the thiol esters once formed.

Rate Acceleration of Thiolysis Associated with Structured Complexation. Table II lists the ratios of thiolytic rate constants for various $RCH(NH_3^+)CO_2C_6H_4NO_2$-*p* esters reacting with cycle $(HSM)_2D(OEOEO)_2E$ vs. noncycle $(HSM)_2D(OEOEOCH_3)_2$. In $CDCl_3$ at 24 °C, cyclic host $(CH_3)_2D(OEOEO)_2E$ (3) complexed with *t*-$BuNH_3^+$ picrate with a k_a value of ~50 000 M^{-1} (eq 6), whereas noncyclic host $(CH_3)_2D(OEOEOCH_3)_2$ (4) gave a value of ~300 M^{-1}.

$$t\text{-}BuNH_3^+ \cdot picrate^- + H \underset{}{\overset{K_a}{\rightleftharpoons}} t\text{-}BuNH_3^+ \cdot H \cdot picrate^- \quad (6)$$

The cyclic host complexed the salt 3 kcal/mol more strongly than the noncyclic host.[12] Since $(HSM)_2D(OEOEO)_2E$ and $(CH_3)_2D(OEOEO)_2E$ on the one hand and $(HSM)_2D(OEOEOCH_3)_2$ and $(CH_3)_2D(OEOEOCH_3)_2$ on the other are very similarly structured, undoubtedly the two cycles bind the various amino ester salts of this study several kilocalories per mole more strongly than their open-chain counterparts to give highly ordered ground-state complexes of the type represented by complex 1. As expected, this difference in binding of the ground states of cyclic and noncyclic complexes resulted in differential stabilization of the transition-state complexes that involved the cyclic and noncyclic thiols. Thus, relative to

their respective equilibrium ground states, the rate-limiting transition states for thiolyses by the cycles are more stabilized than those of the noncycles. This differential stabilization is reflected in the $k_{cycle}/k_{noncycle}$ and $-\Delta(\Delta G^{\ddagger})$ values of Table II.

The glycine, alanine, valine, and leucine ester salts acylated $(HSM)_2D(OEOEO)_2E$ from $>10^2$ to $>10^3$ faster than $(HSM)_2D(OEOEOCH_3)_2$. Thus the free energies of the rate-limiting transition states relative to their equilibrium ground states are lower for the cyclic complexes than for the noncyclic complexes by $\gtrsim 2.9$ to >4.2 kcal/mol ($-\Delta(\Delta G^{\ddagger})$ values). The lower activation energies associated with the acylation reactions of cycle over those of the noncycle clearly are associated with the more ordered structures of the complexes that involve the cycle. This complexation potentially applies both to the ground state and to the transition state, since $\Delta G^{\ddagger}$ is the difference between the two. Covalent bonds are being made or broken in the rate-controlling transition state for both cycle and noncycle. The partial covalent bonds involved are regarded as a binding and organizing site, and the hydrogen bonds between NH^+'s of the NH_3^+ groups and oxygens of the polyether as others. In the transition states that involve the cycle, the two different types of binding are more complementary than in the transition states that involve the noncycle. In other words, the productive organization provided the transition state of the cyclic system by the tripod arrangement of the three $NH^+\cdots O$ hydrogen bonds is regarded as the main source of the observed rate acceleration. This tripod arrangement (see I) probably does not apply to either the ground or transition states of the noncycle.

The above interpretation is supported by additional facts. (1) The ester salt of proline has only two hydrogen bonds available for complexation. The $k_{cycle}/k_{noncycle}$ value equaled 0.8 for this ester. Thus the rate acceleration of the acylation of cycle over that for the noncycle requires three hydrogen bonds. (2) The rate constants ($k \times 10^3$, s^{-1}, Table I) for liberation of *p*-nitrophenol from glycine ester salt in 20% ethanol-CH_2Cl_2 by reaction with solvent are affected only in minor ways by complexation of cycles not containing the thiol group. The absence of cycle in run 1 produced a value of 2.6; the presence of $E(OEOEO)_2E$ in run 2 gave 8.1; the presence of $(HOM)_2D(OEOEO)_2E$ in run 3 gave 7.3. These values are within a factor of 3 of one another, and are close to the value of 5.4 in run 7 observed for the acylation of noncycle $(HSM)_2D(OEOEOCH_3)_2$. Thus highly ordered complexation of the amino ester salt provides only a trivial rate acceleration for acylation of the medium. Furthermore, the rate constants for acylation of the medium are comparable to that for acylation of the noncyclic thiol, $(HSM)_2D(OEOEOCH_3)_2$. (3) The value of $k_{cycle}/k_{noncycle}$ for glycine ester salt acylating hosts with HSM side chains was >130, whereas the ratio for acylating hosts with *o*-HSPhOM side chains was >230. In CPK molecular models of complexes of both cycles with glycine ester salt, the SH nucleophile can readily locate adjacent to the carbonyl of the ester group. Many more degrees of conformational freedom have to be frozen out to provide analogous arrangements for the two noncyclic thiols. Thus the rate accelerations appear to be associated with complexes held together by a tripod hydrogen bonding arrangement which places the acylating group within reach of the thiol nucleophiles. Acceleration factors of $>10^2$ are observed when the sulfur nucleophile is separated from the naphthalene ring by either CH_2 or $CH_2OC_6H_4$-*o*.

Evidence was presented in the previous section that the actual nucleophile was RS^-, present at very low concentrations in equilibrium with RSH. Molecular models of the complexes held together by a tripod of three hydrogen bonds place the positive charge of the NH_3^+ group closer to the SH groups of the host than the less organized complexes held together by one or two hydrogen bonds. These facts suggest that part or all of the rate increase observed for the cycles compared to the noncycles might be due to a field effect in which the NH_3^+ group more intimately bound to the cyclic hosts produces a higher concentration of S^- (and therefore a faster rate) than the NH_3^+ group more distantly bound to the noncyclic hosts.

Runs 24-27 of Table I were made to examine this possibility. All four runs involved L-phenylalanine ester salt at 1.17×10^{-4} M concentration as the acylating agent and 20% EtOH-$CHCl_3$ (v) as the medium, buffered by 0.2 M AcOH and 0.1 M $(Me)_4NOAc$. Run 24 was made in the absence of thiol, and gave a first-order rate constant for acylation of the medium of 1.3×10^{-5} s^{-1}. Run 25 was made in the presence of 2.57×10^{-3} M (*S*)-$(HSM)_2D(OEOEO)_2E$, and gave a pseudo-first-order rate constant for acylation of thiol of 1.3×10^{-1} s^{-1}. Thus thiolysis by the complexing cycle proceeded a factor of 10^4 faster than ethanolysis. Run 26 was identical with 24, and 27 was identical with 25, except that enough KOAc was added to the media of runs 26 and 27 to provide concentrations of 0.0138 M. The first-order rate constant for ethanolysis in run 26 was 1.6×10^{-5} s^{-1}, whereas the pseudo-first-order rate constant for thiolysis of $(HSM)_2D(OEOEO)_2E$ in run 27 was 2.3×10^{-4} s^{-1}. Thus the presence of K^+ in run 27 inhibited the thiolysis of $(HSM)_2D(OEOEO)_2E$ by a factor of 560 over what was observed in its absence in run 25.

In other studies,[12] $(CH_3)_2D(OEOEO)_2E$ was shown to bind K^+ picrate$^-$ in $CDCl_3$ more strongly than *t*-$BuNH_3^+$ picrate$^-$ by 4 kcal/mol. In run 27, $[K^+]/[RNH_3^+] \sim 120$. These facts indicate that inhibition of the acylation of $(HSM)_2D(OEOEO)_2E$ in run 27 was due to competitive and dominant binding of the cyclic thiol by K^+ ion. Complexation of $(HSM)_2D(OEOEO)_2E$ by K^+ places a positive charge close to the CH_2SH group, thereby potentially increasing the concentration of CH_2S^-. The fact that K^+ was a strong thiolysis inhibitor indicates that the presence of the positive charge close to CH_2SH in the complex between acylating agent and cyclic host was not the main source of the rate enhancements shown by the cyclic over the noncyclic host. This leaves the high organization due to the tripod type of hydrogen bonding as the main cause of the rate enhancements observed for the cyclic thiols.

A comparison of the results of runs 42 and 43 with those of runs 25 and 27 (Table I) is instructive. All four runs involved L-$C_6H_5CH_2CH(NH_3^+)CO_2Ar$ as guest. Runs 42 and 43 conducted in 20% MeOH-$CHCl_3$ with (*S*)-$(HSM)_2D(OEOEO)_2E$ and (*S*)-$(HSM)_2D(OEOEOCH_3)_2$ as hosts gave $k_{cycle}/k_{noncycle} = 960$ and $-\Delta(\Delta G^{\ddagger}) = 4.0$ kcal/mol. Runs 25 and 27 involved 20% EtOH-$CHCl_3$ as solvent and (*S*)-$(HSM)_2D(OEOEO)_2E$ as host, which in run 25 was conducted in the absence of and in run 27 in the presence of K^+. The value of $k_{cycle}/k_{cycle}\cdot K^+$ was equal to 560, which provided a $-\Delta(\Delta G^{\ddagger})$ value of 3.8 kcal/mol. The values of k in runs 25 and 42 involving the same host and guest were 0.13 and 0.11 s^{-1}, respectively. The proximity of these values shows that the effect of the difference between 20% EtOH and 20% MeOH was trivial. Importantly, both the noncyclic and the K^+-bound cyclic compounds depressed the rate constants by about the same factor. This result suggests that neither K^+-bound cyclic host nor noncyclic host provides much stabilization of the transition state for thiolysis by structured complexation.

Effect of Medium on Rate Acceleration Factors. In earlier studies of host-guest ground-state complexation of alkylammonium salts and macrocyclic polyethers, it was found that maximum chiral recognition was observed in solvents that were not hydrogen-bond donors or acceptors. Solvents such as $CDCl_3$, *o*-$C_6H_4Cl_2$, or CH_2Cl_2 or mixtures of these solvents with minor amounts of CH_3CN, EtOAc, or alcohols provided the highest chiral recognition.[17] Solvents such as THF or

Table III. Effect of Medium on Rate Acceleration Factors and Activation Free Energy Differences for Thiolysis of $RCH(NH_3^+)CO_2Ar$ (Guest) by $(HSM)_2D(OEOEO)_2E$ (**1**) vs. $(HSM)_2D(OEOEOCH_3)_2$ (**2**) at 25 °C[a]

medium[b]	R of guest	$k_{cycle}/k_{noncycle}$[c]	$-\Delta(\Delta G^{\ddagger})$, kcal/mol[d]	runs compared
0.04% EtOH-3% CH_3CN-$CHCl_3$	$C_6H_5CH_2$	1600	4.4	54 + 57
20% MeOH-$CHCl_3$	$C_6H_5CH_2$	1000	4.1	42 + 43
20% MeOH-$CHCl_3$	H	>2700	>4.7	40 + 41
20% EtOH-CH_2Cl_2	$C_6H_5CH_2$	490	3.7	12 + 13
20% EtOH-CH_2Cl_2	H	>130	>2.9	6 + 7
40% H_2O-CH_3CN	$C_6H_5CH_2$	8.2	1.2	48 + 49
40% H_2O-CH_3CN	H	20	1.8	46 + 47

[a] Complexes of only L-*S* or D-*R* configurations when diastereomeric. [b] By volume; see Table I for buffers. [c] Ratio of rate constants (k) for cycle **1** and noncycle **2**. [d] $\Delta(\Delta G^{\ddagger}) = \Delta G^{\ddagger}_{cycle} - \Delta G^{\ddagger}_{noncycle}$.

CH_3OH provided no chiral recognition. Thus it seemed worth determining the effect of medium variation on the values of $k_{cycle}/k_{noncycle}$ and $-\Delta(\Delta G^{\ddagger})$. Table III records the results. With L-$C_6H_5CH_2CH(NH_3^+)CO_2Ar$ as guest and (*S*)-$(HSM)_2D(OEOEO)_2E$ and (*S*)-$(HSM)_2D(OEOEOCH_3)_2$ as hosts, $k_{cycle}/k_{noncycle}$ values decreased from 1600 to 1000 to 490 to 8.2 as the solvent was changed from 0.04% EtOH-3% CH_3CN-$CHCl_3$ to 20% MeOH-$CHCl_3$ to 20% EtOH-CH_2Cl_2 to 40% H_2O-CH_3CN. With the same changes in solvent, the corresponding $-\Delta(\Delta G^{\ddagger})$ values decreased from 4.4 to 4.1 to 3.7 to 1.2 kcal/mol. With $CH_2(NH_3^+)CO_2Ar$ as guest and the same two hosts, $k_{cycle}/k_{noncycle}$ values decreased from >2700 to >130 to 20 and $-\Delta(\Delta G^{\ddagger})$ values from >4.7 to >2.9 to 1.8 kcal/mol as solvent was changed from 20% MeOH-$CHCl_3$ to 20% EtOH-CH_2Cl_2 to 40% H_2O-CH_3CN.

These results indicate that the highest values for $k_{cycle}/k_{noncycle}$ and for $-\Delta(\Delta G^{\ddagger})$ are observed in almost pure $CHCl_3$, and decrease as the amounts of hydrogen bond donor and acceptor solvents are added to the medium. The data also hint that $CHCl_3 > CH_2Cl_2 > CH_3CN$ in providing the highest values for these parameters. The cyclic host-guest complexes are held together and organized by three $NH^+\cdots$:O and three $N^+\cdots$:O electrostatic interactions which compete with analogous interactions between solvent and host, and solvent and guest.[18] The main advantage the cyclic host possesses over that of noncyclic host or hydroxylic solvents as a binder of alkylammonium ions is its almost ideal organization of 12 electron pairs. As the medium becomes richer in hydroxylic solvents, the advantage is gradually lost because both host and guest become more heavily solvated through a mass law effect. These effects apply both to transition-state and ground-state complexation, as shown by the fact that the kinetic probe for highly structured complexation shows the same type of solvent dependence as does the chiral recognition probe as applied to ground-state equilibria.[17]

Structural Recognition in Transition-State Complexation. Table IV records the rate constants for $(HSM)_2D(OEOEO)_2E$ hosts thiolating L-$RCH(NH_3^+)CO_2Ar$ guests in 20% EtOH-CH_2Cl_2. The lowest 10^3k (s^{-1}) values involved reactions between (*R*)- and (*S*)-$(HSM)_2D(OEOEO)_2E$ and L-$(CH_3)_2CHCH(NH_3^+)CO_2Ar$. Therefore, the value of k for the reaction of *R* host with L-valine ester salt was set equal to unity and the rate factors for *R* host reacting with the other L guests were calculated accordingly. Likewise, the value of k for the reaction of *S* host with L-valine ester salt was set equal to unity and the rate factors for *S* host reacting with the other L guests were calculated. The resulting rate factors are recorded in Table IV.

The data indicate that the rate factors in the *R* host-L guest series decrease with changes in the side chain of the amino ester salt as follows: CH_3, 290; $(CH_3)_2CHCH_2$, 46; $C_6H_5CH_2$, 17; $(CH_3)_2CH$, 1. Thus the larger the steric requirements of the amino acid side chains in the vicinity of its complexing and reacting groups, the slower the reaction rate. The maximum rate factor involves alanine ester salt reacting faster than that of valine by a factor of 290, which provides a $-\Delta(\Delta G^{\ddagger})$ value of 3.4 kcal/mol of structural recognition. The rate factors in the *S* host-L guest series, although somewhat less, are still substantial and fall in the same order. They vary with changes in the side chain as follows: CH_3, 32; $(CH_3)_2CHCH_2$, 32; $C_6H_5CH_2$, 15; $(CH_3)_2CH$, 1. The maximum rate factor of 32 provides a $-\Delta(\Delta G^{\ddagger})$ value of 2.1 kcal/mol of structural recognition. The source of the 1.3 kcal/mol difference in structural recognition for the two diastereomeric series is discussed in the next section.

Table IV. Structural Recognition by $(HSM)_2D(OEOEO)_2E$ (**1**) Hosts of L-$RCH(NH_3^+)CO_2Ar$ Guests in Thiolation Reactions in 20% EtOH-CH_2Cl_2 at 25 °C

confign of host	R of L guest	10^3k, s^{-1}	rate factor[a]	run no.[b]
R	CH_3	700	290	29
R	$(CH_3)_2CHCH_2$	110	46	33
R	$C_6H_5CH_2$	41	17	36
R	$(CH_3)_2CH$	2.4	1	31
S	CH_3	700	32	28
S	$(CH_3)_2CHCH_2$	700	32	32
S	$C_6H_5CH_2$	340	15	35
S	$(CH_3)_2)CH$	22	1	30

[a] See text for definitions. [b] Table I.

Chiral Recognition in Transition-State Complexation. Rate comparisons of reactions that passed through diastereomeric transition states were used as a kinetic probe for chiral recognition in transition-state complexation. The reactions of *p*-nitrophenyl ester salts of L-alanine, L-leucine, D- and L-phenylalanine and L-valine with (*S*)- and (*R*)-$(HSM)_2D(OEOEO)_2E$ and D- and L-phenylalanine with (*S*)-$(HSM)_2D(OEOEOCH_3)_2$ were examined. Table V reports the rate constant ratios for formation of the various diastereomeric thioesters, $(k)_{S\cdot L}/(k)_{R\cdot L}$, or $(k)_{R\cdot D}/(k)_{R\cdot L}$. In 20% EtOH-$CH_2Cl_2$, as the side chains of the amino esters were changed from CH_3 to $(CH_3)_2CHCH_2$ to $C_6H_5CH_2$ to $(CH_3)_2CH$, the $(k)_{S\cdot L}/(k)_{R\cdot L}$ values increased in the order 1, 6.4, 8.3, and 9.2. Thus, as expected, chiral recognition increased with the increase in the steric requirements of the side chains close to their points of attachment to the chiral center.

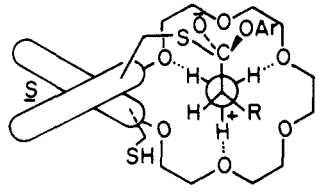
Predictions as to which diastereomeric transition states would be the more stable were made in advance of experiment through CPK molecular model examination of the presumed ortho intermediates, **12** and **13**. These structures are probably close to the rate-limiting transition states in their geometries, and provide steric explanations for both the direction of the chiral bias and the change in extent of the chiral recognition as the R groups are changed. In **12**, which possesses an *S* host to L guest configurational relationship, the R group of the guest

Table V. Chiral Recognition in the Thiolysis by $(HSM)_2D(OEOEO)_2E$ (**1**) of $RCH(NH_3^+)CO_2Ar$ (Guest) at 25 °C

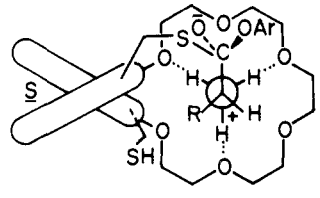
medium[a]	R of guest	$(k)_{S\cdot L}{}^b/(k)_{R\cdot L}$	$(k)_{R\cdot D}{}^b/(k)_{R\cdot L}$	runs compared
20% EtOH-CH_2Cl_2	CH_3	1		28 + 29
20% EtOH-CH_2Cl_2	$(CH_3)_2CHCH_2$	6.4		32 + 33
20% EtOH-CH_2Cl_2	$C_6H_5CH_2$	8.3	8.1	35-38
20% EtOH-CH_2Cl_2	$(CH_3)_2CH$	9.2		30 + 31
20% MeOH-$CHCl_3$	$C_6H_5CH_2$		6.9[c]	42 + 44
0.2% H_2O-3% CH_3CN-$CHCl_3$	$C_6H_5CH_2$		7.4	51 + 52
0.04% EtOH-3% CH_3CN-$CHCl_3$	$C_6H_5CH_2$		7.9	54 + 55
0.04% EtOH-3% CH_3CN-$CHCl_3$	$C_6H_5CH_2$		1.0[c,d]	56 + 57

[a] By volume; see Table I for buffers. [b] *S* or *R* are configurations of thiol ester hosts, and L and D are configurations of amino ester salt guests. [c] Complexes actually involved were enantiomers. [d] Acylation of noncycle (S)-$(HSM)_2D(OEOEOCH_3)_2$ by D- and L-$C_6H_5CH_2CH(NH_3^+)CO_2Ar$.

diverges from the naphthalene "wall" of the host which is shown in cross section. In **13**, which possesses an *S* host to D



12, (S) to (L) relationship, more stable



13, (S) to (O) relationship, less stable

guest relationship, the R group of the guest extends parallel to that "wall". With *S* host and D-alanine ester salt, the CH_3 group and the naphthalene "wall" do not crowd one another. However, as the R groups become branched, particularly at the carbon attached to the asymmetric center, as in valine (R = $CH(CH_3)_2$), some steric compression appears in models of the *S*-D diastereomer. The further away from that carbon the branching occurs, the less the steric compression. In phenylalanine and leucine, the branching occurs further out than in valine. The maximum chiral recognition rate factor which was observed (9.2) involved valine, whose diastereomeric transition states differed in free energy by about 1.3 kcal/mol. Thus of the 3.3 kcal/mol of structural recognition identified in the last section, 1.3 kcal/mol of it was chiral recognition.

The effect of the amount of hydroxylic solvent present in $CHCl_3$ on chiral recognition was studied for the acylation of (R)-$(HSM)_2D(OEOEO)_2E$ by D- and L-$C_6H_5CH_2CH(NH_3^+)CO_2Ar$. In passing from 20% MeOH-$CHCl_3$ to 0.2% H_2O-3% CH_3CN-$CHCl_3$ to 0.04% EtOH-3% CH_3CN-$CHCl_3$, $(k)_{R\cdot D}/(k)_{R\cdot L}$ values went from 6.9 to 7.4 to 7.9. Thus only a modest increase accompanies passing from the first somewhat hydroxylic solvent to the almost nonhydroxylic solvent.

As expected, no chiral recognition was observed when (S)-$(HSM)_2D(OEOEOCH_3)_2$ was acylated by L- and D-$C_6H_5CH_2CH(NH_3^+)CO_2Ar$ in 0.04% EtOH-3% CH_3CN-$CHCl_3$. This observation offers further evidence that the complexes composed of noncyclic hosts are relatively nonstructured, and that those of the cyclic hosts are highly structured.

The question arises as to whether the chiral recognition is associated with both the preequilibrium and the rate-limiting transition state, or only with the latter. In unpublished work, (S)-$(CH_3)_2D(OEOEO)_2E$ (**3**) in $CDCl_3$ at 0 °C was found to extract L-$(CH_3)_2CHCH(NH_3ClO_4)CO_2CH_3$ preferentially from the racemate in D_2O, but the chiral recognition was only about 0.6 kcal/mol. This extraction experiment was carried out under more ideal conditions of solvent and temperature for chiral recognition than the kinetic experiment,[17a,b] yet the latter gave higher chiral recognition. Both experiments provided the same configurational bias. These facts suggest that more of the 1.3 kcal/mol chiral recognition observed in the kinetic experiment with valine ester salt was associated with the organization of the rate-limiting transition state than with the complex formed in the preequilibrium. This conclusion is reasonable, since the transition state with its partial covalent bond acting as an additional binding site should provide a much more structured species than a complex organized only by hydrogen bonding.

Similarities and Differences between the Transacylation Reactions of This Study and Those Catalyzed by Enzyme Systems. Although the hosts of this study are composed of entirely different building blocks than those of the transacylase enzymes, the abiotic and biotic systems qualitatively exhibit remarkably similar behavior in their reactions with *p*-nitrophenyl esters of amino acid salts. The similarity in the forms of their reactions are illustrated in eq 7 and 8, in which G is guest, H is host, S is substrate, E is enzyme, G·H and S·E are complexes, G-H and S-E are thiol esters or esters, P^1 is *p*-nitrophenol, and P^2 is the final solvolysis product of the intermediates, G-H or S-E.

$$G + H \underset{\text{fast}}{\overset{\text{very}}{\rightleftharpoons}} G\cdot H \xrightarrow[\text{fast}]{P^1} G\text{-}H \xrightarrow[\text{slow}]{} P^2 + H \qquad (7)$$

$$S + E \underset{\text{fast}}{\overset{\text{very}}{\rightleftharpoons}} S\cdot E \xrightarrow[\text{fast}]{P^1} S\text{-}E \xrightarrow[\text{slow}]{} P^2 + E \qquad (8)$$

In both the abiotic and biotic systems, a rapidly established equilibrium exists between two reactants, one of which contains a nucleophile and the other an acylating group. In fast reactions, the partners of the complexes react with one another to liberate P^1 and form acylated intermediates. In slower reactions, these acylated intermediates in turn acylate the solvent to give P^2 and liberate the original reactant that contains the nucleophile.

In both the abiotic and biotic systems, the rate of the first acylation is greatly accelerated by complexation, which lowers the free energy of the rate-limiting transition states. The catalysis of the first acylation by complexation in both the abiotic and biotic systems is subject to competitive inhibition by substances that complex reversibly, but do not react. In both the abiotic and biotic systems, the reacting partners show structural recognition of one another by discriminating in their reaction rates between amino ester salts with different side

chains. In the initial reactions between partners, both the abiotic and biotic systems show chiral recognition toward amino ester salts by reacting more rapidly with those of the L-configurational family. The degree of chiral recognition in both the abiotic and biotic systems depends on the side chain of the amino ester salt.[19]

The abiotic and biotic systems also exhibit substantial differences, the most important of which are as follows. (1) The liberation of the acylated intermediate is catalyzed by complexation in the biotic, but not in the abiotic, system. Complexation by the enzyme promotes both the acylation and deacylation reactions, but complexation of the host promotes only the acylation reaction. Thus the enzyme is a catalyst for conversion of amino ester salt to its solvolysis product, whereas the host is not. (2) The similarities between the biotic and abiotic systems are qualitative. Particularly with respect to structural and chiral recognition, the enzymes show much larger effects.

Other synthetic systems are being designed, synthesized, and tested which we hope will more closely approximate the remarkable properties of enzymes as catalysts.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl just prior to use. Reagent- or spectral-grade solvents were used throughout. Dichloromethane was fractionally distilled before use. Spectra, ^1H NMR, were taken in $CDCl_3$ on a T-60 spectrometer with $(CH_3)_4Si$ as internal standard. Melting points were taken on a Mel-Temp apparatus. Optical rotations were measured in 10-cm jacketed cells thermostated at 25 °C with a Perkin-Elmer 141 polarimeter. Gel permeation chromatographic columns were as follows: column A, 20 ft by $\frac{3}{8}$ in. 100 Å Styragel in CH_2Cl_2, exclusion limit 1500 mol wt, 30–70 μm particle size, run at a flow rate of about 4 mL/min and 200–400 psi; column B, 18 ft by $\frac{3}{4}$ in. on Biobeads SX-8 in THF, exclusion limit 1000 mol wt. Mass spectra were determined at 70 eV on an AEI Model MS-9 double-focusing spectrometer.

(*S*)-2,3:4,5-Bis[1,2-(3-sulfhydrylmethylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*S*)-1). Diol (*S*)-**7** of maximum rotation[14] was converted to its dichloro derivative as before.[12] A solution of 4.6 g (7.8 mmol) of this material and 1.9 g (24.7 mmol) of thiourea in DMF (50 mL, distilled from CaH_2 and stored over 4 Å molecular sieves) was heated at 70–80 °C for 3 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 50 mL of morpholine and heated at 70–80 °C for 3 h. The solvent was evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 (150 mL), and the solution was washed with 100 mL of 10% hydrochloric acid. The solution was dried ($MgSO_4$) and evaporated, and the residue was submitted to chromatography on 100 g of silica gel with gradient elution (CH_2Cl_2 to 2% EtOH–CH_2Cl_2 (v)) to give 2.2 g (49%) of crude (*S*)-**1** as a light yellow syrup. This material was submitted to gel permeation chromatography on column B (retention volume 130 mL of THF), and the oil obtained was triturated with $CHCl_3$ to form a crystalline solvate with $CHCl_3$, mp 92–102 °C with loss of $CHCl_3$ (bubbles), wt after drying out the $CHCl_3$ 1.32 g (29%). This material gave $[\alpha]_{578}^{25}$ +11°, [Å]$_{546}^{25}$ +13°, and $[\alpha]_{436}^{25}$ +19° (*c* 1.8, $CHCl_3$); ^1H NMR δ 2.33 (t, *J* = 8 Hz, SH, 2 H), 3.1–3.9 (m, OCH_2, 20 H), 4.04 (d, *J* = 8 Hz, $ArCH_2$, 4 H), 7.0–7.5 (m, ArH, 6 H), 7.7–8.0 (m, ArH, 4 H); M^+ *m/e* 580; TLC R_f 0.8 (by v, 5% EtOH–CH_2Cl_2, alumina). For analysis, the sample was dried for 48 h at 165 °C (0.1 mm). Anal. ($C_{32}H_{36}O_6S_2$) C, H.

Similarly, (*R*)(*S*)-**1** was prepared (29%) from (*R*)(*S*)-**7**,[12,14] mp 116–118 °C (sealed tube under vacuum, not a solvate), and gave identical ^1H NMR and chromatographic behavior with (*S*)-**1**. Similarly (*R*)-**1** was prepared (31%) from (*R*)-**7**, $[\alpha]_{578}^{25}$ +27.7°, $[\alpha]_{546}^{25}$ + 32.3°, $[\alpha]_{436}^{25}$ +69.3° (*c* 1.0, THF), and gave $[\alpha]_{578}^{25}$ −11°, $[\alpha]_{546}^{25}$ −12°, $[\alpha]_{436}^{25}$ −20° (*c* 1.8, $CHCl_3$), retention volume, TLC R_f value, and ^1H NMR spectrum identical with those of (*S*)-**1**. Anal. ($C_{32}H_{36}O_6S_2$) C, H.

These thiols were stable when stored under argon at −10 °C in sealed vials, but decomposed in hours at 25 °C when exposed to air.

(*R*)(*S*)- and (*S*)-3,3′-Bis(hydroxymethyl)-2,2′-bis(1,4,7-trioxaoctanyl)-1,1′-dinaphthyl. To 20 g (16.7 mmol) of 1,4,7-trioxaoctane in 50 mL of dry pyridine stirred at 0 °C was added 43 g (22.5 mmol) of tosyl chloride. After complete dissolution, the reaction mixture was stored at 0 °C for 24 h. The mixture was stirred at 0 °C with crushed ice (50 g), diluted with 100 mL of water, and extracted with 200 mL of CH_2Cl_2. The organic layer was washed with 200 mL of ice-cold 15% hydrochloric acid and dried ($MgSO_4$). Evaporation of the solvent left 1,4,7-trioxaoctanyl tosylate as a viscous syrup, 43 g, 94%: ^1H NMR δ 2.3 (s, $ArCH_3$, 3 H), 3.2–3.8 (m, OCH_3 and OCH_2, 9 H), 4.0–4.4 (m, OCH_2, 2 H), 7.2–7.9 (AA′BB′ q, ArH, 4 H). To a solution of 13.9 g (40.1 mmol) of 3,3′-bis(hydroxymethyl)-2,2′-dihydroxy-1,1′-dinaphthyl[20] in 300 mL of THF stirred under N_2 was added 5.3 g (80.3 mmol) of 80% KOH in 10 mL of H_2O. To this solution was added 22 g (80.3 mmol) of the above tosylate dissolved in 50 mL of THF. The reaction mixture was held at reflux under N_2 for 42 h (neutral), the solvent was evaporated under reduced pressure, and the residue was partitioned between 300 mL of CH_2Cl_2 and 400 mL of 10% hydrochloric acid. The organic layer was dried, the solvent was evaporated under reduced pressure, and the residue was chromatographed on 280 g of Merck activity I alumina. Gradient elution of the column with Et_2O to 4% *i*-Pr_2O–Et_2O (v) gave diol product which crystallized on standing, 14 g (63%). A sample recrystallized from $CHCl_3$–Et_2O gave mp 96–98 °C; ^1H NMR δ 3.0–3.7 (m, OCH_3 and OCH_2, 22 H), 4.4 (m, OH, 2 H), 4.9 (m, $ArCH_2$, 4 H), 7.0–7.5 (m, ArH, 6 H), 7.7–8.0 (m, ArH, 4 H); TLC R_f 0.4 (2% EtOH–CH_2Cl_2 (v), alumina); M^+ *m/e* 550; dried for 24 h at 0.1 mm for analysis. Anal. ($C_{32}H_{38}O_5$) C, H.

The *S* diol was similarly prepared from 7 g (20.2 mmol) of (*S*)-3,3′-bis(hydroxymethyl)-2,2′-dihydroxy-1,1′-dinaphthyl[20] of maximum rotation in 53% yield. The *S* diol was a syrup that resisted attempts at crystallization, and after film drying at 50 °C (0.1 mm) gave ^1H NMR and mass spectra identical with those of racemic diol: $[\alpha]_{578}^{25}$ +84°, $[\alpha]_{546}^{25}$ +98°, $[\alpha]_{436}^{25}$ +190° (*c* 2.2, THF).

(*S*)- and (*R*)(*S*)-3,3′-Bis(sulfhydrylmethyl)-2,2′-bis(1,4,7-trioxaoctanyl)-1,1′-dinaphthyl ((*S*)-2 and (*R*)(*S*)-2). To a solution of 5.0 g (9.1 mmol) of the above *S* diol in 50 mL of dry C_6H_6 was added 5 mL of thionyl chloride, and the mixture was refluxed for 0.5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in 150 mL of Et_2O. The resulting solution was washed quickly with 5% $NaHCO_3$ aqueous solution (100 mL) and then brine. The solution was dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the residue was chromatographed on 110 g of silica gel with gradient elution with CH_2Cl_2 to 2% EtOH–CH_2Cl_2 to give on evaporation of the appropriate fractions the corresponding dichloride as a syrup, 5.1 g (95%). This material (5.1 g, 8.7 mmol) was treated with thiourea (2.0 g, 26.3 mmol) and then morpholine by the same procedure used to prepare bisthiol **1**. The final product was chromatographed on 90 g of silica gel and eluted with 2% EtOH–CH_2Cl_2 (v) to give a light yellow syrup, 2.3 g (53%). This material was submitted to gel permeation chromatography on column B to give (*S*)-**2** with a retention volume 115 mL of THF, 1.5 g (36%), glass (after drying for 24 h at 25 °C, 0.1 mm). This material exhibited the following properties: ^1H NMR δ 2.2 (t, *J* = 8 Hz, SH, 2 H), 3.1–3.7 (m, OCH_3, OCH_2, 22 H), 4.03 (d of d, *J* = 8 and 2 Hz, $ArCH_2$, 4 H) 7.0–7.5 (m, ArH, 6 H), 7.7–7.9 (m, ArH, 4 H); TLC R_f 0.8 (5% EtOH–CH_2Cl_2 (v), alumina); M^+ *m/e* 582; $[\alpha]_{578}^{25}$ +105°, $[\alpha]_{546}^{25}$ +122°, $[\alpha]_{436}^{25}$ +241° (*c* 1.7, $CHCl_3$). For analysis, the sample was dried for 48 h at 165 °C (0.1 mm). Anal. ($C_{32}H_{38}O_6S_2$) C, H.

The racemic dithiol, (*R*)(*S*)-**2**, was similarly prepared as a glass from the corresponding (*R*)(*S*)-diol. This material exhibited ^1H NMR and mass spectra and TLC behavior identical with those for (*S*)-**2**.

These dithiols were stored under argon in sealed vials at −20 °C.

Bis(*S*-tetrahydropyranyl) Ether of (*R*)(*S*)-2,3:4,5-Bis[1,2-[3-(2-sulfhydrylphenoxymethyl)naphtho]]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*R*)(*S*)-8). Thiocatechol[14] (4.30 g, 34.1 mmol), dihydropyran (2.87 g, 34.1 mmol), and acidic ion exchange resin (Dowex 50 W-X8, 1.15 g) were stirred in 25 mL of Et_2O under N_2 for 37 h. The reaction mixture was filtered, solvent was removed, and the residue was chromatographed on silica gel (300 g) with CH_2Cl_2 to give 5.68 (79%) of the *S*-tetrahydropyranyl ether of thiocatechol, M^+ *m/e* 210. To a stirred mixture under N_2 of 0.336 g of NaH (6.99 mmol, 50% mineral oil suspension) in THF (25 mL) was added a solution of 1.49 g (7.09 mmol) of the above ether in 10 mL of THF. After hydrogen evolution ceased, a solution of 0.70 g (1.2 mmol) of 2,3:4,5-bis[1,2-(3-chloromethylnaphtho)]-1,6,9,12,15,18-hexaoxacy-

cloeicosa-2,4-diene[12,14] in 20 mL of THF was added. The mixture was stirred at 25 °C under N_2 for 25 h, and solvent was evaporated under reduced pressure. The residue was shaken with 30 mL of CH_2Cl_2, and 30 mL of H_2O. The aqueous phase was extracted with 30 mL of CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give 2.0 g of residue which was chromatographed on 100 g of silica gel. Gradient elution of product from the column with from CH_2Cl_2 to 5% EtOH in CH_2Cl_2 (v) gave material which was subjected to gel permeation chromatography on column A to give (*R*)(*S*)-**8** as a white foam, 1.11 g (99%), homogeneous to TLC (silica gel, 10% EtOH in CH_2Cl_2 (v)); ^1H NMR δ 1.30–2.35 (m, 12 H), 2.90–3.90 (m, 24 H), 3.9–4.56 (m, 2 H), 5.27–5.67 (m, 2 H), 2.55 (broad s, 4 H), 6.51–7.70 (m, 14 H), 7.77–8.03 (m, 2 H), 8.32 (broad s, 2 H); mass spectra (12 eV) *m/e* 762, 764 (no M^+). For analysis, the sample was dried for 24 h at 80 °C (0.01 mm). Anal. ($C_{56}H_{60}S_2O_{10}$) C, H.

(*R*)(*S*)-2,3:4,5-Bis{1,2-[3-(2-sulfhydrylphenoxymethyl)naphtho]}-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene ((*R*)(*S*)-5). A degassed (bubbling argon) solution of 0.401 g (0.430 mmol) of (*R*)(*S*)-**8** in 17 mL of $CHCl_3$ and 30 mL of MeOH was stirred under an argon atmosphere as degassed 10 mL of concentrated hydrochloric acid was added quickly. The reaction mixture was refluxed for 5 h and stirred at 25 °C. The product was quickly distributed under argon between 50 mL of CH_2Cl_2 and 20 mL of H_2O, the organic phase was dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue under argon was immediately subjected to preparative gel permeation chromatography on column A to give product, retention volume 183 mL of CH_2Cl_2, evaporation of which gave (*R*)(*S*)-**5** as a white foam, 100 mg (30%): ^1H NMR δ 3.00–4.10 (m, OCH_2CH_2, 20 H), 3.95 (s, SH, 2 H), 5.59 (bs, $ArCH_2$, 4 H), 6.87–7.62 (m, ArH, 14 H), 7.83–8.12 (m, ArH, 2 H), 8.22 (bs, ArH, 2 H); M^+ *m/e* 764. The sample was dried at 138 °C (0.01 mm) for 2 h for analysis. Anal. ($C_{44}H_{44}S_2O_8$) C, H.

Compound (*R*)(*S*)-**5** was stored under argon at −20 °C, and it proved to be highly susceptible to air oxidation, particularly during its purification. The substance was unstable on silica gel, but could be filter chromatographed on neutral Merck activity III alumina with only partial polymerization.

Bis(*S*-tetrahydropyranyl) Ether of (*R*)(*S*)-3,3′-Bis[3-(2-sulfhydrylphenoxymethyl)]-2,2′-bis(1,4,7-trioxaoctanyl)-1,1′-dinaphthyl ((*R*)(*S*)-9). To a stirred suspension under N_2 of NaH (397 mg, 8.27 mmol, 50% mineral oil suspension) in 25 mL of THF was added 1.77 g (8.42 mmol) of the *S*-tetrahydropyranyl ether of thiocatechol (see above for preparation). After hydrogen evolution ceased, 920 mg (1.57 mmol) of 3,3′-bis(chloromethyl)-2,2′-bis(1,4,7-trioxaoctyl)-1,1-dinaphthyl (see above for preparation) was quickly added dissolved in THF. The resulting mixture was stirred under N_2 for 5 days. When TLC indicated the reaction to be incomplete, 0.17 g of 18-crown-6 was added, and the mixture was stirred for an additional 1 day and then refluxed for 5 h. The solvent was evaporated and the residue was distributed between 30 mL of CH_2Cl_2 and 40 mL of a solution of 30 mL of H_2O and 10 mL of NH_4Cl-saturated water. The aqueous phase was extracted with two additional 30-mL portions of CH_2Cl_2, the combined organic phases were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The yellow residue was chromatographed on 90 g of silica gel with 5% EtOH in CH_2Cl_2 (v) as eluting agent. The product was subjected to gel permeation chromatography on column A, retention volume 167 mL of CH_2Cl_2. Evaporation under reduced pressure of the appropriate band gave, after film drying at 0.01 mm, 0.742 g (51%) of (*R*)(*S*)-**9** as an oil: ^1H NMR δ 1.37–2.30 (m, 12 H), 3.18 (s, 6 H), 3.13–3.41 (m, 18 H, partly a sharp singlet at 3.30), 4.00–4.50 (m, 5 H), 5.38–5.6 (m, 2 H), 5.60 (broad s, $ArCH_2$, 4 H), 6.93–7.70 (m, ArH, 14 H), 7.78–8.03 (m, 2 H), 8.30 (broad s, 2 H); mass spectrum *m/e* 764, 766, no observable molecular ion. The analytical sample was dried by heating at 0.01 mm for 4 h at 80 °C. Anal. ($C_{54}H_{62}S_2O_{10}$) C, H.

(*R*)(*S*)-3,3′-Bis[3-(2-sulfhydrylphenoxymethyl)]-2,2′-bis(1,4,7-trioxaoctanyl)-1,1′-dinaphthyl ((*R*)(*S*)-6). A solution of 298 mg (0.318 mmol) of (*R*)(*S*)-**9** in 9 mL of CH_3OH, 9 mL of $CHCl_3$, and 18 mL of 6 N hydrochloric acid was refluxed under an argon atmosphere for 9 h. Solvent was evaporated under reduced pressure and the residue was distributed between 50 mL of CH_2Cl_2 and 40 mL of H_2O. The aqueous phase was extracted with 30 mL of CH_2Cl_2, the combined organic phases were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give a clear syrup. This material was submitted to gel permeation chromatography on column A, and (*R*)(*S*)-**6** gave a retention volume of 174 mL of CH_2Cl_2, which was film dried at 50 °C (0.01 mm) to give a glass, 215 mg (88%). The substance gave M^+ *m/e* 766; ^1H NMR δ 3.21 (s, 6 H), 3.27–3.83 (m, 16 H, OCH_2CH_2O), 4.00 (s, SH, 2 H), 5.58 (broad s, $ArCH_2$, 4 H), 6.60–7.60 (m, ArH, 14 H), 7.82–8.10 (m, ArH, 2 H), 8.20 (broad s, ArH, 2 H). Anal. ($C_{44}H_{46}S_2O_8$) C, H.

This material was much more stable than (*R*)(*S*)-**5**, and was stored at −20 °C under argon without decomposition. At 25 °C in contact with air, it slowly polymerized.

***p*-Nitrophenylamino Ester Hydrobromide Salts.** The *N*-carbobenzoxy derivatives of amino acid *p*-nitrophenyl esters purchased from Sigma were converted to their corresponding ester hydrobromides with HBr–AcOH as reported earlier.[21] After recrystallization from the solvents indicated, they had the following physical properties: glycyl, mp 207–210 °C dec (lit.[21] 208–209 °C dec), Et_2O–MeOH; L-alanyl, mp 176–178 °C dec (lit.[21] 179–180 °C dec), Et_2O–MeOH; D-alanyl, mp 179–181 °C dec (lit.[21] 179–180 °C dec), Et_2O–MeOH; L-phenylalanyl, mp 211–212 °C dec (lit.[21] 213–215 °C dec), Et_2O–EtOH, $[\alpha]^{25}_{589}$ +48° (*c* 1.4, EtOH) (lit.[22] $[\alpha]^{25}_{589}$ +46.8°); D-phenylalanyl, mp 211–212 °C dec, Et_2O–EtOH, $[\alpha]^{25}_{589}$ −48° (*c* 1.4, EtOH); L-valyl, mp 197–199 °C dec (lit.[23] 199–200 °C dec), Et_2O–MeOH; L-leucyl, mp 198–199 °C dec (lit.[22] 199 °C), Et_2O–EtOH; L-prolyl, mp 195–196 °C dec (lit.[21] 198–199 °C), Et_2O–MeOH.

Spectrophotometric Kinetics. A Cary 15 UV–vis spectrometer was used whose cell compartment was thermostated at 25 °C with a Lauda Model NB circulating bath. For buffer systems whose pH was less than 7 (referred to water), the release of *p*-nitrophenol was monitored at 345 nm. For those with pH greater than 7, the *p*-nitrophenoxide formation was monitored at 425 nm. Stock solutions of buffer were prepared under argon in degassed solvents and used for any series of runs requiring the same solutions, but were not stored over 6 h. Freshly prepared amino acid solutions and buffer (2 mL) were equilibrated thermally in the cell compartment, and 20 μL of those solutions were added to the buffer–host solutions. The mixtures were quickly stirred and the changes in absorbance vs. time were recorded. Kinetic parameters, $A_\infty - A_t$ vs. time, were plotted on semilog graph paper.[24] Half-lives were determined from the plots, and pseudo-first-order rate constants (k_{obsd}) were determined from the equation $k_{obsd} = 0.693/t_{1/2}$. The pseudo-first-order rate constants for the host-moderated reactions (k) were calculated from $k = k_{obsd} - k_{buffer}$. With buffer C (see Table I), the end points were not conveniently determined, and k_{obsd} were determined by the Guggenheim method.[25] Arbitrarily selected runs were subjected to least-squares analysis, and k_{obsd} agreed within 2% or better with the graphic rate constants. Correlation coefficients of 0.999 or better of 15 points or more per run were observed. Three or more kinetic runs were made and averaged to determine the k values of Table I (except when indicated otherwise in the footnotes of Table I).

Buffer solutions A and B were prepared from $(CH_3)_4NOAc$ (Eastman) which was dissolved in a minimum amount of $CHCl_3$, the mixture was filtered, and pentane was added until precipitation occurred. This material was filtered, washed several times with C_6H_6, and dried at 80 °C (0.01 mm) over P_2O_5 for 48 h. Buffer solution E contained $(Bu)_4NClO_4$ prepared by neutralizing $(Bu)_4NOH$ with $HClO_4$, lipophilizing the aqueous solution, recrystallizing the residue from $CHCl_3$–pentane, and drying the product. Buffer solution F contained $(Et)_4NClO_4$ purchased from Aldrich Chemical Co. Operations were conducted under a dry N_2 atmosphere in a Schlenk apparatus, and transfers were made with syringes due to the hygroscopic nature of the material. The salts were stored in a drybox under N_2. Reagent-grade collidine was fractionally distilled, and a middle cut was used and stored over 3 Å molecular sieves. Spectral-grade solvents were used for preparation of the buffer solutions.

Polarimetric Kinetics. The reaction was initiated by adding L-phenylalanine *p*-nitrophenyl ester hydrobromide (36.7 mg, 0.100 mmol) to 10.0 mL of (*S*)-**1** (0.020 M) in 20% EtOH (v) in CH_2Cl_2 buffered with 0.20 M AcOH and 0.10 M $(CH_3)_4NOAc$ and equilibrated at 25.0 °C. After the rapid initial burst of *p*-nitrophenol release (5 min), a slow exponential decay was observed. Data points (19) were taken at selected intervals until a stable infinity point was identified by the lack of change of rotation for a 12-h period. Rotations were taken at 546 nm. The first-order polarimetric rate constant of 2.0×10^{-5} s^{-1} was calculated by the method of least-squares analysis to give a correlation coefficient of 0.9979. A solution of the same (*S*)-**1** used for the polarimetric run in the same buffer solvent, and L-phenylalanine ethyl ester in the same concentrations as those used in the

polarimetric run was prepared; α_{obsd} of this solution agreed within 7% with that observed for the end point of the kinetic run. Because of the strong absorbances in the ultraviolet region by the host's naphthalene rings and the *p*-nitrophenyl ester group, the rate of ethanolysis of the thiol ester intermediate could not be followed spectrophotometrically.

References and Notes

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Ground States of Molecules. 55.[1] MINDO/3 Study of Rearrangements of C_4H_7 Radicals

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Abstract: MINDO/3 calculations are reported for seven stationary points on the C_4H_7 potential surface, corresponding to various isomeric C_4H_7 radicals and the transition states for their interconversion. The results are consistent with the available experimental evidence.

Introduction

One of the first well-defined rearrangements of free radicals to be reported involved the isomerization of alkenyl radicals formed by addition of isopropyl or *tert*-butyl radical to acetylene in the gas phase.[3-6] Thus, isopropyl radical (**1**) was found to react with acetylene (**2**) to form 1-pentene (**3**) as well as the expected 3-methyl-1-butene (**4**) (eq 1).

$$\underset{\mathbf{1}}{(CH_3)_2CH} + \underset{\mathbf{2}}{HC{\equiv}CH} \longrightarrow \underset{\mathbf{3}}{CH_3CH_2CH_2CH{=}CH_2} + \underset{\mathbf{4}}{(CH_3)_2CH{-}CH{=}CH_2} \quad (1)$$

The first step in the reaction must involve formation of the vinyl radical **5**, which is converted to **4** by abstraction of hydrogen from some other molecule. Benson and DeMore[6] explained the formation of **3** in terms of a rearrangement mechanism first suggested by Slaugh et al.,[7] i.e., rearrangement of **5** by hydrogen migration of **6**, which, by vinyl migration, forms **7** (eq 2).

They interpreted the conversion of **6** to **7** in terms of an intermediate cyclopropylcarbinyl radical **8**, formed by intermolecular addition of the radical center to the C=C bond:

$$1 + 2 \longrightarrow \underset{\mathbf{5}}{(CH_3)_2CH{-}CH{=}\dot{C}H} \longrightarrow \underset{\mathbf{6}}{CH_3\overset{\overset{CH_2\cdot}{|}}{C}H{-}CH{=}CH_2} \longrightarrow \underset{\mathbf{7}}{CH_3{-}\overset{\overset{CH_2{-}CH{=}CH_2}{|}}{C}H\cdot} \quad (2)$$

$$\underset{\mathbf{6}}{H_3C\overset{\overset{CH_2}{/\ \backslash}}{C}H{-}CH}CH_2\cdot \longrightarrow \underset{\mathbf{7}}{} \quad (3)$$

8

Cyclopropylmethyl radicals readily undergo exothermic conversion to 3-butenyl radicals.[8]

This mechanism involves the intramolecular addition of a radical to the penultimate carbon atom in a terminal olefin. Normally radicals add preferentially to the terminal atoms of terminal olefins,[9] giving rise to secondary radicals that are more stable than terminal ones. However, the reverse usually seems to be the case in the cyclization of terminally unsatu-

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