ibrations between phases and conformers were essentially instantaneous on the human time scale. With hosts **8**, **9**, and **10**, equilibration between conformers in the organic phase was observable on the human time scale, although equilibration of guest between phases was essentially instantaneous. With these hosts, the mixing times in tightly stoppered Pyrex tubes of the two phases was extended as needed to reach equilibrium between noncomplexed guest in the D_2O phase and complexed guest in the $CDCl_3$ phase. Those times are recorded in the footnotes of Table I.

Because of the insolubility of diol $A(UFCH_2)_2F$ (**9**) in $CDCl_3$, a 0.001 M solution of this diol was prepared by dissolving 4.0 mg of the substance in 0.20 mL of MeOH and 1 mL of $CDCl_3$. The methanol was washed out of this solution with 3 mL of deionized water, as shown by the absence of CH_3OH peaks in the ^1H NMR of the washed solution. The resulting $CDCl_3$ solution was used to determine the K_a and $-\Delta G°$ values.

The distribution constant, K_d, of piperidinium picrate between $CDCl_3$ and D_2O was determined by the same method used for determining the K_d values for the other salts.[16] The piperidinium picrate used was precipitated and recrystallized from ethanol and dried at 110 °C under high vacuum. Triplicate determinations of ϵ and K_d were performed: ϵ = 17300 ± 300 M^{-1} cm^{-1}; K_d = 8.0 ± 0.7 M^{-1} (90–95% confidence limits). The K_a for $A(UGCH_2)_2Py$ (**10**) complexing this salt was determined at initial concentrations of 0.015 M for host and guest. The phases were equilibrated for 24 h. The two phases gave $-\Delta G°$ values that agreed to within 0.2 kcal mol^{-1}.

Registry No. **3**, 83604-23-3; **3**·LiPic, 91129-27-0; **3**·*t*-$BuNH_3ClO_4$, 91129-28-1; **3**·$MeNH_3ClO_4$, 91129-29-2; **4**, 84011-90-5; **5**, 84011-89-2; **6**, 69605-90-9; **8**, 91084-78-5; **9**, 91084-76-3; **10**, 42062-54-4; **11**, 67350-30-5; **12**, 83604-28-8; **13**, 83604-29-9; **14**, 83604-30-2; **15**, 83604-32-4; **16**, 84011-91-6; **17**, 91129-24-7; **18**, 84011-94-9; **19**, 84011-95-0; **20**, 84011-98-3; **23**, 16069-36-6; **24**, 84027-48-5; **25**, 91129-26-9; 2-methoxy-3-nitro-5-methylaniline, 83604-27-7; 2-fluoroisophthaloyl dichloride, 91129-30-5; *N,N'*-bis(2-hydroxy-1,1-dimethylethyl)-2-fluoro-1,3-benzenedicarboxamide, 91129-31-6; L-alanine *p*-nitrophenyl ester perchlorate, 84011-92-7; *β*-alanine 4-nitrophenyl ester perchlorate, 91129-32-7; L-phenylalanine 4-nitrophenyl ester perchlorate, 91129-33-8; glycine 4-nitrophenyl ester perchlorate, 91129-34-9.

Host–Guest Complexation. 31. A Transacylase Partial Mimic[1]

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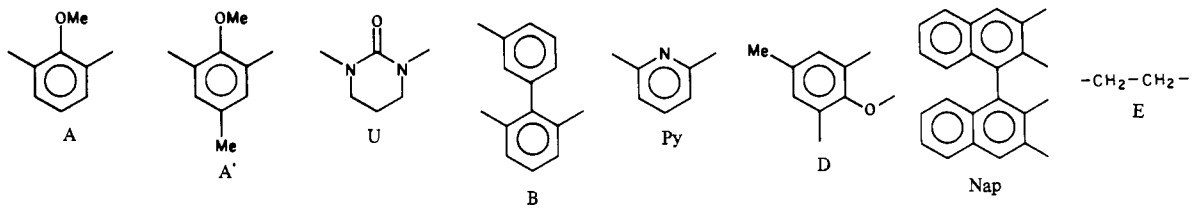
Contribution from the Department of Chemistry of the University of California at Los Angeles, Los Angeles, California 90024. *Received January 16, 1984*

Abstract: The first two stages are reported of an incremental approach to the synthesis of hosts that mimic serine transacylases. The hosts are 20-membered macrocycles and are composed by attaching to one another aryloxy, cyclic urea, pyridyl, biphenyl, ethylene, methylene, and oxygen units. The structures and points of attachment of all but the latter two units are drawn and are symbolized by capital letters. The structures of the hosts and synthetic intermediates are indicated by line formulas consisting



of sequences of letters, which represent sequences of units bonded to one another in the host. In the first stage of our approach the compound $U(A'UCH_2)_2A'$ was designed and prepared and its binding properties toward Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and *t*-$BuNH_3^+$ picrates in $CDCl_3$ at 25 °C were determined. The free energies of binding ($-\Delta G°$ values) varied from a low of 12.1 to a high of 15.2 kcal mol^{-1}. A crystal structure of the complex $U(A'UCH_2)_2A'$·*t*-$BuNH_3ClO_4$ indicated the substance possessed the expected organization. The complex is held together by the three hydrogen bonds, $RN^+(H\cdots O{=}C)_3$, in which the carbonyl groups are parts of the three cyclic urea units (U). The high binding power of $U(A'UCH_2)_2A'$ is attributed to the presence of the three cyclic urea units and particularly to their high degree of preorganization. The key ring-closing reaction involved H–U–A'–U–A'–U–H reacting with $BrCH_2$–A'–CH_2Br in tetrahydrofuran–NaH to produce $U(A'UCH_2)_2A'$·NaBr (50%). In the second stage, host $U(A'UCH_2)_2BCH_2OH$ was designed and prepared by a similar reaction between H–U–A'–U–A'–U–H with $(BrCH_2)_2BCH_2OCH_3$ to produce $U(A'UCH_2)_2BCH_2OCH_3$ (36%), which was converted to $U(A'UCH_2)_2BCH_2OH$. This compound contains both a binding site complementary to RNH_3^+ guests and a nucleophilic hydroxyl group complementary to the guest carbonyl group in complexes such as $U(A'UCH_2)_2BCH_2OH{\cdot}CH_3CH(CO_2C_6H_4NO_2\text{-}p)NH_3ClO_4$. The $-\Delta G°$ values of $U(A'UCH_2)_2BCH_2OH$ binding the above picrate salt series in $CDCl_3$ at 25 °C varied from a low of 10.6 to a high of 15.4 kcal mol^{-1}. When the alanine complex of this nucleophilic host was dissolved in CH_2Cl_2–10% pyridine (by volume) at 25 °C, transacylation occurred to give $U(A'UCH_2)_2BCH_2O_2CCH(CH_3)NH_3ClO_4$. The kinetics of transacylation were followed in $CDCl_3$ buffered with R_3N–R_3NHClO_4 (R_3N is diisopropylethylamine). Pseudo-first-order (saturation) kinetics were observed under conditions where host concentration greatly exceeded that of guest. The reaction was first order in buffer ratio, and therefore the active nucleophile was O^-. Under the same reaction conditions, the noncomplexing model compound, H_2BCH_2OH, underwent no detectable reaction. Upper limits were placed on its rate of acylation. Comparisons of the bimolecular acylation rates by $CH_3CH(CO_2C_6H_4NO_2\text{-}p)NH_3ClO_4$ of $U(A'UCH_2)_2BCH_2OH$ and of H_2BCH_2OH were made to assess all the effects of complexing. The complexing system has a second-order rate constant for acylation that is $\approx 10^{11}$ times greater than the second-order rate constant of the noncomplexing system. Addition of $NaClO_4$ acted as a competitive inhibitor for acylation of $U(A'UCH_2)_2BCH_2OH$. The kinetics of acylation of two other possible hosts were examined, $A[UD(CH_2OH)CH_2]_2Py$ and $E(OEOEO)_2Nap(CH_2OH)_2$. Although rate accelerations were observed, the amine base (R_3N) appeared to deprotonate the RNH_3^+ group of the complexes competitively with deprotonating the CH_2OH groups. As a result, the rates were not first order in R_3N–RNH_3ClO_4 ratio. We have demonstrated that molecular design and syntheses of hosts highly preorganized to be complementary to guest reactants can through tailored complexation produce enormous rate acclerations in chemical reactions.

The structure and mechanism of action of the serine transacylases have been thoroughly enough studied to stimulate the design and synthesis of nonpeptide model catalysts. The active sites contain a complexing cavity, an acyl-accepting and -releasing

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hydroxymethyl group, and a proton-transfer system that is organized to complement the structures of certain amides and esters and to catalyze their hydrolyses.[2] The naturally occurring cyclodextrins neatly combine a torus-shaped complexing cavity, one of whose two rims is lined with six–eight hydroxymethyl groups (nucleophiles). These readily available compounds have been successfully modified to provide systems that exhibit some of the features of the transacylases.[3]

A family of new systems of which **1** and **2** are typical has been designed with the help of CPK molecular models. These systems in a cooperative arrangement, similar to that of the transacylases, combine a binding site, a hydroxymethylene, an imidazole, and a carboxyl group. Models of these macrocycles are complementary to models of the general structure, $RCH(NH_3^+)CO_2R$ and $RCH(NH_3^+)CONHR$. The three cyclic urea units of the hosts provide three carbonyl groups organized to enter into tripod hydrogen binding with the NH_3^+ groups of the guest. In the host itself, the hydroxyl group is oriented to have its proton removed by the imidazole nitrogen, whose other nitrogen is hydrogen bonded to the carboxyl group in a near-linear proton relay system. In the envisioned complex, the oxyanion produced by proton transfer is proximate to the carbonyl group of the guest, and is positioned to add nucleophilically to that carbonyl to give the ortho intermediate common to base-catalyzed acyl transfers. The protonated imidazole remains in a position to facilitate the proton transfer required to complete the transacylation.

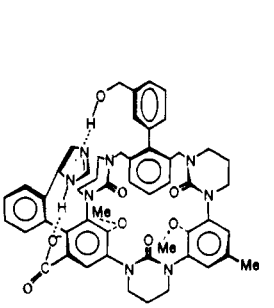
Since the synthesis of **1** or **2** is a formidable undertaking, we adopted an incremental strategy that involved the following stages. (1) Synthesize the much simpler host **3**,[4] which contains only the binding site, measure its binding power, and obtain a crystal structure of its complex with an alkylammonium salt. (2) Synthesize system **5**, which combines the binding and orientating site with the strategically oriented hydroxylic nucleophile. Synthesize **4** as well, and compare the binding abilities of **4** and **5**. Examine the kinetics of acylation of **5** by $CH_3CH(CO_2C_6H_4NO_2\text{-}p)NH_3ClO_4$ in the presence of tertiary amino buffer, and compare the rates with those for the nonbinding model compound **6**.[5a] (3) Synthesize **1** or **2** with the imidazole in place, but without the carboxyl group, and see if the proximate imidazole can take the place of the stronger external amine base used to catalyze the reaction. (4) Synthesize **1** or **2** with *all groups in place*, and examine the system for turnover catalysis and stereospecificity. This paper reports the completion of the first two stages.

As part of the evolution of **1** and **2** as target compounds, we studied hosts **7–10**.[5b] Host **7** provides a highly organized binding site complementary to RNH_3^+ guests, whereas **9** combines that complexing site with two strategically located hydroxymethyl nucleophiles. Host **8** resembles **9** except that it is open chain and is a much poorer binder of RNH_3^+ than **9** Chorands **10** and **11** were available from other studies.[6] The former combines a relatively weak complexing site with attached hydroxymethyl groups complementary in models to protonated α-amino esters. The rates of acylation of **8–10** by $CH_3CH(CO_2C_6H_4NO_2\text{-}p)NH_3ClO_4$ were examined for comparison with those of **5** and **6**.

The syntheses of **3** to **5** are described and discussed in the first section of the paper. The structures of these hosts and their complexes are found in the second section. The third section deals with the binding properties of **3–5**, **7–9**, and **11**, a model for **10**. The acylations of **5** and **9** by $CH_3CH(CO_2C_6H_7NO_2\text{-}p)NH_3ClO_4$ and the product structures are discussed in section four. The kinetics of acylation are described in section five. Section six is devoted to a discussion of rate acceleration due to complexation. Throughout the Results and Discussion, the structures of the hosts and their precursors will be represented by sequences of capital letters, each letter standing for the structural unit and its points of attachment, which are indicated at the end of the abstract. The Experimental Section provides *Chemical Abstracts* names for the compounds.

Results and Discussion

Syntheses. Hosts **3–5** were prepared by the following reactions.



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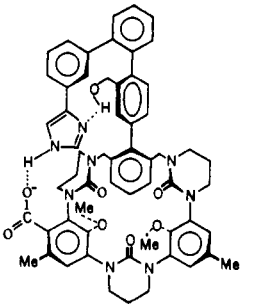

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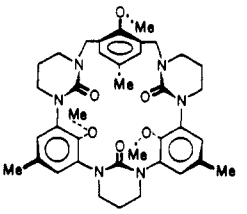
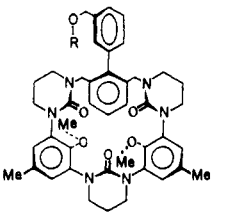
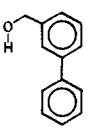


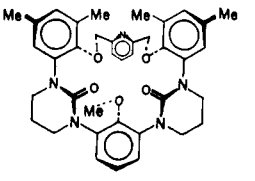
3, U(A'UCH$_2$)$_2$A'



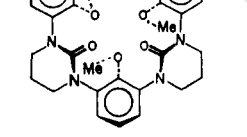
4, R=CH$_3$, U(A'UCH$_2$)$_2$BCH$_2$OCH$_3$
5, R=H, U(A'UCH$_2$)$_2$BCH$_2$OH



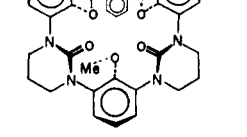
6. H$_2$BCH$_2$OH



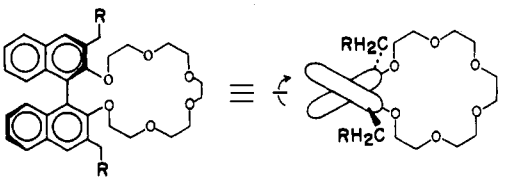
7, A[UD(CH$_3$)CH$_2$]$_2$Py



8. A[UD(CH$_2$OH)CH$_3$]$_2$



9, A[UO(CH$_2$OH)CH$_2$]$_2$Py



10, E(OEOEO)Nap(CH$_2$OH)$_2$, R=OH
11, E(OEOEO)Nap(CH$_3$)$_2$, R=H

(1) We thank the Public Health Service for Grant GM 12640, which supported all of the results reported here except those on host **3**. We are grateful to the National Science Foundation for the support of the research that involved **3**.

(2) (a) Blow, D. M.; Birktoft, J. J.; Hartley, B. S. *Nature (London)* **1969**, *103*, 337–340. (b) Hamilton, S. E.; Zerner, B. *J. Am. Chem. Soc.* **1981**, *103*, 1827–1831 and references therein.

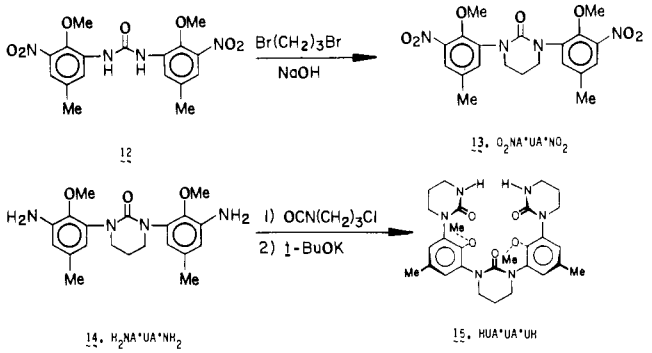
(3) (a) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer-Verlag: New York, 1977; pp 1–79. (b) Breslow, R.; Trainor, G.; Ueno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739–2744 and references therein.

(4) Cram, D. J.; Dicker, I. B.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 6828–6830.

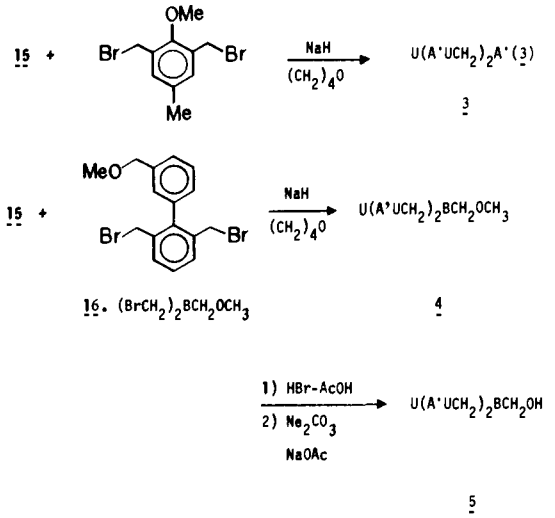
(5) (a) Cram, D. J.; Katz, H. E. *J. Am. Chem. Soc.* **1983**, *105*, 135–137; (b) preceding paper in this issue.

(6) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928–4941.

Selective reduction of one nitro group of 2,6-dinitro-4-methylanisole[7] with $(NH_4)_2S$ in hot CH_3OH[8] gave 2-amino-4-methyl-6-nitroanisole (55%), 2 mol of which were coupled with $COCl_2$ to give $O_2NA'NHCONHA'ND_2$ (**12**, 90%). The urea group of **12** was cyclized by treatment of the substance with $Br(CH_2)_3$-Br–NaOH in C_6H_6–H_2O under phase-transfer conditions to produce $O_2NA'UA'NO_2$ (**13**, 70%). Allylation of the NH groups

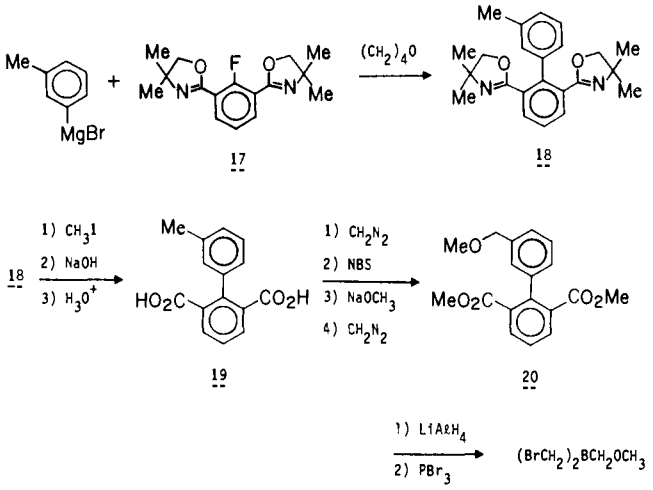


of **12** was the main side reaction. The two nitro groups of **13** were reduced with Fe–HCl[9] to provide $H_2NA'UA'NH_2$ (**14**, 98%). The two amino groups of **14** were added to the isocyanate groups of 2 mol of $OCN(CH_2)_3Cl$[10] to give U-$(A'NHCONHCH_2CH_2CH_2Cl)_2$, which without purification was doubly annulated to yield key intermediate HUA'UA'UH (**15**, 65% overall). This tris(urea) compound is somewhat soluble in water but only sparingly soluble in nonpolar solvents. Its disodium salt formed with NaH–$(CH_2)_4O$ was mixed under high-dilution conditions with 2,6-bis(bromomethyl)-4-methylanisole[11] to yield $U(A'UCH_2)_2A'$ (**3**, 50%), which was purified through its (C-



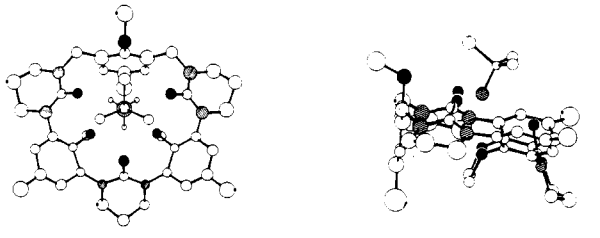
$H_3)_3CNH_3ClO_4$ complex. Similarly, the disodium salt of HUA'UA'UH (**15**) was treated with $(BrCH_2)_2BCH_2OCH_3$ (**16**) to give $U(A'UCH_2)_2BCH_2OCH_3 \cdot H_2O$ (**4**·H_2O, 36%), which was initially isolated as its NaBr complex. Both $U(A'UCH_2)_2A' \cdot NaBr$ and $U(A'UCH_2)_2BCH_2OCH_3 \cdot NaBr$ were decomplexed by dissolving them in refluxing aqueous methanol and allowing the methanol to evaporate. In each case, the free host precipitated leaving the NaBr in the water. Thus decomplexation was driven by phase transfer. Compound $U(A'UCH_2)_2BCH_2OCH_3 \cdot H_2O$ (**4**·H_2O) was demethylated by treatment with HBr–AcOH to produce $U(A'UCH_2)_2BCH_2Br$, which without characterization was hydrolyzed with Na_2CO_3–NaOAc–H_2O to give (initially) $U(A'UCH_2)_2BCH_2OH \cdot NaBr$, decomplexation of which gave $U(A'UCH_2)_2BCH_2OH \cdot 2H_2O$ (**5**·$2H_2O$, 60% overall).

The second key intermediate in the synthesis of **5** was $(BrCH_2)_2BCH_2OCH_3$ (**16**), whose synthesis is outlined below. The



Grignard reagent prepared from 3-bromotoluene was used as a nucleophile to displace the fluorine from bis(oxazoline) derivative **17**, which had been synthesized[12] from 2-fluoro-1,3-benzenedicarboxylic acid by the Meyers method.[13] Product **18** (96%) was N-methylated with CH_3I and hydrolyzed to produce diacid **19** (73%). This material was converted to its dimethyl ester, whose arylmethyl group was monobrominated with *N*-bromosuccinimide. The benzyl bromide produced was substituted with $NaOCH_3$ to yield **20** (54% overall). Reduction of the two carboxyl groups of **20** with $LiAlH_4$ to two hydroxymethyl groups and transformation of these groups with PBr_3 gave $(BrCH_2)_2BCH_2OCH_3$ (**16**, 67% overall). Model compound H_2BCH_2OH has been previously described.[14]

Structures of Hosts and Complexes. Host $U(A'UCH_2)_2A'$, when mixed with $(CH_3)_3CNH_3ClO_4$, readily formed the complex $U(A'UCH_2)_2A' \cdot (CH_3)_3CNH_3ClO_4$, whose crystal structure was determined.[4] Face and side views of the structure are represented by **21** and **22**, respectively. As these views indicate, the complex



21 **22**

contains a mirror plane. The structure was not refined enough to locate the three NH protons, but they undoubtedly possess a staggered conformation with respect to the three methyls of the attached $(CH_3)_3C$ group as in five other crystal structures of complexes that involve $(CH_3)_3CNH_3^+$ as guest.[15] The three methyls in **21** of the guest overlie the three A' groups of the host, and the organizations of the anisyl and cyclic urea units are those required to provide the expected tripod binding. The three cyclic urea oxygens are tilted upward to provide an ideally arranged

(7) Baroni, E.; Kleinau, W. *Monatsh. Chem.* **1936**, *68*, 251–260.
(8) Porter, H. K. *Org. React.* **1973**, *20*, 455–481.
(9) Mahood, S. A.; Schaffner, P. V. L. "Organic Syntheses"; Wiley: New York, 1943; Collect Vol. II, pp 160–163.
(10) Siefken, W. *Justis Liebigs Ann. Chem.* **1949**, *562*, 75–136.
(11) Koenig, K. E.; Lein, G. M. Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566.
(12) We warmly thank Dr. M. P. deGrandpre, who first synthesized **17** and studied its nucleophilic substitution reactions (unpublished work).
(13) Meyers, A. I.; Williams, B. E. *Tetrahedron Lett.* **1978**, 223–226.
(14) Hammond, G. S.; Reeder, C. E. *J. Am. Chem. Soc.* **1958**, *80*, 573–575.
(15) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43–106.

receptor site for the three hydrogen bonds. The axis of the C–N bond of the guest is normal to the plane of the three hydrogen-bonded oxygens. The two A′ groups at 4 and 8 o'clock in **21** are tilted downward so their oxygens underlie the best plane of the macroring with the orbitals of their unshared electron pairs facing inward–upward and with their methyl groups downward. The A′ group at 12 o'clock is tilted in the opposite direction so that its *p*-methyl group contacts the two methyls of the two methoxyls of the other two A′ units to form an uninterrupted skin of C–H bonds on the bottom of the complex. The OCH_3 group at 12 o'clock tilts away from the methyls of the guest, with the unshared electron pairs of the oxygen facing inward and the attached methyl group facing outward. *This crystal structure conforms in detail with that predicted from the CPK molecular model examination that inspired the synthesis of the complex.* The geometric constraints imposed on the host by its six rings provides a very high degree of preorganization, which leads to a unique structure for this complex.[4]

The 200-MHz ^1H NMR spectrum of complex U-$(A'UCH_2)_2A'\cdot(CH_3)_3CNH_3ClO_4$ (**3**·$(CH_3)_3CNH_3ClO_4$) in $CDCl_3$ is consistent with the structure of its crystal. Only a single isomer was present, as indicated by the singlets for the nine $(CH_3)_3C$ protons at δ 0.76, the six equivalent $ArOCH_3$ protons at δ 3.58, the three equivalent $ArOCH_3$ protons at δ 3.55, the six equivalent $ArCH_3$ protons at δ 2.23, the three equivalent $ArCH_3$ protons at δ 2.40, and the single AB quartet for the $ArCH_2N$ protons with signals at δ 5.315 and 6.391 (J = 15.0 Hz). The $(CH_3)_3C$ protons of $(CH_3)_3CNH_3ClO_4$ in $CDCl_3$ occur at δ 1.40,[16] and their movement upfield to δ 0.76 in the complex reflects their proximity to the shielding region of the two identical A′ aryl groups which they overlie.

The ^1H NMR spectrum of free host $U(A'UCH_2)_2A'$ (**3**) shows it to be a mixture of four conformers equilibrating rapidly on the human but slowly on the spectral time scale at 28 °C. Four different AB quartets are visible for the $ArCH_2N$ protons (identified by selective decoupling experiments) in a ratio of 1:1:0.3:1, and five different $ArCH_3$ signals are observable. Molecular model examination of the free host suggests that the A′ and U units undergo ring inversion to provide a variety of interconverting conformers. Addition of excess lithium picrate or $(CH_3)_3CNH_3ClO_4$ to a spectral solution of **3** in $CDCl_3$ provides spectra for single complexes. However, addition of $CH_3NH_3ClO_4$ gave a spectrum for two complexes in a 3:1 ratio, as shown particularly well by the presence of two AB quartets. Molecular model examination suggests the dominant structure to be similar to that of the $(CH_3)_3CNH_3^+$ complex, and the subordinant structure to be the same except with the A′ of the $CH_2A'CH_2$ group ring inverted by about 180°. An isomeric structure for the $(CH_3)_3CNH_3^+$ complex similar to this subordinate structure appears in models to be considerably more strained than the observed structure.

The 200-MHz ^1H NMR spectra of U-$(A'UCH_2)_2BCH_2OCH_3\cdot H_2O$ (**4**) in $CDCl_3$ also showed it to be a mixture of conformers. Thus five $ArCH_3$ and seven $ArOCH_3$ singlets are distinguishable, as well as two $ArCH_2OCH_3$ singlets and several AB quartets attributed to the $ArCH_2N$ protons. When a sample of **4** in $(CD_3)_2SO$ was heated in the probe, the spectra indicated that the signals due mainly to two conformers coalesced reversibly to one time-averaged conformer at about 370 K. On the basis of Ar H, Ar CH_2, and Ar CH_2O signals, a value of $\Delta\nu$ = 20 Hz was estimated. With the equation $k_{370\,K} = (2^{1/2}(\Delta\nu)$,[17] $k_{370\,K}$ was estimated to be ~90 s^{-1}, which indicates that $\Delta G^{\ddagger}_{370\,K}$ is approximately 18 kcal mol^{-1} for interconversion of the two conformers. Molecular model examination suggests that the major difference between conformers is the placement of the $C_6H_4CH_2OCH_3$ portion of the B unit relative to the two OCH_3 groups of the two A′ units. Two strain-free conformations can be constructed. In the first, all three CH_3O groups occupy the same face of the macroring. In the second, the two CH_3O groups are found on one face, and the $C_6H_4CH_2OCH_3$ group is on the opposite face. Variants of these two general conformations can also be constructed in which the CH_2OCH_3 group can face either toward or away from the face of the macroring. In models of either major conformer, a model of water can beautifully hydrogen bond and thereby bridge the carbonyl groups of any two U units (C=O··HOH··O=C). The ^1H NMR spectrum of U-$(A'UCH_2)_2A'\cdot$NaBr (**4**·NaBr) (through which the host was purified) showed the presence of only two conformers, which we believe correspond to the two mentioned above, except that occupation of the cavity by Na^+ rigidifies the system.

The 200-MHz spectrum of $U(A'UCH_2)_2BCH_2OH\cdot 2H_2O$ (**5**) in $CDCl_3$ suggested the conformational mixture to be dominated by a simple symmetrical and a single unsymmetrical conformer. Molecular model examination indicates that when the two CH_3O groups attached to the A′ units occupy that face of the macroring opposite to that occupied by the $C_6H_4CH_2OH$ part of the B group, the oxygens of the three U units and the CH_2OH group are all on the same side of the macrocycle in an ideal arrangement for

Table I. Association Constants (K_a) and Binding Free Energies ($-\Delta G°$) of Hosts for Picrate Salt Guests at 25 °C in $CDCl_3$ Saturated with D_2O[a]

host	guest cation	K_a, M^{-1}	$-\Delta G°$, kcal mol^{-1}
$U(A'UCH_2)_2A'$ (**3**)	Li	7.2×10^8	12.1
	Na	1.6×10^{11}	15.3
	K	2.2×10^{11}	15.5
	Rb	1.4×10^{10}	14.2
	Cs	3.9×10^9	13.1
	NH_4	3.5×10^{10}	14.4
	CH_3NH_3	3.5×10^{10}	14.4
	t-$BuNH_3$	4.5×10^9	13.1
$U(A'UCH_2)_2BCH_2OH$ (**5**)	Li	9.0×10^8	12.2
	Na	1.2×10^{11}	15.0
	K	2.1×10^{11}	15.4
	Rb	1.9×10^9	12.6
	Cs	4.9×10^8	11.8
	NH_4	9.7×10^9	13.6
	CH_3NH_3	2.2×10^9	12.7
	t-$BuNH_3$	6.3×10^7	10.6
$U(A'UCH_2)_2BCH_2OCH_3$ (**4**)	Rb	1.3×10^{10}	13.7
	CH_3NH_3	1.1×10^9	13.6
$A[UD(CH_2OH)CH_3]_2$ (**8**)[b]	Na		<6.0
	CH_3NH_3	2.3×10^4	5.9
	t-$BuNH_3$	3.7×10^4	6.2
$A[UD(CH_2OH)CH_2]_2Py$ (**9**)[c]	Na	5.4×10^8	11.7
	K	1.9×10^8	11.3
	CH_3NH_3	4.2×10^7	10.4
	t-$BuNH_3$	8.4×10^6	9.4
$E(OEOEO)_2Nap-(CH_3)_2$ (**11**)[b,d]	Li	2.3×10^4	6.0
	Na	1.7×10^6	8.5
	K	4.3×10^7	10.4
	Rb	4.7×10^5	9.1
	Cs	5.8×10^5	7.9
	NH_4	3.2×10^6	8.9
	CH_3NH_3	1.7×10^5	7.1
	t-$BuNH_3$	4.9×10^4	6.4
dicyclohexano-18-crown-6 (**23**)[b,e]	Li	1.92×10^5	7.2
	Na	2.3×10^6	8.7
	K	2.0×10^8	11.3
	Rb	5.1×10^6	9.1
	Cs	1.8×10^6	8.5
	NH_4	6.7×10^7	10.7
	CH_3NH_3	8.3×10^6	9.4
	t-$BuNH_3$	1.3×10^5	7.0

[a] Initial concentrations of host and guest were 0.0010 M and equilibration times were 1 min, unless otherwise noted. [b] Host and guest concentrations were 0.015 M. [c] Equilibration time was 25 h. [d] See ref 6. [e] See ref 11.

(16) Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398–6405.

(17) Jackman, L. M.; Sternhall, S. "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press: New York, 1969; p 56.

forming a hydrogen-bonding network with 1 or 2 mol of water. **5** illustrates this conformer. In its molecular models, a molecule of water can bridge the two urea oxygens at 2 and 10 o'clock that flank the B unit and, at the same time, accept the hydrogen bond of the CH_2OH group to give a structure with a mirror plane. Alternatively, the water can bridge the carbonyls at 2 and 6 o'clock or at 10 and 6 o'clock in **5** and in turn accept the hydrogen bond of the CH_2OH group to give overall unsymmetrical structures. A second molecule of water can also bridge with two hydrogen bonds to the appropriate oxygens among the seven present (three carbonyls, two methoxy ethers, one CH_2OH, and one H_2O). These hypothetical structures explain both the ^1H NMR spectra and the fact that **5** crystallizes with 2 mol of water.

The ^1H NMR spectrum of the $U(A'UCH_2)_2BCH_2OH{\cdot}NaClO_4$ complex (**5**·$NaClO_4$) also shows the presence of two conformers, both of which appear to contain a mirror plane, or the equivalent. The structures of these conformers probably resemble those for $U(A'UCH_2)_2BCH_2OCH_3{\cdot}NaBr$ (**4**·NaBr) discussed above.

The structures of hosts **7–9** and their complexes have been discussed in the companion paper.[5b] The crystal structures of the free host $E(OEOEO)_2Nap(CH_3)_2$ (**11**) and its $(CH_3)_3CNH_3ClO_4$ complex have been reported.[15] This free host is a close relative of $E(OEOEO)_2Nap(CH_2OH)_2$ (**10**) used in this investigation. Complex **11**·$(CH_3)_3CNH_3ClO_4$ is held together by the usual tripod hydrogen bonding by the guest of alternate oxygens of the chorand.[15] Two methyl groups of the guest contact that methyl group of the naphthalene ring found on the same face as that occupied by the guest in this perching complex. This structure indicates that in a complex such as $E(OEOEO)_2Nap(CH_2OH)_2{\cdot}RCH(CO_2Ar)NH_3ClO_4$ (**10**·$RCH(CO_2Ar)NH_3ClO_4$), the CH_2OH of the host and the carbonyl of the guest are proximate.

Free Energies of Complexation. The association constants (K_a) and free energies of association ($-\Delta G°$) of hosts **3–5** were measured by the picrate extraction method.[6] Solutions of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrates in D_2O were extracted into $CDCl_3$ at 25 °C in the absence and presence of host. The hosts and their complexes are soluble essentially only in the $CDCl_3$ layer. The K_a and $-\Delta G°$ values at 25 °C in $CDCl_3$ saturated with D_2O were calculated from the results and are reported in Table I, along with those for compounds $A[UD(CH_2OH)CH_3]_2$ (**8**),[5b] $A[UD(CH_2OH)CH_2]_2Py$ (**9**),[5b] $E(OEOEO)_2Nap(CH_3)_2$ (**11**),[6] and dicyclohexano-18-crown-6 (**23**).[11] Compound **11** serves as a model for $E(OEOEO)_2Nap(CH_2OH)_2$ (**10**)[6] whose values unfortunately are not available.

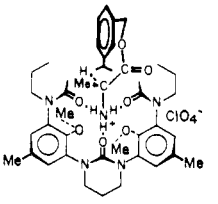
In all cases, the $CDCl_3$ layer was saturated with D_2O. The total amount of D_2O present in each determination might have varied slightly as the guest cation was changed due to differential solvation. If such changes exist they are small since the concentrations of guest vary from <0.015 to <0.001 M. Variation of host concentration over this range with hosts that reach the sensitive parts of the 0.015 and 0.001 M scales has no discernible effect on K_a and $-\Delta G°$ values (unpublished results).

Hosts **3** and **5** are the best general binders of the alkali metal, ammonium, and alkylammonium ions that have been prepared thus far. Dicyclohexano-18-crown-6 (**23**), the prototypical commercial chorand, binds the eight cations with $-\Delta G°_{av}$ = 9.0 kcal mol^{-1}, compared to values of 14.0 and of 13.0 kcal mol^{-1} for $U(A'UCH_2)_2A'$ (**3**) and $U(A'UCH_2)_2BCH_2OH$ (**5**), respectively. The maximum discrimination in binding of the five metal cations, $-\Delta(\Delta G°)$ in kcal mol^{-1}, is only 3.4 for **3** and 4.8 for **4**, as compared to 4.3 for **23**. Peak binding for all three hosts occurs with K^+, which **3** binds better than **23** by 4.2 and **5** better by 4.1 kcal mol^{-1}. The important ion Na^+ is bound ~7000 more strongly by **3** and ~5000 more strongly by **5** than by chorand **23**. The superior binding by **3** and **5** over that of **23** is attributed to the fact that **3** and **5** are more highly organized for complexation during synthesis than is chorand **23** (principle of preorganization[18]). The oxygens of the three U and two A′ units of **3** and **5** all generally must converge on the cavity. Molecular models of the complexes of **3** and **5** with the Li^+, Na^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ ions indicate that only three–five oxygens can directly ligate the guests, whereas **23** can ligate with six oxygens all ions but possibly Li^+. Thus, preorganization as well as the intrinsically better ligating power of the urea oxygens[19] more than compensate for their deficit in the numbers of ligands.

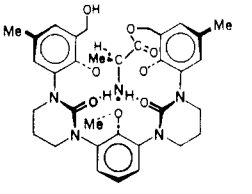
Hosts $U(A'UCH_2)_2A'$ (**3**) and $U(A'UCH_2)_2BCH_2OH$ (**5**) dissolved in $CDCl_3$ instantaneously extract metal ions from water as does dicyclohexano-18-crown-6. This rapid extraction rate correlates with the very high complexation rate constants (k_1) for **3**, which have been measured in $CDCl_3$ saturated with D_2O.[20] With *tert*-butylammonium picrate, $k_1 \sim 10^{12}$ mol^{-1} s^{-1}, whereas $k_{-1} \sim 7 \times 10^2$ s^{-1}. Molecular models of **3** and **5** indicate that the three urea oxygens are highly exposed to potential guests and can ligate one at a time, while water or other guests are displaced. The diameter of the cavity in **3** and **5** is highly flexible, both because of the 20-membered macroring and the variability of the dihedral angles between the A′–U pairs. **We believe that U-$(A'UCH_2)_2A'$ (3) as a generally neutral extraction agent for cations will be difficult to improve upon because of its balance between rigidity and flexibility, between hydrophilicity and lipophilicity, and between hard and soft ligating sites.**

The complexing powers of the other hosts of Table II have already been discussed.[5b,11] As expected from their structures, $A[UD(CH_2OH)CH_2]_2Py$ is in between $U(A'UCH_2)_2BCH_2OH$ (**5**) and modified chorand $E(OEOEO)_2Nap(CH_3)_2$ (**11**) in binding power.

Transacylation. The guest reactants, L-alanine,[5b] β-alanine, L-phenylalanine, and glycine *p*-nitrophenyl ester perchlorates were synthesized by treating the corresponding *N*-(*tert*-butoxycarbonyl) derivatives with perchloric acid and crystallizing the ester perchlorate salts. Of these reactants, the alanyl derivative was the most useful, in part because its easily observable doublet in the ^1H NMR spectrum allowed the progress of acylation to be monitored. Equal molar quantities of L-alanine *p*-nitrophenyl ester perchlorate were mixed with $U(A'UCH_2)_2BCH_2OH$ (**5**) in dry CH_2Cl_2 and dry pyridine (10:1, v/v) at 25 °C to give a solution from which was isolated (Li_2CO_3–H_2O), then $HClO_4$ wash) $U(A'UCH_2)_2BCH_2O_2CCH(CH_3)NH_3ClO_4{\cdot}H_2O$ (**24**·H_2O), which



24. $U(A'UCH_2)_2BCH_2O_2CCH(CH_3)NH_3ClO_4$



25. $A[UD(CH_2OH)CH_2][UD(CH_2O_2CCH(CH_3)NH_3ClO_4)CH_2]Py$

was fully characterized (C, H, and N were within 0.16% of theory). Similarly from the same guest reactant and host reactant $A[UD(CH_2OH)CH_2]_2Py$ (**9**) was produced $A[UD(CH_2OH)CH_2][UD(CH_2O_2CCH(CH_3)NH_3ClO_4)CH_2]Py$ (**25**), which was fully characterized (C, H, N, and Cl were within 0.15 of theory).

Structures **24** and **25** are views in which those parts of the hosts are omitted that are hidden behind the covalently bound guest. In molecular models of **24**, the dihedral angle for the groups attached to the C–N atoms are a comfortable 60°, whereas this important condition is fulfilled in models of **25** only by generation of nonbonded repulsions. Models of **24** and **25** indicate that plenty of space is available for bulky R groups of the amino ester moiety. Molecular models of the presumed ortho ester intermediates involved in the formation of **24** are sterically compatible with leaving groups as large as $OC_6H_4NO_2$-*p* and ester substituent groups such as $C_6H_5CH_2$. However, models of those producing **25** are substantially more compressed. In **25**, the use of two urea oxygens

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(19) (a) Mitsky, J.; Jaris, L.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 3442–3445. (b) Atkins, H. W.; Gilkerson, W. R. *Ibid.* **1973**, *95*, 8551–8559.

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Table II. Kinetics of Acylation of Hydroxymethyl Hosts by *p*-Nitrophenyl Esters of Amino Acid Salt Guests at 10^{-4} M Concentrations in $CDCl_3$ Buffered by Diisopropylethylamine (R_3N)–R_3NHClO_4 at 24 ± 0.1 °C

	host or nucleophile			concn, M, R_3N/ R_3NHClO_4	cosolvent		inhibitor		rate constants × 10^3	
run	structure	concn, M	guest structure		kind	%[a]	kind	concn, M	k_1, min^{-1} [b]	k_2, min^{-1} M^{-1} [c]
1	none		L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			0.18[d]	
2	none		L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.003	DMF	10			0.17	
3	none		L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.003/0.001	DMF	10			0.23	
4	none		L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	10			0.23	
5	none		L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.10/0.001	DMF	10			0.30	
6	none		L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	CH_3CN	10			0.039	
7	none		L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	CH_3CN	10	$NaB(Ph)_4$	0.002	0.10	
8	A[UD(CH_3)-$CH_2]_2$Py (**7**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			0.24	
9	H_2O	0.06	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10	$NaClO_4$	0.015	0.31	
10	H_2O	0.12	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10	$NaClO_4$	0.030	0.42	
11	EtOH	0.10	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			0.25	
12	EtOH	0.50	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			0.13	0.26
13	EtOH	1.00	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			0.42	0.42
14	EtOH	1.50	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			0.84	0.56
15	H_2BCH_2OH (**6**)	0.016	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	0.15			<0.005[e]	<0.3[f]
16	H_2BCH_2OH (**6**)	0.032	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	0.15			<0.005[e]	<0.15[f]
17	H_2BCH_2OH (**6**)	0.022	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	CH_3CN	10			0.1	5
18	H_2BCH_2OH (**6**)	0.022	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	10			0.3	14
19	A[UD(CH_2OH)-$CH_3]_2$ (**8**)	0.0090	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			2.2[d]	240
20	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.003	DMF	10			0.83	550
21	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			1.2[d]	800
22	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.003/0.003	DMF	10			1.2	800
23	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.003/0.001	DMF	10			1.6	1100
24	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	10			1.8	1200
25	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.010/0.001	DMF	10			2.0	1300
26	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0010	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			0.83	830
27	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10	$NaClO_4$	0.0075	0.29	190
28	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10	$NaClO_4$	0.015	0.26	170
29	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	$ArO_2CCH_2NH_3ClO_4$	0.001/0.001	DMF	10			1.5	1000
30	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	L-$C_6H_5CH_2CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			0.15	100
31	A[UD(CH_2OH)-$CH_2]_2$Py (**9**)	0.0015	$ArO_2CCH_2CH_2NH_3ClO_4$	0.001/0.001	DMF	10			0.31	200
32	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	0.15			2.8	
33	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.003/0.003	DMF	0.15			2.2	
34	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.003/0.001	DMF	0.15			9.1	
35	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	0.15			17[d]	
36	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.010/0.001	DMF	0.15			24	
37	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0007	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	0.15			19[d]	
38	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	CH_3CN	10			10	
39	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	10			4.0	
40	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0016	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	0.15	$NaClO_4$[g]	0.0016	0.43	
41	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	CH_3CN	10	$NaB(Ph)_4$	0.002	0.30[d]	
42	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	CH_3CN	10	$NaB(Ph)_4$	0.004	<0.10	
43	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	10	$NaB(Ph)_4$	0.006	0.20	
44	U(A′U$CH_2)_2$-BCH_2OH (**5**)	0.0014	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.010/0.001	DMF	10	$NaB(Ph)_4$	0.0075	0.60	

Table II (Continued)

run	host or nucleophile: structure	host or nucleophile: concn, M	guest structure	concn, M, R_3N/R_3NHClO_4	cosolvent: kind	cosolvent: %[a]	inhibitor: kind	inhibitor: concn, M	rate constants × 10^3: k_1, min^{-1} [b]	rate constants × 10^3: k_2, min^{-1} M^{-1} [c]
45	$E(OEOEO)_2Nap-(CH_2OH)_2$ (**10**)	0.0016	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.003/0.001	DMF	0.15			13	8000
46	$E(OEOEO)_2Nap-(CH_2OH)_2$ (**10**)	0.0016	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	0.15			9	5600
47	$E(OEOEO)_2Nap-(CH_2OH)_2$ (**10**)	0.0016	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.010/0.001	DMF	0.15			10	6000
48	$E(OEOEO)_2Nap-(CH_2OH)_2$ (**10**)	0.0032	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	DMF	0.15			18	5600
49	$E(OEOEO)_2Nap-(CH_2OH)_2$ (**10**)	0.0016	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	CH_3CN	10			5.2	3200
50	$E(OEOEO)_2Nap-(CH_2OH)_2$ (**10**)	0.0017	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			3.8	2200
51	$E(OEOEO)_2Nap-(CH_2OH)_2$ (**10**)	0.0030	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.001/0.001	DMF	10			6.7	2200
52	$E(OEOEO)_2Nap-(CH_2OH)_2$ (**10**)	0.0016	L-$CH_3CH(CO_2Ar)NH_3ClO_4$	0.006/0.001	CH_3CN	10	$NaB(Ph)_4$	0.002	<0.1	<60

[a] Percent by volume of total volume. [b] Values reported for control runs 1–11 are k_{obsd}; units for k_1 or k_{obsd} are $min^{-1} \times 10^{-3}$. [c] Units are min^{-1} mol^{-1} $L \times 10^{-3}$. [d] Run in triplicate or duplicate. [e] Values for k_{obsd}[b]. [f] Values for k_{obsd}[b]/[H_2BCH_2OH]. [g] Preformed $U(A'UCH_2)_2BCH_2OH \cdot NaClO_4$ was used.

and a pyridyl nitrogen ($NH^+ \cdot\cdot N$) as binding sites draws the guest more deeply into the cavity than do the three urea oxygen binding sites of **24**.

Kinetics of Transacylation. The kinetics of acylation of the benzyl alcohol reactants by the *p*-nitrophenyl ester amino acid perchlorate guest–reactant were followed by the appearance at 350 nm of p-$NO_2C_6H_4O^-$ liberated in a quartz UV spectrophotometer cell at 25 °C. End-point absorbances (A_∞) were 0.200–0.600 units higher than initial absorbance (A_i), and A_∞ values were stable within experimental error. The solvent was $CDCl_3$, diluted with *N,N*-dimethylformamide (DMF) or acetonitrile that varied between 0.15% and 10% by volume. The solution was buffered with diisopropylethylamine (R_3N) and its perchlorate salt (R_3NHClO_4). The amino ester salt concentration was 10^{-4} M, that of R_3N varied between 10^{-3} and 10^{-2} M, that of R_3NHClO_4 between 10^{-3} and 3×10^{-3}, that of the nucleophilic host between 7×10^{-4} and 90×10^{-4} M, and those of potential competitive inhibitors such as $NaB(Ph)_4$ or $NaClO_4$ between 150×10^{-4} and 20×10^{-4}. Since the host/guest molar ratio was usually 14 to 16, the concentration of the nucleophilic host did not change enough during the reaction to perturb the observed pseudo-first-order kinetics.

Plots of ln ($A_\infty - A_i$) vs. time (t) for 8–18 points covering 2–3 half-lives of reaction were linear, and they gave correlation coefficients of 0.999–0.980. The negatives of the slopes of these lines, calculated by least-square analyses, gave pseudo-first-order rate constants (k_{obsd}) for the rates of release of *p*-nitrophenol. The rate constants for transesterification by specific nucleophiles (k_1) were obtained by subtracting the appropriate solvent/buffer rates from k_{obsd}. Second-order rate constants (k_2) were calculated where appropriate by dividing k_1 by the nucleophile concentration. Table II reports the conditions and the results of runs 1–52, the more important of which were made in duplicate or triplicate (footnote *d* of Table II). Values were reproducible within 10–20%. The rate constants are not corrected for the numbers of OH groups per host. The formation of acylated host (in addition to *p*-nitrophenol) as the product of the reaction under study was verified by ^1H NMR spectra with $U(A'UCH_2)_2BCH_2OH$ (**5**) or $A[UD(CH_2OH)CH_2]_2Py$ (**9**) as reactants. The spectra of the products formed under the same conditions as those used in the kinetic experiments were identical with those recorded for the independently synthesized acylated hosts.

Controls performed in the absence of added nucleophilic reactant (runs 1–7, Table II) established base-line rates of approximately 10^{-4} min^{-1} for *p*-nitrophenol release in the reaction of $CH_3CH(CO_2C_6H_4NO_2\text{-}p)$ with the medium ($CHCl_3$–10% DMF or CH_3CN). The addition of the nonnucleophilic host $A[UD(CH_3)CH_2]_2Py$ (**7**) had no effect on this background rate (run 8). When water, ethanol, or noncomplexing compound H_2BCH_2OH (**6**) were present in concentrations of 0.01–0.50 M, the rates of p-$NO_2C_6H_4OH$ release were not significantly higher (runs 9–12, 17, and 18). Ethanol present at 1.0 or 1.5 M increased the rate by a factor of 2–3 (runs 13 and 14). This effect could have been due as much to a change in solvent polarity as to the increased concentration of the nucleophile.

Runs 20–31 report results of the acylations of $A[UD(CH_2OH)CH_2]_2Py$ (**9**). These experiments were conducted in $CDCl_3$–10% DMF, since this host was insoluble in media containing less DMF and was in fact close to saturation in the media used. Values of k_1 for 0.0015 M solutions of **9** in runs 20–25 were 6–9 times higher than the base-line rates. Variation in the concentrations of **9** (runs 21 and 26) gave k_2 values that suggest the reaction is first order in host. Variation in the buffer concentration in runs 21 and 22 produced no change in k_1 value. Variation in buffer ratio in runs 21 and 23–25 indicated that k_1 has a dependence on specific base concentration between zero and first order. The presence of $NaClO_4$ in runs 27 and 28 depressed the k_1 value of run 21 by a factor of 4–5, pointing to competitive complexation of the host system by Na^+.

Host $A[UD(CH_2OH)CH_3]_2$ (**8**) is a relatively poor binding open-chain analogue of **9**, yet comparison of k_2 values for runs 19 and 21 indicate that the much better binding host **9** acylates at a rate only about 3 times that of **8**. A comparison of the k_2 value for $A[UD(CH_2OH)CH_2]_2Py$ (**9**) in run 24 with that of nonbinding compound H_2BCH_2OH (**6**) in run 18 indicates that **9** acylates faster than **6** by about 100.

These collective results suggest that complexation by $A[UD(CH_2OH)CH_2]_2Py$ (**9**) of $CH_3CH(CO_2Ar)NH_3^+$ does accelerate the reaction rate but that the pK_a of tripod-bound $CH_3CH(CO_2Ar)NH_3^+$ is not high enough to allow R_3N: of the buffer to remove the proton of the $ArCH_2OH$ group without competitively removing it from the nitrogen of $CH_3CH(CO_2Ar)NH_3^+$. The free amine is a weak complexing agent compared to its salt, and the result is low acceleration due to complexation, low sensitivity of the rate to the presence of complexing inhibitors, and a low sensitivity to buffer ratio. Saturation kinetics were not observed for this system.

In runs 29–31, $ArO_2CCH_2NH_3ClO_4$, $C_6H_5CH_2CH(CO_2Ar)NH_3ClO_4$, and $ArO_2CH_2CH_2NH_3ClO_4$ (Ar is p-$NO_2C_6H_4$) acylated $A[UD(CH_2OH)CH_2]_2Py$ under the standard conditions used for $CH_3CH(CO_2Ar)NH_3ClO_4$ (run 21). The rate for $ArO_2CCH_2NH_3ClO_4$ was 4 times higher than that for the standard guest, and the rate for $C_6H_5CH_2CH(CO_2Ar)NH_3ClO_4$ was lower by a factor of 2.4. Molecular models of the complexes indicate the probable presence of steric compression in formation of the complexed transition states in generating the usual ortho

intermediate for transacylation. Since $C_6H_5CH_2 > CH_3 > H$ in bulk, the rate order correlates with expectations based on steric effects. The fact that $ArO_2CCH_2NH_3ClO_4$ in run 29 gives a k_2 value 5 times higher than that for homologue $ArO_2CH_2CH_2NH_3ClO_4$ in run 31 correlates with the fact that, in models, the acyl group of the former is more proximate than the latter to the CH_2OH group in the respective complexes. These effects probably would be greatly magnified were it not for the "buffering" effect associated with the pK_a relationships of the CH_2OH and NH_3^+ groups mentioned in the last paragraph.

In runs 45–52, the nucleophilic host is $E(OEOEO)_2Nap(CH_2OH)_2$ and the electrophilic guest is L-$CH_3CH(CO_2C_6H_4NO_2$-$p)NH_3ClO_4$. In $CDCl_3$–0.15% DMF, the constancy of k_2 in runs 46 and 48, when host concentrations are varied by a factor of 2, suggests the reaction is second order and that saturation kinetics are not observed. The k_2 value obtained is $> 10^4$ higher than that for H_2BCH_2OH (**6**) run under the same conditions (runs 15 and 16). However, the k_2 value of $E(OEOEO)_2Nap(CH_2OH)_2$ (**10**) shows little sensitivity to buffer ratio. This host is too weak a complexing agent to increase the pK_a of the bound RNH_3^+ enough to allow CH_2O^- and RNH_3^+ to be present in the same complex at rate-influencing concentrations. The observed rate enhancement is probably due to reactions between complexed RNH_2 with CH_2O^- as nucleophile. In $CDCl_3$–10% CH_3CN in run 49, k_2 is greater for $E(OEOEO)_2Nap(CH_2OH)_2$ than for H_2BCH_2OH by $> 6 \times 10^2$. Furthermore, this rate enhancement factor is reduced by $>10^2$ when $NaB(Ph)_4$ is present at a concentration slightly greater than that of the host reactant. This result indicates that Na^+ is acting as a competitive inhibitor and that the guest reactant is complexed in the transition state for transacylation.

Host reactant $U(A'UCH_2)_2BCH_2OH$ (**5**) was studied in runs 32–44, with L-$CH_3CH(CO_2C_6H_4NO_2$-$p)NH_3ClO_4$ as the guest reactant. In runs 35 and 37, carried out in $CHCl_3$–0.5% DMF, the host concentration was changed by a factor of 2 without affecting k_1, indicating that essentially all of the guest was complexed and that the reaction was zero order in host (saturation kinetics). In runs 32 and 33, carried out in $CHCl_3$–0.5% DMF, the *buffer concentration* was increased by a factor of 3 with no change within experimental error in k_1. In runs 32 and 34–36, the *buffer ratio* was varied by a factor of 10, and k_1 changed by a similar factor, indicating the reaction to be first order in specific base (R_3N of the buffer). Thus, the active nucleophile in the acyl transfer appears to be CH_2O^-, and the transition state for transacylation contains both an $O^-\cdots C{=}O$ and an $N^+(H\cdots O{=}C)_3$ group. In water, the pK_a of $CH_3CH(CO_2Ar)NH_3^+$ is ~ 7[21] and that of the $ArCH_2OH$ ~ 15,[22] whereas that of the buffer R_3NH^+ is ~ 10.8.[23] Clearly, complexing $CH_3CH(CO_2Ar)NH_3^+$ with $U(A'UCH_2)_2BCH_2OH$ in this medium dramatically raises the pK_a of the NH_3^+ group relative to the CH_2OH group, probably by many units. This hypothesis is compatible with the 13–14 kcal mol^{-1} range of $-\Delta G°$ values for which CH_3NH_3 picrate is bound in $CDCl_3$ by the tris(urea) systems **3–5** (see Table I). In run 40, the presence of $NaClO_4$ at a concentration identical with that of host reduced k_1 by a factor of 57 (compare with run 35). Thus, Na^+ is acting as a competitive inhibitor of RNH_3^+. When the concentration of DMF in the medium was increased from 0.15% to 10%, the k_1 value decreased by a factor of about 4 (run 39 v. 35). When the diluent was CH_3CN, the decrease was only by a factor of about 2 (run 38 vs. 35). Addition of $NaB(Ph)_4$ to $CDCl_3$–10% DMF or $CDCl_3$–10% CH_3CN in runs 41–43 decreased k_1 values by factors ranging from 20 to >100 (compare to runs 38 and 39). Thus, competitive inhibition is observed in the more polar media as well as in the less polar.

Effects of Complexation on Rate Constant Enhancement Factors and Rate Acceleration. Of the hosts studied, only the acylation of $U(A'UCH_2)_2BCH_2OH$ (**5**) by L-$CH_3CH(CO_2C_6H_4NO_2$-$p)NH_3ClO_4$ exhibited saturation kinetics and first-order dependence on buffer ratio in $CDCl_3$–0.5% DMF as the medium. Here we address the questions of how complexation of these reactants in this medium affects their second-order rate constants on the one hand and rate accelerations on the other. Comparisons are made between the kinetic behavior of $U(A'UCH_2)_2BCH_2OH$ (**5**) and of its noncomplexing model, H_2BCH_2OH (**6**), under the same reaction conditions. Since the acylations of **5** and **6** go by different mechanisms, we base our comparisons of rate constants on the solutions of *uncomplexed* $CH_3CH(CO_2Ar)NH_3ClO_4$, $U(A'UCH_2)_2BCH_2OH$ (**5**), and H_2BCH_2OH (**6**) *as our standard starting states* and the *rate-controlling transition states as our standard final states*. The resulting rate constant enhancement factors measure all of the effects associated with complexation.[24]

Calculation of the rate constant enhancement factors involves the following definitions and reasonable assumptions about mechanism. The reaction of $CH_3CH(CO_2C_6H_4NO_2$-$p)NH_3ClO_4$ (gL) with $U(A'UCH_2)_2BCH_2OH$ (hOH) to give $U(A'UCH_2)_2BCH_2O_2CCH(CH_3)NH_3ClO_4$ (gOh) and p-$NO_2C_6H_4OH$ (HL) is presumed to involve an overall bimolecular rate constant k_a and to go by the following mechanism in which [B] is the concentration of R_3N:

$$gL + hOH \xrightarrow{k_a} gOh + LH$$

$$gL + hOH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} gL{\cdot}hOH \quad K_1 = k_1/k_{-1}$$

$$gL{\cdot}hOH + B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} gL{\cdot}hO^-{\cdot}BH^+ \qquad K_2 = k_2/k_{-2}$$

$$gL{\cdot}hO^-{\cdot}BH^+ \xrightarrow{k} gOh + LH + B$$

Experimentally, [hOH] and [B] are constant, K_1 is very high valued, and k_{-1} is expected to be $>k$. Thus, the observed first-order rate constant, ($k_{obsd}{}^a$) for the appearance of LH can be described by eq 1. With the reasonable assumption that $k_{-1} > k_2[B]$, the

$$k_{obsd}{}^a = kK_2[B] \tag{1}$$

second-order rate constant (k_a) for acylation of hOH by gL can be expressed by eq 2, which when combined with eq 1 gives eq 3.

$$k_a = kK_1K_2[B] \tag{2}$$

$$k_a = k_{obsd}{}^aK_1 \tag{3}$$

A conservative estimate of the value of K_1 for $CH_3CH(CO_2C_6H_4NO_2$-$p)NH_3ClO_4$ complexing $U(A'UCH_2)_2BCH_2OH$ is 10^9 M^{-1}. This value is based on the following comparisons. The K_1 value for CH_3NH_3 picrate complexing **5** in $CDCl_3$–0.2% D_2O at 25 °C is 2×10^9 M^{-1}. In the same medium, chorand hosts complexed t-$BuNH_3ClO_4$ with K_1 values ~ 60 times those of t-$BuNH_3$ picrate.[25] The K_1 values for $U(A'UCH_2)_2BCH_2OH$ complexing Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates vary only from extremes of 10^8 and 10^{11} M^{-1}, suggesting that the value for the alanyl ester perchlorate should fall somewhere near the middle of this range.

The reaction of gL with H_2BCH_2OH (bOH) to give acylated product gOb and HL is presumed to involve an overall bimolecular rate constant k_b and to go by the following mechanism:

$$gL + bOH \xrightarrow{k_b} gOb + HL$$

$$bOH + B \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} bO^-{\cdot}HB^+ \qquad K' = k'_1/k'_{-1}$$

$$gL + bO^-{\cdot}HB^+ \xrightarrow{k'} gOb + HL + B$$

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With [bOH] > [gl] and [B] constant, [bO⁻·HB⁺] is constant, and the reaction should follow the first-order kinetics (k_{obsd}^{b}) of eq 4. Equation 5 expresses k_b as a function of k'_1, k'_{-1}, k', and [B].

$$k_{obsd}^{b} = k'[bO^{-}\cdot HB^{+}] \quad (4)$$

$$k_b = [B]k'_1k'/(k'_{-1} + k'[gL]) \quad (5)$$

Since $k'_{-1} > k'[gL]$, eq 5 reduces to eq 6. The rate constant factor

$$k_b = k_{obsd}^{b}/[bOH]\ M^{-1} \quad (6)$$

due to all effects of complexation is k_a/k_b, whose values at constant [B] can be estimated through eq 7.

$$k_a/k_b = (k_{obsd}^{a}/k_{obsd}^{b})K_1[bOH] \quad (7)$$

Unfortunately, the acylation of H_2BCH_2OH (**6**) by $CH_3CH(CO_2Ar)NH_3ClO_4$ was too slow to measure in $CDCl_3$–0.1% DMF, but lower limits of k_{obsd}^{b} of 0.005×10^{-3} min^{-1} could have been detected under our reaction conditions for runs 15 and 16 of Table II. The k_a/k_b ratio of eq 7 was calculated to be 5.4×10^{10} through use of k_{obsd} values of runs 15 and 35 and the [bOH] value of run 15. Use of the k_{obsd} values of runs 16 and 37 and the [bOH] value of run 16 gave 1.2×10^{11}. Thus, $k_a/k_b \approx 10^{11}$ for the second-order rate constant ratio for acylation of $U(A'UCH_2)_2BCH_2OH$ (**5**) vs. its open-chain model compound, H_2BCH_2OH (**6**). Although this value is approximate and subject to uncertainties, there is no doubt that the rate constant enhancement factor associated with all the effects of complexation are very large indeed.

Perspective is gained on this large rate constant enhancement factor by exploring the conditions under which equally large rate acceleration could be observed.[26a] The overall rate of the acylation of hOH by gL is represented by eq 8. The concentration of

$$V_a = kK_1K_2[B][gL]_a[hOH] \quad (8)$$

uncomplexed guest, $[gL]_a$, is expressed in eq 9 as a function of

$$[gL]_a = [gL]_{Ta} - [gL\cdot hOH] \quad (9)$$

$[gL]_{Ta}$, the concentration of total guest used. Substitution of eq 10 into eq 9 gives eq 11. Substitution of eq 11 into eq 8 gives

$$[gL\cdot hOH] = K_1[gL]_a[hOH] \quad (10)$$

$$[gL]_a = [gL]_{Ta}/(1 + K_1[hOH]) \quad (11)$$

eq 12, and eq 1 into eq 12 gives eq 13.

$$V_a = kK_1K_2[B][gL]_{Ta}[hOH]/(1 + K_1[hOH]) \quad (12)$$

$$V_a = k_{obs}^{a}K_1[gL]_{Ta}[hOH]/(1 + K_1[hOH]) \quad (13)$$

The rate of acylation of bOH by $[gL]_b$ is represented by eq 14.

$$V_b = k'K'[B][gL]_b[bOH] \quad (14)$$

The observed second-order rate constant (k_2^{b}) for this reaction is expressed in eq 15. Substitution of eq 15 into eq 14 gives eq 16.

$$k_2^{b} = k'K'[B] \quad (15)$$

$$V_b = k_2^{b}[gL]_b[bOH] \quad (16)$$

Dividing eq 16 by eq 13 gives eq 17, which provides a ratio of rates which is the inverse of the rate acceleration. Under the conditions of our experiments, $[bOH] \simeq [bOH]_t$, $[hOH] \simeq [hOH]_T$, and $[gL]_b = [gL]_{Tb}$. If *rate acceleration* is defined as the ratio of rates under conditions where the starting concentrations of reagents are equal, then eq 17 reduces to eq 18.

$$\frac{V_b}{V_a} = \left(\frac{V_a}{V_b}\right)^{-1} = \left(\frac{k_2^{b}}{k_{obsd}^{a}}\right)\left(\frac{[gL]_b}{[gL]_{Ta}}\right)\left(\frac{[bOH]}{[hOH]}\right)\left(\frac{1}{K_1}\right) + \left(\frac{k_2^{b}}{k_{obsd}^{a}}\right)\left(\frac{[gL]_b}{[gL]_{Ta}}\right)[bOH] \quad (17)$$

$$V_b/V_a = (V_a/V_b)^{-1} = (k_2^{b}/k_{obsd}^{a})(1/K_1) + (k_2^{b}/k_{obsd}^{a})[bOH] \quad (18)$$

Equation 18 has two terms. The first term predominates when $(1/K_1) > [bOH]$ and the second term when $[bOH] > (1/K_1)$. In the limit when $(1/K_1) \gg [bOH]$, eq 18, reduces to eq 19. In

$$V_a/V_b = (k_{obsd}^{a}/k_2^{b})K_1 \quad (19)$$

the limit when $[bOH] \gg (1/K_1)$, eq 18 reduces to eq 20.

$$V_a/V_b = (k_{obsd}^{a}/k_2^{b})(1/[bOH])\ M^{-1} \quad (20)$$

Because of the very large value of K_1, it was practical only to conduct experiments under the limiting conditions of eq 20 in which essentially all guest was complexed. Under these conditions, the ratio of rates that provides the *rate acceleration* is a function of the concentration of bOH. Run 37 of Table II was made at our lowest concentration of [gL] = 0.007 M and provided a value for $k_{obsd}^{a} = 19 \times 10^{-3}$ min^{-1}. Run 16 gave a value of $k_2^{a} = < 0.15 \times 10^{-3}$ min^{-1} M^{-1} for the reaction of bOH with gL. If [bOH] is set equal to 0.007 for a model reaction involving equal amounts of bOH and gL and if eq 20 is applied, a value of $V_a/V_b > 1.8 \times 10^{5}$ M^{-1} is calculated for the largest *rate acceleration* calculable from our data. This number is about 10^6 lower than the 10^{11} *rate constant enhancement factor* calculated from eq 7. In effect, the 10^{11} *rate constant enhancement factor* is an extrapolation of the rate acceleration to a low enough concentration of bOH relative to $1/K_1$, so that the limiting conditions of eq 19 apply. Under these conditions, V_a/V_b becomes dimensionless and is a real factor based only on the free energies of uncomplexed starting states and those of the rate-limiting transition states.

The high magnitude of this 10^{11} value provides an impression of the importance of collection and orientation[26b] by complexation to rate constant enhancement in a medium such as $CDCl_3$. If the crystal structure of the complex $U(A'UCH_2)_2A'\cdot(CH_3)_3CNH_3ClO_4$ (**21**) is used to extrapolate by means of molecular models to the structure of the transition state for reaction of $U(A'UCH_2)_2BCH_2O^{-}\cdot CH_3CH(CO_2R)NH_3^{+}$, the CH_2O^{-} of the host is beautifully complementary to the C=O group of the guest. We visualize the transition state as a complex held together and stabilized by $N^{+}(H\cdots O{=}C)_3$ and $(CH_2O\cdots C{=}O)^{-}$ as the binding sites. The transition state for reaction of ester with H_2BCH_2OH is held together only be $(CH_2O\cdots C{=}O)^{-}$ as the binding site. The extra stabilization associated with the extra binding sites in the former transition state lowers its free energy enough to provide the factor of 10^{11} in rate constant.

The interesting question arises as to the relative contributions of the effects of collection and of orientation to this large enhancement. The value $K_1 \sim 10^9$ *provides no measure* of the contribution that *collection* makes to the rate constant factor of 10^{11}. The K_1 value is high because of strong enthalpic driving forces that stabilize both host and guest by complexation and that changes their electronic characters accordingly. For example, the acidity of the NH_3^{+} group of the guest decreases by several powers of 10 upon complexation, which by a reduced inductive effect must reduce the electrophilicity of the carbonyl group of the ester. The pK_a of the CH_2OH group of the host is undoubtedly modified by complex formation, but it is impossible to guess the outcome of opposing electronic and steric effects. The fact that the presence of an equal molar amount of $NaClO_4$ in run 40 reduced k_{obsd}^{a} by a factor of about 50 from that in runs 35 and 37 simply had the effect of reducing the concentration of free host. It is highly improbable that the mechanism of reaction was changed to one in which the Na^{+} complex was acylated in a bimolecular reaction with $CH_3CH(CO_2Ar)NH_3^{+}$. Unfortunately, the insolubility of sodium salts in $CDCl_3$ prevented us from increasing the concentration of $NaClO_4$ beyond that of the host present. The solvation free energies of uncomplexed host and guest on the one hand and

(26) (a) We warmly thank Dr. Steve J. McLain for suggesting the treatment involving eq 8–20. (b) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969; pp 1–242.

of complex on the other are entirely different, as are the steric effects associated with complexed vs. noncomplexed acylations. All these effects make H_2BCH_2OH and $CH_3CH(CO_2Ar)NH_3^+$ and the attendant transition state poor models for U-$(A'UCH_2)_2BCH_2OH{\cdot}CH_3CH(CO_2Ar)NH_3$ and its attendant transition state for transacylation. We conclude that K_1 integrates collecting and orienting effects and that it is impossible to dissect our 10^{11} rate constant enhancement ratio into contributions from each of these two factors.

Encouragement to make this study was derived from the success of our first use of a thiol chorand[27] as a host for transacylation of amino ester salts and by the subsequent findings by others that two other thiol chorand hosts behaved similarly.[28] Current efforts are being made to synthesize compounds such as **1** and **2** in which provision is made for intramolecular proton transfers within the complex.

The title of this paper requires comment. Our transacylase partial mimic falls far short of what transacylases are able to do in the following respects. (1) Enzymes make use of aqueous solutions of reactants, whereas ours do not. (2) Enzymes are turnover catalysts, whereas ours are not. (3) Although our rate constant factor is close to rate constant factors for enzymes, our absolute rates of transacylation are remarkable only as compared to a noncomplexing model compound in $CHCl_3$ as medium, whereas enzymes provide remarkable absolute rates. (4) Although our system undoubtedly possesses structural recognition in transacylation, the degrees of structure recognition found with transacylases are of a much higher order. We claim to have demonstrated that molecular design and synthesis of hosts highly preorganized to be complementary to guest reactants can, through tailored complexation, produce enormous rate constant enhancements in chemical reactions.

Experimental Section

General. Solvents were fractionally distilled before use, Et_2O and tetrahydrofuran (THF) from sodium benzophenone ketyl, *t*-BuOH and CH_2Cl_2 from CaH_2, and C_6H_6 from $LiAlH_4$. Alkyllithium reagents were employed as dispersions in hydrocarbon solvents. Organic solutions obtained during isolation of products were dried with $MgSO_4$ unless otherwise indicated. Silica gel chromatography was performed with E. Merck silica gel, particle size 0.063–0.200 mm (gravity columns) or 0.040–0.063 mm (medium-pressure columns). The medium-pressure scrubber column was 250 × 25 mm (inner diameter). Silica gel TLC was performed on E. Merck glass plates, 0.5 or 1.0 mm thick. Alumina for column chromatography was MCB, 80–325 mesh. Alumina TLC plates were E. Merck plastic sheets. Columns for GPC (high pressure) were 20 ft by 0.375 in. (outer diameter) packed with either 100-Å Styragel (Waters) or SX-12 Bio Beads (Bio-Rad, 200–400 mesh). Elution of GPC columns was carried out with doubly distilled CH_2Cl_2. Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. Reported R_f values are approximate and are given mainly for comparisons of starting materials and the various products. Solvents for R_f values are always v/v. All new compounds gave elemental analyses within 0.30% of theory. Analytical samples were dried at 140 °C whenever practical. Mass spectra were taken on an AE-1 model MS-9 double-focusing spectrometer interfaced by Kratos to a Data General Nova 3. Data were obtained at 16 eV unless otherwise indicated, and at the indicated probe temperature. Infrared spectra were obtained on a Perkin-Elmer Model 297 instrument in the indicated media. Peak positions are in reciprocal centimeters. Nuclear magnetic resonance spectra were recorded on a 200-MHz Bruker WP-200 spectrometer unless specified otherwise. Chemical shifts are reported in parts per million downfield from internal $(CH_3)_4Si$. Coupling constants (J values) are given in hertz. Assignments of coupled protons were confirmed by homonuclear decoupling.

2-Methoxy-3-nitro-5-methylaniline. To a refluxing solution of 2,6-dinitro-4-methylanisole[7] (56.5 g, 0.266 mol) in 550 mL of methanol was added over a period of 0.5 h 250 mL of a 22% solution of ammonium sulfide.[8] The black solution was refluxed for an additional 10 min and poured into 1.5 L of ice water. The orange solid that separated after 2 h was collected, washed well with water, and air dried. This material was dissolved in CH_2Cl_2, filtered from an insoluble yellow solid, and chromatographed on a 12-cm diameter by 6-in. length silica gel column (medium pressure, 40 mL per min flow rate). Product (pure by TLC) was eluted with 3 L of CH_2Cl_2, weight 26.8 g (55%). This material was used directly in the next step. Recrystallization of a sample from hot cyclohexane gave thin orange needles: mp 55–56 °C; ^{1}H NMR ($CDCl_3$) δ 2.269 (s, 3 H, Ar CH_3), 3.868 (s, 3 H, OCH_3), 3.95 (br s, 2 H, H_2N), 6.763 (m, 1 H, ArH), 7.009 (m, 1 H, Ar H); MS (70 eV, 190 °C), *m/e* 182 (M^+, 100). Anal. Calcd for $C_8H_{10}N_2O_3$: C, H, N.

1,3-Bis(2-methoxy-3-nitro-5-methylphenyl)urea (12). To a refluxing solution of 73.41 g (0.4030 mol) of 2-methoxy-3-nitro-5-methylaniline, 45.4 mL of pyridine, and 600 mL of THF was added dropwise a solution of 20.9 g (0.212 mol) of phosgene in 300 mL of THF. After the addition (6 h), reflux was continued for 24 h. The cooled reaction mixture was filtered, and the filtrate discarded. The filter cake was washed well with ether and swirled with 1 L of methanol (making certain that the solid was finely divided), and the mixture was filtered into a fresh flask. The filter cake was washed with methanol and dried under vacuum. Water was added to the combined methanolic filtrates causing more product to separate, which was collected and washed well with water, methanol, and then ether. This material was dried and added to the larger amount of product to give 70.4 g (90%) of **1**, pure by TLC (10% ether/dichloromethane, R_f 0.7) and ^{1}H NMR analysis. A small sample was recrystallized from 2-butanol: ^{1}H NMR ($CDCl_3$) δ 2.397 (s, 6 H, Ar CH_3), 3.925 (s, 6 H, OCH_3), 7.393 (m, 4 H, Ar H), 8.271 (s, 2 H, Ar NH); MS (70 eV, 240 °C), *m/e* 390, (M^+, 9). Anal. Calcd for $C_{17}H_{18}N_4O_7$: C, H, N.

1,3-Bis(2-methoxy-3-nitro-5-methylphenyl)tetrahydro-2(1*H*)-pyrimidinone (13). To a stirred mixture of 60.03 g (0.1538 mol) of urea **12**, 3 L of benzene, and a solution of 550 g of NaOH in 550 mL of water was added 101 g (0.50 mol) of 1,3-dibromopropane and 9.72 g of benzyltriethylammonium bromide. The flask, fitted with a reflux condenser, was heated to 46 °C, and the mixture was vigorously stirred for 4 days. The reaction was monitored by TLC; **12** gave R_f 0.3 and **13** R_f 0.25, 5% ether/CH_2Cl_2 on silica gel. The reaction mixture was cooled to 25 °C, and filtered through a 2 in. thick Celite pad on a sintered-glass funnel, and the pad plus product was washed with 100 mL of benzene. The filtrate layers were separated, and the water layer was diluted with 1 L of water, which caused it to heat. This aqueous solution was cooled and extracted with three 100-mL portions of ethyl acetate, and the extracts were added to the initial benzene layer. The solution was dried ($MgSO_4$), filtered, and evaporated under vacuum to give a viscous oil. This oil was extracted with four 100-mL portions of pentane (swirling and decanting) to remove the excess 1,3-dibromopropane. The oil was then sonicated with 200 mL of pentane for 4 min and the pentane layer again decanted. The remaining oil was dissolved in 100 mL of CH_2Cl_2, and 400 mL of ether was added to the solution, which precipitated product. This material was collected and washed well with ether and dried to give 4.16 g (6.3%) of **13**. The main portion of the product was recovered by washing the Celite pad with 300 mL of CH_2Cl_2. The filtrate was washed with 100 mL of water and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residual oil was dissolved in 60 mL of CH_2Cl_2, and to the solution was added 400 mL of ether. The product that separated after 1 day was collected, washed with ether, and dried to give 41.28 g (62.7%) of additional **13**, total yield 45.4 g (70%), pure enough for use in the next step. A sample was recrystallized from CH_2Cl_2–ether: mp 238.5–240 °C; ^{1}H NMR ($CDCl_3$) δ 2.3–2.4 (m, 2 H, $NCH_2CH_2CH_2N$), 2.364 (s, 6 H, Ar CH_3), 3.7–3.85 (m, 4 H, NCH_2), 3.938 (s, 6 H, OCH_3), 7.366 (d, J = 1.9 Hz, 2 H, Ar H), 7.563 (d, J = 1.9 Hz, 2 H, Ar H); MS (70 eV, 220 °C), *m/e* 399 (M^+ – 31, 100). Anal. Calcd for $C_{20}H_{22}N_4O_7$: C, H, N.

1,3-Bis(2-methoxy-3-amino-5-methylphenyl)tetrahydro-2(1H)-pyrimidinone (14). A vigorously stirred mixture of 10.0 g (0.0233 mol) of bis(nitro) urea **13**, 20 g of iron powder, 125 mL of ethanol, and 125 mL of water[9] was heated to just below reflux temperature, and 3 mL of concentrated hydrochloric acid was added. The mixture was refluxed for 3 h. The hot reaction mixture was then filtered quickly through a 2-in. cake of Celite, the cake was washed well with 200 mL of *hot* ethanol, and the filtrate was evaporated to dryness yielding a white solid. This solid was dissolved in 300 mL of CH_2Cl_2, and the solution was washed with 200 mL of brine. The aqueous layer was extracted with two 50-mL portions of CH_2Cl_2, and the combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, evaporated to dryness, and placed under high vacuum overnight to give 8.40 g (97.6%) of **14**, pure by ^{1}H NMR and TLC (10% MeOH/CH_2Cl_2, R_f 0.3). A sample of this diamine was recrystallized from a small amount of CH_2Cl_2 at −20 °C to give a white solid: mp 241–242 °C; ^{1}H NMR ($CDCl_3$) δ 2.1–2.3 (m, 2 H, $NCH_2CH_2CH_2N$), 2.191 (s, 6 H, Ar CH_3), 3.3–3.9 (bs, NH), 3.696 (*t*, J^4 = 5.6 Hz, 4 H, NCH_2), 3.818 (s, 6 H, OCH_3), 6.475 (s, 2 H, Ar H), 6.517 (s, 2 H, Ar

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H); MS (70 eV, 230 °C), *m/e* 370 (M^+, 12), 339 ($M^+ - 31$, 100). Anal. Calcd for $C_{20}H_{26}N_4O_3$: C, H, N.

1,3-Bis[2-methoxy-3-(1-tetrahydro-2(3*H*)-pyrimidinonyl)-5-methylphenyl]tetrahydro-2(1*H*)-pyrimidinone (15). To a stirred mixture of 8.40 g (0.0226 mol) of diamine **14** and 50 mL of CH_2Cl_2 was added 10.3 g of 3-chloropropaneisocyanate.[10] The mixture was warmed slightly at first and over a 1.5-h period became cloudy as the diamine dissolved and was replaced by two immiscible liquid phases. After an additional hour the mixture became homogeneous. Stirring was continued for 47 h, and 250 mL of ether was then added causing the product to separate. After scraping the sides of the flask with a spatula to ensure the powdery material was entirely mobile, the mixture was filtered and the filter cake was washed with 200 mL of ether. This product was dried under high vacuum to give 13.52 g of the intermediate dichloride–tris(urea) as a yellow-white powder, essentially one spot on TLC (10% MeOH/CH_2Cl_2, silica gel). This material was suspended in 800 mL of dry, distilled *tert*-butyl alcohol (CaH_2). Dry potassium *tert*-butoxide (9.6 g) was added with stirring. The resulting mixture was stirred for 15 h at 32 °C, and the *tert*-butyl alcohol was evaporated under vacuum. The residue was dissolved in 300 mL of CH_2Cl_2, and the solution was washed with 100 mL of water (the mixture was acidified with 6 N hydrochloric acid to pH 0 to break an emulsion). The aqueous layer was extracted with two 50-mL portions of CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to yield a viscous amber oil. Dichloromethane (50 mL) was added, followed by 300 mL of THF. The yellow solution was evaporated at 30 mm of pressure to approximately a 100-mL volume. A small amount of a dark oil separated. The solution was decanted into another flask (the dark oil was discarded), an additional 200 mL of THF was added, and the solution was again evaporated. The product began to separate as a beige powder. After standing for 1 day, the precipitated material was collected, and the cake was washed well with 125 mL of THF to give after drying under high vacuum 7.35 g (61.8%) of **15**, pure by TLC (12% MeOH/CH_2Cl_2, silica gel) and ^1H NMR. A sample was twice recrystallized from acetonitrile to give a white solid, mp 293–300 °C dec. The mother liquor was evaporated to dryness to give a white foam. Additional product was obtained by chromatographing the foam on silica gel at medium pressure with 10–15% MeOH/CH_2Cl_2. Compound **15** tails badly on silica gel; ^1H NMR ($CDCl_3$) δ 1.993–2.108 (m, 4 H, $NCH_2CH_2CH_2N$), 2.201–2.3 (m, 2 H, $NCH_2CH_2CH_2N$), 2.262 (s, 6 H, Ar CH_3), 3.413 (t, J^4 = 5.6 Hz, $HNCH_2$), 3.555 (t, J^4 = 5.37 Hz, 4 H, Ar $NCH_2CH_2CH_2NH$), 3.726 (t, J^4 = 5.6 Hz, 4 H, $ArNCH_2CH_2CH_2NAr$), 3.852 (s, 6 H, OCH_3), 5.028 (br s, 2 H, HN), 6.955 (d, J_{meta} = 1.5 Hz, 2 H, Ar H), 7.034 (d, M_{meta} = 1.9 Hz, 2 H, Ar H); MS (70 eV, 230 °C), *m/e* 536 (M^+, 1), 505 ($M^+ - 31$, 100). Anal. Calcd for $C_{28}H_{36}N_6O_5$: C, H, N.

33,35,37-Trioxo-34,36,38-trimethoxy-4,15,26-trimethyl-1,7,11,19,23,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{13,17}.1^{19,23}.1^{24,28}]octaconta-34(2),3,5,36(13),14,16,38(24),25,27-nonaene (3). To a stirred mixture of 1.4 g (2.61 mmol) of tris(urea) **15** and 100 mL of THF was added 1.0 g of 50% NaH (washed first with pentane). The mixture was heated to reflux under argon for 3 h, cooled to 25 °C, and 0.80 g (2.6 mmol) of 2,6-(bromomethyl)-4-methylanisole[11] was added. The mixture was stirred for 26 h, 5 mL of water was added, and the THF was removed under reduced pressure. The residue was shaken with CH_2Cl_2 and water (acidified with concentrated hydrochloric acid to break an emulsion). The water layer was washed with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was mixed with a small amount of acetonitrile and filtered to give a 1.6883 g of crude **3**·NaCl as an oily solid. Gel permeation chromatography of this material in CH_2Cl_2 gave a fraction collected from 155 to 182 mL retention volume. The fraction was evaporated under reduced pressure, and the residue was dissolved in 30 mL of $CHCl_3$. The cycle was decomplexed by washing this solution with two 500-mL portions of conductivity water. The wet organic layer was dried by adding benzene and evaporating the solvent under reduced pressure to give crude **3** as an oil. This material was purified by a complexation–purification–decomplexation procedure as follows. To a solution of this oil in 3 mL of acetonitrile was added 0.23 g of *tert*-butylammonium perchlorate. Tetrahydrofuran (50 mL) was added, the solution was evaporated under reduced pressure to a small volume (3 mL), and 50 mL more of THF was added. The solvents were completely removed under reduced pressure, and 50 mL of THF was again added. The complex crystallized; the crystals were filtered and washed with THF. The mother liquors were evaporated, and a second crop of complex was recovered. The combined crops gave 0.4877 g (22%) of **3**·*t*-$BuNH_3ClO_4$. This material was dissolved in 25 mL of methanol, the solution was heated to reflux, and 75 mL of conductivity water was added dropwise. (The mixture is usually homogeneous at this point. If the material precipitates too quickly, it will include complex. If the solution is cloudy, methanol should be added until it is clear.) After 24 h the mixture had become slightly cloudy. The condenser was removed, and the solvent was allowed to evaporate slowly until **3** precipitated. This product was collected on a fine sintered-glass funnel, washed with water, and dried (100 °C, 0.01 mm, 24 h) to give 0.2112 g (11.2%) of **3**, mp 220–240 °C. For analysis and K_a determination, a portion of the product was recrystallized from CH_2Cl_2–EtOAc and dried (200 °C, 0.01 mm, 24 h): mp 225–236 °C (slight yellowing); ^1H NMR ($CDCl_3$) δ 2.040–2.364 (m, 15 H, Ar, CH_3, $NCH_2CH_2CH_2N$), 2.979–4.138 (m, 23 H, ArO CH_3, $NCH_2CH_2CH_2N$, Ar CH_2N), 4.816, 4.884 ($^1/_2$AB, *J* = 13.7 Hz, 0.6 H, $ArCH_2N$), 4.928, 4.997 ($^1/_2$AB, *J* = 13.7 Hz, 0.3 H, Ar CH_2N), 5.250, 5.328 ($^1/_2$AB, *J* = 15.6 Hz, 0.6 H, Ar CH_2N), 5.438, 5.516 ($^1/_2$AB, *J* = 15.6 Hz, 0.6 H, Ar CH_2N), 6.746–7.390 (m, 6 H, Ar H); MS (70 eV, 230 °C), *m/e* 682 (M^+, 7), 651 ($M^+ - 31$, 100). Anal. Calcd for $C_{38}H_{46}N_6O_6$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.71; H, 6.80; N, 12.17.

The complex **3**·LiPic was prepared by mixing equal molar amounts of **3** and lithium picrate in $CDCl_3$: ^1H NMR ($CDCl_3$) δ 1.952–2.345 (m, 6 H, $NCH_2CH_2CH_2N$), 2.257 (s, 6 H, Ar CH_3), 2.345 (s, 3 H, Ar CH_3), 3.455 (s, 3 H, Ar OCH_3), 3.545–4.067 (m, 14 H, $NCH_2CH_2CH_2N$, Ar CH_2N), 3.655 (s, 6 H, Ar OCH_3), 5.204, 5.285 ($^1/_2$AB, *J* = 10.7 Hz, 2 H, Ar CH_2N), 6.866 (s, 2 H, Ar H), 6.890 (s, 2 H, Ar H), 7.080 (s, 2 H, Ar H), 8.764 (s, 2 H, Pic).

The complex **3**·*t*-$BuNH_3ClO_4$ was prepared by mixing equal molar amounts of **3** and *t*-$BuNH_3ClO_4$ in CH_2Cl_2 and crystallizing: ^1H NMR ($CDCl_3$) δ 0.762 (s, 9 H, *t*-Bu), 2.295–2.362 (m, 6 H, $NCH_2CH_2CH_2N$), 2.234 (s, 6 H, Ar CH_3), 2.398 (s, 3 H, Ar CH_3), 3.552 (s, 3 H, Ar OCH_3), 3.579 (s, 6 H, Ar OCH_3), 3.619–3.889 (m, 10 H, $NCH_2CH_2CH_2N$), 4.099–4.160 (m, 2 H, $NCH_2CH_2CH_2N$), 5.315, 6.391($^1/_2$AB, *J* = 15 Hz, 2 H, Ar CH_2N), 6.726 (br s, 3 H, $^+NH_3$), 6.88 (s, 4 H, Ar H), 7.183 (s, 2 H, Ar H).

The complex **3**·$MeNH_3ClO_4$ (two isomers, 3:1 ratio) was prepared by adding equal molar quantities of **3** and $MeNH_3ClO_4$ in $CDCl_3$: ^1H NMR ($CDCl_3$) δ 2.069 (s, 3 H, $CH_3{}^+NH_3$), 2.249 (s, 6 H, Ar CH_3), 2.249–2.415 (m, 6 H, $NCH_2CH_2CH_2N$), 2.415 (s, 3 H, $ArCH_3$), 3.067–4.138 (m, 23 H, Ar OCH_3, $NCH_2CH_2CH_2N$, Ar CH_2N), 5.166, 5.242 ($^1/_2$AB, *J* = 15.1 Hz, 0.57 H, Ar CH_2N), 5.361, 5.439 ($^1/_2$AB, *J* = 15. 6 Hz, 1.43 H, Ar CH_2N), 6.252 (br s), 6.614 (br s, 3 H, $^+NH_3$), 6.873 (s, 2 H, Ar H), 6.907 (s, 2 H, Ar H), 7.105 (s, 1.5 H, Ar H), 7.245 s, 0.5 H, Ar H).

2-Fluoroisophthaloyl Dichloride. A mixture of 47.10 g (255.80 mmol) of 2-fluoroisophthalic acid,[29] 1 mL of dry DMF, 250 mL of benzene, and 76 mL (1.06mol) of thionyl chloride was refluxed for 5 h. The resulting solution was concentrated under reduced pressure leaving a solid, which was recrystallized from hexane to give product as thick, white crystals (54.56 g, 246.86 mmol, 97%): mp 62.5–64 °C; ^1H NMR ($CDCl_3$) δ 7.48 (d of t, 1 H, J_o = 8.0 Hz, J_{H-F} = 1.0 Hz), 8.37 (d of d, 2 H, J_o = 8.0, J_{H-F} = 6.5 Hz); MS, *m/e* 220 (M^+, 1), 187 (40), 185 (100), 129 (28), 122 (30), 94 (26), 75 (18). Anal. Calcd for $C_8H_3Cl_2FO_2$: C, H, Cl.

***N,N'*-Bis(2-hydroxy-1,1-dimethylethyl)-2-fluoro-1,3-benzenedicarboxamide.** To 28.11 g (3.153 mmol) of 2-amino-2-methyl-1-propanol in 30 mL of CH_2Cl_2 stirred at 0 °C was added 17.39 g (78.68 mmol) of 2-fluoroisophthaloyl dichloride as a solid slowly over 30 min. The thick, white mass was then stirred 15 min at 25 °C and filtered. The solid was washed well with distilled water and dried over P_2O_5 in vacuo to provide the bis(amide) as a white solid (20.7 g, 63.4 mmol, 81%), mp 168–171 °C. An analytical sample was recrystallized from water to give white flakes: mp 171.5–172.5 °C; ^1H NMR ($CDCl_3$) δ, 1.44 (s, 12 H, CH_3), 3.71 (s, 4 H, CH_2), 6.56 (br d, 2 H, NH), 7.29 (t, 1 H, Ar H, *J* = 7.6 Hz), 8.01 (t, 2 H, Ar H, *J* = 7.6 Hz); MS, *m/e* 326 (M^+) (absent). Anal. Calcd for $C_{16}H_{23}FN_2O_4$: C, H, N.

1,3-Bis(4,4-dimethyl-2-oxazolin-2-yl)-2-fluorobenzene (17). To a suspension of 10.78 g (33.03 mmol) of the above bisamide in 225 mL of CH_2Cl_2 was added 1.5 mL of dry DMF. This mixture was cooled to 0 °C, and 14.3 mL (199 mmol) of thionyl chloride was added slowly. The mixture gradually changed into a colorless solution. After stirring for 1 h at 0 °C, the now milky suspension was stirred for an additional 44 h at 25 °C. The reaction mixture was partitioned between 200 mL of 10% aqueous NaOH and 250 mL of CH_2Cl_2. The aqueous layer was extracted with 200 mL of CH_2Cl_2, and the combined organic layers were washed with 200 mL of water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was flash chromatographed (SiO_2, 12 × 10 cm, 1/1 ether/hexane → ether) to give pure oxazoline, **17**, as a colorless oil, which slowly solidified upon standing at room temperature to give a waxy solid (7.77 g, 26.76 mmol, 81%). An analytical sample was prepared by recrystallization from CH_2Cl_2–hexane to give white crystals: mp 60.5–64 °C; ^1H NMR ($CDCl_3$) δ 1.39 (s, 12 H, CH_3), 4.10 (s, 4 H, CH_2), 7.20 (t, 1 H, Ar H_5, *J* = 7.7 Hz), 7.94 (d of d, 2 H, Ar $H_{4,6}$, *J* = 7.7, J_{H-F} = 6.5 Hz); MS, *m/e* 290 (M^+, 6), 275 (100). Anal. Calcd for $C_{16}H_{19}FN_2O_2$: C, H, N, F.

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2,2′-(3′-Methyl[1,1′-biphenyl]-2,6-diyl)bis(4,5-dihydro-4,4-dimethyloxazole) (18). Resublimed magnesium turnings (720 mg, 30 mmol) were stirred in 60 mL of THF under N_2. A few drops of 3-bromotoluene dissolved in 1 mL of THF were reacted in a test tube with magnesium until the mixture self-heated to reflux. This mixture was added to the stirred Mg/THF followed by 4.6 g (27 mmol) of additional 3-bromotoluene. The mixture was stirred for 2.5 h just above ambient temperature (due to self-heating) and for 0.5 h nearly at reflux. The mixture was cooled to 25 °C, and transferred by cannula into a stirred solution of 1,3-bis(4,4-dimethyl-2-oxazolin-2-yl)-2-fluorobenzene (**17**) (2.6 g, 9.0 mmol) in 100 mL of THF. A yellow-orange color developed over time. The half-time for biaryl formation was about 15 min, as evidenced by TLC (R_f of fluoroaryl 0.28 R_f of biaryl 0.21, EtOAc/silica gel). The mixture was stirred for 18 h, 100 mL of dilute aqueous NaOH was added, and the THF was evaporated. The residue was mixed with 250 mL of ether, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on 60 g of silica gel, and product was eluted with EtOAc. Fractions of 15 mL were collected. Fractions 13–53 gave on evaporation 3.1 g (96%) of **18** as a yellow oil, which became a soft white solid on standing: ^{1}H NMR ($CDCl_3$) δ 1.21 (s, $C(CH_3)_2$, 12 H), 2.34 (s, Ar CH_3, 3 H), 3.70 (s, CH_2, 4 H), 7.1–7.3 (m, Ar H, 4 H), 7.39 (A of AB_2, J = 8 Hz, Ar H, 1 H), 7.72 (B_2 of AB_2, J = 8 Hz, Ar H, 1 H); MS (190 °C), m/e 362 (M^+, 30). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, H, N.

3′-Methyl[1,1′-biphenyl]-2,6-dicarboxylic Acid (19). Compound **18** (3.1 g, 8.6 mmol) and 11 mL (177 mmol) of CH_3I were dissolved in 15 mL of nitromethane, with stirring and heating at 40 °C. After 2.5 h, some solid had precipitated, and 10 mL of additional CH_3NO_2 was added. After one additional hour, 11 mL of additional CH_3I was added. After an additional hour at 40 °C, the solvents were evaporated at reduced pressure, and the residue was dissolved in 40 mL of toluene and reconcentrated. A solution of 8 g NaOH in 50 mL of H_2O was added, and the mixture was heated for 24 h at reflux. The solution was cooled, diluted to 100 mL with water, and washed with 100 mL of ether. The aqueous layer was then acidified with concentrated aqueous HCl and extracted with 200 mL of ether, excluding an emulsion that formed between the layers. This ether extract was washed with a solution of $Na_2S_2O_3$ and HCl in water to remove I_2, dried, filtered, and concentrated. Crystallization of the residue from 5 mL of ether/30 mL of benzene with removal of the ether, followed by addition of hexane to the cloud point, gave 1.6 g (73%) of **19** as white crystals, mp 192–195 °C, of adequate purity for further reaction. A sample was recrystallized from MeOH/H_2O, yielding white plates: mp 214–215 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 2.32 (s, CH_3, 3 H), 7.0–7.2 (m, Ar H, 4 H), 7.56 (A of AB_2, J = 8 Hz, Ar H, 1 H), 7.87 (B_2 of AB_2, J = 8 Hz, Ar H, 2 H); MS (210 °C), m/e, 256 (M^+ 100). Anal. Calcd for $C_{15}H_{12}O_4$: C, H.

Dimethyl 3′-(Methoxymethyl)[1,1′-biphenyl]-2,6-dicarboxylate (20). Biaryl diacid **19** (1.5 g, 5.9 mmol) was dissolved in 20 mL of ether. The resulting solution was cooled to 0 °C and titrated with a diazomethane/ether solution prepared from 6 g of *N*-methyl-*N*-nitrosourea in 60 mL of ether. When gas evolution ceased and a yellow color persisted in the biaryl solution, the CH_2N_2 addition was halted and formic acid was added dropwise to exactly titrate the excess CH_2N_2, until the yellow color faded. The solution was dried, filtered, and concentrated to give the dimethyl ester of **19**, 1.6 g (96%), as a white crystalline solid: mp 71–73 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.4 (s, Ar CH_3, 3 H), 3.6 (s, OCH_3, 6 H), 7.0–8.0 (m, Ar H, 7 H). This diester (1.55 g, 5.46 mmol) was dissolved in 40 mL of CCl_4. To this solution was added 1.02 g (5.73 mmol) of *N*-bromosuccinimide. The mixture was stirred and irradiated with a 250-W infrared lamp. An initiator, azobisisobutyronitrile, was added in three 30-mg portions over 10 min. After 30 min at reflux, the mixture was cooled to 0 °C, filtered, and concentrated to give 2 g of yellow oil, which was found to be predominantly the bromomethyl biaryl diester: R_f 0.4 (CH_2Cl_2, silica gel); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.5 (s, OCH_3, 6 H), 4.5 (s, CH_2Br, 2 H), 7.0–8.0 (m, Ar H, 7 H). This oil was dissolved in 20 mL of dry methanol, and NaH (275 mg, 5.7 mmol as a 50% dispersion in oil) was cautiously added. After 6 h, the excess $NaOCH_3$ was neutralized with 50 mg of $NaHCO_3$, the MeOH was evaporated, and the residue was partitioned between 100 mL of ether and 50 mL of water. The organic layer was dried, filtered, and concentrated to 1.4 g, and the residue was chromatographed on 50 g of silica gel. A forerun of 200 mL of CH_2Cl_2 and then 160 mL of 5% ether/95% CH_2Cl_2 was eluted, to give 180 mg (12%) of nonmethoxylated diester. Elution with 300 mL of 5–20% ether/CH_2Cl_2 gave 920 mg (52% from **19**) of product **20** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 3.36 (s, OCH_3, 3 H), 3.55 (s, $COOCH_3$, 6 H), 4.48 (s, CH_2, 2 H), 7.1–7.4 (m, Ar H, 4 H), 7.48 (A of AB_2, J = 8 Hz, Ar H, 1 H), 7.88 (B_2 of AB_2, J = 8 Hz, Ar H, 2 H); MS (160 °C), m/e 314 (M^+, 100). Anal. Calcd for $C_{18}H_{18}O_5$: C, H.

2,6-Bis(bromomethyl)-3′-(methoxymethyl)-1,1′-biphenyl (16). A mixture of $LiAlH_4$ (330 mg, 9.5 mmol) in 100 mL of ether was stirred and cooled to 0 °C. Diester **20** (920 mg, 2.9 mmol) was added as a solution in 20 mL of ether. After 30 min, the excess hydride was quenched with 2.5 mL of EtOAc, 2.5 mL of concentrated aqueous NaOH, and 5 mL of H_2O. The mixture was dried with $MgSO_4$, and the organic solution was filtered and concentrated to give 670 mg (2.6 mmol, 89%) of the derived diol as a viscous oil: R_f 0.65 (EtOAc, silica gel); ^{1}H NMR (60 MHz) δ 2.2 (br t, J = 5 Hz, OH, 2 H), 3.3 (s, OCH_3, 3 H), 4.3 (br d, J = 5 Hz, CH_2O, 4 H), 4.4 (s, CH_2OC, 2 H), 7.0–7.4 (m, Ar H, 7 H). This diol was dissolved in 5 mL of CH_2Cl_2, and 100 mL of benzene was then added. Phosphorus tribromide (240 μL, 2.6 mmol) was added by syringe with stirring. After 90 min, the solution was poured into 100 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 50 mL of additional benzene, and the combined organic layers were washed with saturated aqueous NaCl, dried, filtered, and concentrated. The residue was chromatographed on 15 g of silica gel, eluting with CH_2Cl_2. Fractions of 6 mL were collected, and product was obtained from fractions 4–10. The yield was 670 mg (67%) of dibromide **16**, obtained as a colorless liquid which crystallized on standing: mp 52–53 °C; R_f 0.55 (CH_2Cl_2, silica gel): bp < 100 °C (0.1 torr); ^{1}H NMR ($CDCl_3$) δ 3.42 (s, OCH_3, 3 H), 4.21 (s, CH_2Br, 4 H), 4.54 (s, CH_2O, 2 H), 7.3–7.5 (m, Ar H, 7 H); MS (210 °C), m/e 384 (M^+, 17). Anal. Calcd for $C_{16}H_{16}Br_2O$: C, H, Br.

33,35,37-Trioxo-34,38-dimethoxy-4,26-dimethyl-36-[3-(methoxymethyl)phenyl]-1,7,11,19,23,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{13,17}.1^{19,23}.1^{24,28}]octaconta-34(2),3,5,36(13),14,16,38(24),25,27-nonaene (4). Tris(urea) **16** (936 mg, 1.74 mmol) was added as a powder to 600 mL of THF with stirring. The mixture was heated at reflux for 20 min under N_2. Sodium hydride (oil free, 400 mg, 17 mmol) was added, and the mixture was heated at reflux for 4 h. The suspension was allowed to cool slowly to 25 °C and then was further cooled to −78 °C. A solution of biaryl dibromide **16** (670 mg, 1.74 mmol) in 200 mL of dry THF was added by cannula to the stirred suspension, and the mixture was allowed to react over a 40-h period as the cooling bath slowly warmed to room temperature. Water was added to quench the excess NaH, and the THF was evaporated at reduced pressure. The residue was partitioned between 300 mL of CH_2Cl_2 and 150 mL of H_2O. The organic layer was dried, filtered, and concentrated, and the residue was chromatographed on a 100-Å gel permeation chromatography column. Most of the material was eluted in a sharp band, retention volume ~160 mL. Concentration of the eluate gave 1.14 g (61–76%, depending on the run) of a beige foam, which was largely the desired cycle as **4**·NaBr, R_f 0.25, compared to the starting tris(urea), R_f 0.1 (10% MeOH/90% CH_2Cl_2/silica gel): ^{1}H NMR ($CDCl_3$, when two signals are noted for a single group, the peak for the major conformer is listed first) δ 2.25 and 2.26 (s, Ar CH_3, 6 H), 2.4 (m, CCH_2C, 6 H), 3.40 and 3.32 (s, OCH_3, 3 H), 3.54, 3.61 and 3.51, 3.59 ($^1/_2$AB, J = 16 Hz, Ar CH_2N, 2 H), 3.7–4.0 (m, NCH_2C, 12 H), 3.81 (s, Ar OCH_3, 6 H), 4.44 and 4.36 (s, CH_2O, 2 H), 4.43, 4.49 and 4.44, 4.50 ($^1/_2$AB, J = 13 Hz, $ArCH_2N$, 2 H), 6.84 (s, Ar H, 2 H), 6.86 (s, Ar H, 2 H), 6.92 (s, Ar H, 1 H), 7.2–7.4 (m, Ar H, 3 H), 7.40 (d, A_2 of A_2B, J = 8 Hz, Ar H, 2 H), 7.66 (t, B of A_2B, J = 8 Hz, Ar H, 1 H). A portion of this material (300 mg) was dissolved in 20 mL of MeOH and 20 mL of deionized water. The solution was heated several hours at reflux, and then the condenser was removed, allowing solvent to slowly evaporate. Additional water was added to maintain a total volume of about 20 mL. When the boiling temperature reached 100 °C, the mixture was allowed to cool. A white powder (125 mg, 47%) was collected by filtration and was found to be the desired cycle, **4**, mp 200 °C dec. A gummy residue was left, which contained complexed cycle and also whatever impurities eluted during gel chromatography. **4**: ^{1}H NMR ($CDCl_3$, mixture of conformers) δ 2.154, 2.230, 2.245, 2.271, 2.284 (5 s, Ar CH_3, 6 H), 2.1–2.3 (m, CCH_2C, 6 H), 3.016, 3.289, 3.316, 3.323, 3.403, 3.779, 3.784 (7 s, OCH_3, 9 H), 3.2–4.0 (m, NCH_2, 12–14 H), 4.39 and 4.48 (s, CH_2O, 2 H), 4.5–5.1 (various AB, Ar CH_2N, 2–4 H), 6.6–7.9 (m, Ar, H, 11 H); IR (KBr) 3450 (br, H_2O), 2920 (m), 2850 (m), 1640 (s), 1490 (s), 1440 (s), 1340 (w), 1300 (m), 1200 (m), 1100 (m), 1000 (m), 760 (m); MS (220 °C), m/e 766 M^+ + 23 − 15, Na^+ complex, 9), 758 (M^+, 47), 743 (82), 727 (100), 713 (10), 697 (11), 681 (20). Anal. Calcd for $C_{44}H_{50}N_6O_6\cdot H_2O$; C, 68.02; H, 6.75; N, 10.82. Found: C, 67.75, H, 6.49; N, 11.18.

33,35,37-Trioxo-34,38-dimethoxy-4,26-dimethyl-36-[3(hydroxymethyl)phenyl]-1,7,11,19,23,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{13,17}.1^{19,23}.1^{24,28}]octaconta-34(2),3,5,36(13),14,16,38(24),25,27-nonaene (5). A sample of analytically pure methyl-blocked free cycle **4** (160 mg, 0.21 mmol) was dissolved in 10 mL of acetic acid, and the solution was saturated with dry HBr gas. After 20 min, the solution was poured into 200 mL of water and neutralized with Na_2CO_3. When the pH reached 10, the solution was decanted and heated for 20 h at gentle reflux. The hot solution was quickly filtered to remove colored impurities and then

cooled to ambient temperature. The product was extracted from the aqueous solution with three 35-mL portions of CH_2Cl_2. (The organic layer could be treated with 5% $NaClO_4/H_2O$ solution at this point in order to produce the $NaClO_4$ complex, otherwise the NaBr complex is isolated, as shown by a positive $AgNO_3$ test.) The organic layer was dried, filtered, and concentrated to give **5**·NaBr as a colorless glass (145 mg, 51–80%). This material was dissolved in a minimum amount of CH_2Cl_2 and precipitated as a powder by adding ether. This complex moves more slowly on silica gel (10% MeOH/90% CH_2Cl_2 eluant) than the **4**·NaBr. The ^1H NMR spectrum of **5**·NaBr in $CDCl_3$ is substantially the same as that of **5**·$NaClO_4$, which exists as two conformers: ^1H NMR δ 2.250 and 2.259 (s, Ar CH_3, 6 H), 2.4 (m, C CH_2 C, 6 H), 3.515, 3.592 and 3.537, 3.616 ($^1/_2$AB, J = 16 Hz, Ar CH_2N, 2 H), 3.7–4.0 (m, NCH_2C, 12 H), 3.80 (s, Ar OCH_3, 6 H), 4.41, 4.49 ($^1/_2$AB, J = 15 Hz, Ar CH_2N, 2 H), 4.55 and 4.68 (s, OCH_2, 2 H), 6.82 (s, Ar H, 2 H), 6.85 (s, Ar H, 2 H), 6.96 (s, Ar H, 1 H), 7.2–7.5 (m, Ar H, 3 H), 7.41 (d, A_2 of A_2B, J = 7.5 Hz, Ar H, 2 H), 7.66 (t, B of A_2B, J = 7.5 Hz, Ar H, 1 H). Decomplexation of **5**·NaBr was accomplished by the same procedure used for **4**·NaBr, except that no gummy residue was produced. The yield was 100 mg (79%) of free cycle **5**, which was a white powder: mp 250 °C (decomposition); ^1H NMR ($CDCl_3$, mixture of conformers) 2.16, 2.24, 2.28 (3 s, Ar CH_3, 6 H), 2.1–2.3 (m, CCH_2C, 6 H), 2.89, 3.31, 3.74 (3 s, ArOCH_3, 6 H), 3.4–4.0 (m, NCH_2, 12–14 H), 4.3–4.8 (m, NCH_2 and OCH_2, 4–6 H), 6.7–7.9 (m, Ar H, 11 H); IR (KBr) 3430 (s, H_2O), 2930 (m), 2850 (m), 1640 (s), 1630 (s), 1490 (s), 1430 (s), 1350 (m), 1300 (m), 1200 (m), 1000 (m), 760 (m); MS (250 °C), m/e 744, (M^+, 100), 743 (23), 730 (82), 729 (20), 728 (19), 727 (29), 713 (72), 699 (29), 697 (15), 681 (24). Anal. Calcd for $C_{43}H_{48}N_6O_6 \cdot 2H_2O$: C, 66.14; H, 6.71. Found: C, 65.92, H, 6.47.

[1,1′-Biphenyl]-3-methanol (6). Since this compound has been previously described,[14] its synthesis by a different method will be only outlined. Reduction of 3-bromobenzaldehyde with $NaBH_4$ gave 3-bromobenzyl alcohol, which with $(CH_3O)_2SO_2$ and NaH in THF gave 3-bromobenzyl methyl ether (oil, 80% overall). This material in ether was treated with $(PPh_3)_2NiCl_2$ and C_6H_5MgBr in ether to give after reflux for 21 h and purification by silica gel chromatography, 3-(methoxymethyl)-1,1′-biphenyl as an oil (40%). This material was demethylated at 25 °C in glacial AcOH saturated with HBr (20 min) followed by hydrolysis with aqueous Na_2CO_3 to give **6** (75%) as an oil: R_f 0.20 (CH_2Cl_2 on silica gel); ^1H NMR ($CDCl_3$) δ 1.76 (br s, OH, 1 H), 4.75 (s, CH_2, 2 H), 7.2–7.7 (m, Ar H, 9 H); MS (190 °C), m/e 184 (M^+, 100). Anal. Calcd for $C_{13}H_{12}O$: C, H.

L-Alanine 4-Nitrophenyl Ester Perchlorate. This compound was prepared as previously reported.[5b]

β-Alanine 4-Nitrophenyl Ester Perchlorate. The *N*-(*tert*-butoxycarbonyl) derivative of β-alanine *p*-nitrophenyl ester (0.50 g, 1.6 mmol) was dissolved in 2 mL of EtOH. Almost 1 equiv of 7 N $HClO_4$ (0.20 mL, 1.5 mmol) was added, and the solution was stirred for 1 h. A small amount of product precipitated but was dissolved by adding 25 mL of additional EtOH and 25 mL of ether. The mixture was concentrated to a solid under reduced pressure and crystallized from hot EtOH to yield 320 mg (64%) of product as clear needles: mp 204–205 °C; ^1H NMR (CD_3CN, 60 MHz) δ 2.5 (br s, NH_3, 3 H), 3.2 (m, A_2B_2, J = 4 Hz, CH_2CH_2, 4 H), 7.39 (d, $^1/_2$AA′BB′, J = 9 Hz, Ar H, 2 H), 8.27 (d, $^1/_2$AA′BB′, J = 9 Hz, Ar H, 2 H). Anal. Calcd for $C_9H_{11}ClN_2O_8$; C, H, N, Cl.

L-Phenylalanine 4-Nitrophenyl Ester Perchlorate. The *N*-*tert*-butoxycarbonyl) derivative of l-phenylalanine *p*-nitrophenyl ester (0.62 g, 1.6 mmol) and 7 N $HClO_4$ (0.20 mL, 1.5 mmol) were added to a solution of 10 mL of EtOH and 5 mL of CH_2Cl_2. After gentle heating and stirring of the mixture to dissolve the ester, stirring was continued for 1 h at 25 °C. The solvents were evaporated at reduced pressure to give crude product, which was crystallized from $EtOH/CH_2Cl_2$/pentane to yield 500 mg (81%) as thin white needles: mp 197–8 °C; ^1H NMR (60 MHz, CD_3CN) δ 3.1 (br s, NH_3, 3 H), 3.42 (d, J = 7 Hz, CH_2, 2 H), 4.63 (t, J = 7 Hz, CH, 1 H), 7.33 (d, $^1/_2$AA′BB′, J = 9 Hz, Ar H, 2 H), 7.40 (s, Ar H, 5 H), 8.26 (d, $^1/_2$AA′BB′, J = 9 Hz, Ar H, 2 H). Anal. Calcd for $C_{15}H_{15}ClN_2O_8$: C, H, Cl, N.

Glycine 4-Nitrophenyl Ester Perchlorate. The *N*-(*tert*-butoxycarbonyl) derivative of glycine *p*-nitrophenyl ester (0.90 g, 3.0 mmol) and 7 N $HClO_4$ (0.42 mL, 2.9 mmol) were dissolved in 4 mL EtOH, and the mixture was stirred for 1 h. Concentration and precipitation of the product from EtOH/ether/pentane gave 450 mg (50%) of the desired compound as a white solid, mp 193–197 °C; ^1H NMR (60 MHz, CD_3CN) δ 3.8 (s, NH_3, 3 H), 4.20 (s, CH_2, 2 H), 7.46 (d, $^1/_2$AA′BB′, J = 9 Hz, Ar H, 2 H), 8.34 (d, $^1/_2$AA′BB′, J = 9 Hz, Ar H, 2 H). Anal. Calcd for $C_8H_9ClN_2O_8$: C, H, Cl, N.

L-Alanine 7,8,17,18-Tetrahydro-23-(hydroxymethyl)-35-methoxy-3,21-dimethyl-34,36-dioxo-16*H*,31*H*-5,9:15,19-dimethano-10,14-metheno-26,30-nitrilo-6*H*,25*H*-dibenzo[*b*,*s*][1,21,4,8,14,18]-dioxatetraazacyclooctacosine-1-methyl Ester Perchlorate (25). Diol **9** (124 mg, 0.182 mmol) was dissolved in 8 mL of pyridine and 100 mL of dry distilled CH_2Cl_2, and 57 mg (0.183 mmol) of L-alanine *p*-nitrophenyl ester perchlorate was added. The mixture was stirred for 5 days at ambient temperature. A small amount of white solid precipitated. The mixture was washed 3 times with 100-mL of portions of water saturated with Li_2CO_3, with 100 mL of H_2O, twice with 100 mL of dilute $HClO_4$ (pH 1–2 after separation from the CH_2Cl_2 layer), and with 50 mL of H_2O. This washing did not affect the ^1H NMR spectrum of the product. The organic layer was dried, filtered, concentrated, and crystallized from acetone/THF with slow evaporation of the acetone to produce 64 mg (41%) of **25**: mp > 250 °C dec; ^1H NMR (10% CD_3OD/90% $CDCl_3$) δ 0.94 (d, J = 7 Hz, CH_3 of Ala moiety, 3 H), 2.35 (s, Ar CH_3, 3 H), 2.36 (s, Ar CH_3, 3 H), 2.4 (m, CCH_2C, 4 H), 3.31 (s, OCH_3, 3 H), 3.6–4.2 (m, NCH_2 and CH of Ala, 9 H), 4.66 and 4.68 (AB q, J = 12 Hz, OCH_2Ar, 2 H), 4.95 and 5.58 (AB q, J = 12.7Hz,2H), 5.11 and 5.34 (AB q, J = 13.2 Hz, 2 H), 5.12 and 5.53 (AB q, J = 12.7 Hz, 2 H), 7.1 (m, Ar H, 4 H), 7.2 (m, Ar H, 3 H), 7.34 (d, J = 8 Hz, Py H3, 1 H), 7.40 (d, J = 8 Hz, Py H5, 1 H), 7.89 (t, J = 8 Hz, Py H4, 1 H); IR 1750 (ester CO), 1630 cm^{-1} (urea CO); $[\alpha]^{25}$ (15.6 mg dissolved in 0.11 mL of CH_3CN + 1.0 mL of $CDCl_3$) +5.6° (589 nm), +5.6° (578 nm), +6.8° (546 nm), +14.6° (436 nm). Anal. Calcd for $C_{41}H_{47}ClN_6O_{12}$: C, 57.85; H, 5.56; Cl, 4.16; N, 9.87. Found: C, 57.70; H, 5.50; Cl, 4.20; N, 9.88.

L-Alanine 33,35,37-Trioxo-34,38-dimethoxy-4,15,26-trimethyl-1,7,11,19,23,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{13,17}.1^{19,23}.1^{24,28}]octaconta-34(2),3,5,36(13),14,16,38(24),25,27-nonaene-36-yl Ester Perchlorate (24). A sample of the free cycle **5** (29 mg, 0.039 mmol) was dissolved in 20 mL of distilled CH_2Cl_2 and 2 mL of dry pyridine. The perchlorate salt of L-alanine *p*-nitrophenyl ester (12.1 mg, 0.039 mmol) was added and the solution was stirred 2 days at 25 °C. The solution was diluted to 50 mL with CH_2Cl_2 and washed with three 50-mL portions of water saturated with Li_2CO_3, 50 mL of H_2O, 50 mL of dilute aqueous $HClO_4$ twice to a pH of <2, and 50 mL of deionized H_2O. The solution was evaporated to give adduct complex **24** (30 mg, 34%) as a colorless glass: ^1H NMR ($CDCl_3$) δ 0.62 (d, J = 7 Hz, CH_3 of Ala, 3 H), 2.24 (s, Ar CH_3, 3 H), 2.27 (s, Ar CH_3, 3 H), 2.4 (m, CCH_2C, 6 H), 3.5–3.65 (2 right halves of AB quartets, $ArCH_2N$, 2 H), 3.69 (s, OCH_3, 3 H), 3.76 (s, OCH_3, 3 H), 3.6–4.1 (m, NCH_2C and CH of Ala, 13 H), 4.50 (d, J = 14 Hz, left half of AB, Ar CH_2N, 1 H). 4.57 (d, J = 14 Hz, left half of AB, Ar CH_2N, 1 H), 5.28, 5.40, (AB q, J = 13 Hz, CH_2O, 2 H), 6.885 (s, Ar H, 2 H), 6.894 (s, Ar H, 2 H), 7.1–7.7 (m, Ar H, 7 H). Anal. Calcd for $C_{46}H_{54}N_7O_{11}Cl \cdot H_2O$: C, 59.12; H, 6.04; N, 10.49. Found: C, 59.28; H, 5.94; N, 10.53.

Acylation of Host 5 by L-alanine *p*-Nitrophenyl Ester Perchlorate in Medium Used for Kinetics. The free cycle **5** (2 mg) was dissolved in 1 mL of $CDCl_3$ containing 1 drop of DMF-d_7. This solution gave a stable ^1H NMR spectrum substantially the same as that listed for **5** in pure $CDCl_3$. Upon the addition of 1 equiv of L-alanine *p*-nitrophenyl ester perchlorate, a stable mixture of two conformationally isomeric complexes formed instantaneously. When diisopropylethylamine buffer was added, a single adduct was formed over 0.5 h, characterized especially by Ar CH_2OCO signals at 5.3 ppm (AB quartet) and two "left halves" of AB quartets at about 4.6 ppm. This adduct remained stable for 24 h in this medium: ^1H NMR (alanine ester complex, $CDCl_3$ containing 1 drop of DMF-d_7) δ 2.22 (2 s, Ar CH_3), 2.3 (m, CCH_2C), 3.6–4.2 (m, NCH_2), 3.8 (4 s, ArOCH_3), 4.6–5.0 (4 left halves) of AB quartets, NCH_2Ar), 4.7 (2 s, CH_2O), 6.6–8.2 (Ar, including left half of AA′BB′ of the *p*-$NO_2C_6H_4$ group, 8.2 ppm; the right half is smeared at 7.2 ppm). This spectrum is substantially the same as the independently synthesized adduct (see above).

^1H NMR Analysis of the Product from the Kinetics Experiments Involving Diol 9. A solution of DMF (0.20 M), diol **9** (4 mg, 0.006 mmol), buffer (0.90 mL of a $CHCl_3$ solution which was 0.020 M in diisopropylethylamine and in the amine perchlorate, 0.018 mmol each), L-alanine *p*-nitrophenyl ester perchlorate (0.30 mL of a solution which was 0.20 M in ester, prepared (see below) as in the kinetics experiments, 0.006 mmol), and $CHCl_3$ (2 mL, dried with H_2SO_4 and K_2CO_3 and distilled from $CaCl_2$) was allowed to stand in a Kimax flask for 2 days. Half of the solution was concentrated at reduced pressure. The other half was washed twice with ion-free water and then concentrated. The ^1H NMR spectrum of the washed sample was substantially the same as that of the unwashed sample, except for the removal of peaks due to buffer and a diminution of peaks due to *p*-nitrophenol (δ 6.9, 8.1, AA′BB′) and DMF, with concomitant improvement in resolution, in the washed sample. The spectrum was also identical with that of the independently synthesized adduct recorded in $CDCl_3$: ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 7 Hz, CH_3 of Ala moiety, 3 H), 2.35 (s, Ar CH_3, 6 H), 2.35 (m, CCH_2C, 4 H), 3.32 (s, OCH_3, 3 H), 3.6–4.2 (m, NCH_2 and CH of Ala moiety, 9 H), 4.6–5.6 (4 AB quartets, 8 H, see following experiment), 7.0–7.2 (m, Ar H, 7 H), 7.32 (d, J = 8 Hz, Py H3, 1 H), 7.44 (d, J =

8 Hz, Py H5, 1 H), 7.86 (t, J = 8 Hz, Py H4, 1H).

Acylation Kinetics. All volumetric flasks (Kimax) were washed with chromerge, rinsed with water, dilute NH_4OH, and deionized water, and oven dried. Graduated pipets and syringes were used as convenient to transfer liquids. These were washed with acetone and reagent CH_2Cl_2 and blown dry with air. They were also rinsed with liquids to be transferred immediately prior to their use in transferring those same liquids. Small amounts of $CHCl_3$ and $CDCl_3$ were transferred using disposable soda lime glass Pasteur pipets. Spectrophotometer cells (Hellma suprasil) and their Teflon-brand stoppers were washed with spectral grade CH_3CN and dried in a stream of argon. The solvents $CDCl_3$ (pure) and $CHCl_3$ (spectral grade, "stabilized with EtOH") were treated with K_2CO_3 and filtered immediately before use. Dimethylformamide was dried over BaO and distilled at aspirator pressure. Acetonitrile was spectral grade. Tetraphenylboron sodium was Aldrich "Gold Label" (99+%). Diisopropylethylamine was distilled from toluenesulfonyl chloride and stored under nitrogen. The perchlorate salt of this amine was prepared by reacting the amine with 1 equiv of $HClO_4$ in EtOH followed by precipitation of the salt with ether. Sodium perchlorate was used as the monohydrate. Ethanol was dried over 3 Å molecular sieves. Host compounds **7**-**9**[5b] and racemic **10**[6] were available from other studies.

Stock solutions, which were 0.020 M or 0.080 M in diisopropylethylamine, diisopropylethylamine perchlorate salt, or both, were made up by the syringe addition of the amine (0.348 mL, 0.258 g, 2.00 mmol) and/or the transfer of solid salt (0.45 g, 2.00 mmol) into a 100- or 25-mL volumetric flask containing some $CHCl_3$ or $CDCl_3$. The solutions were brought to their final volumes with additional $CHCl_3$ or $CDCl_3$, respectively. A solution 3.0 M in $NaClO_4$ was made in a 5-mL volumetric flask by dissolving 2.1 g of $NaClO_4 \cdot H_2O$ (0.015 mol) in 1 mL of H_2O and adding sufficient DMF to make up the final volume. A stock solution of $NaBPh_4$ (0.075 M) was made by dissolving 256 mg of the salt in 1 mL of DMF and making up the volume to 10 mL with $CDCl_3$. Dimethylformamide solutions 0.015 M in diol **9** were prepared in 2-mL volumetric flasks with the aid of sonication and mild heating, followed by cooling to room temperature, since crystalline **9** (20.5 mg, 0.030 mmol) could not be fully dissolved in 2 mL of DMF by simply mixing the components at room temperature. Host **5** was handled as a 0.0040 M stock solution in $CDCl_3$, prepared by dissolving 15.7 mg of $\mathbf{5} \cdot 2H_2O$ in 5 mL of $CDCl_3$. The racemic binaphthyl cycle **10** was transferred as a 0.0050 M stock solution (13.8 mg in 5.0 mL of $CDCl_3$). Amino acid p-nitrophenyl ester perchlorate stock solutions (0.010 M) were prepared in 5-mL volumetric flasks by dissolving each ester (0.050 mmol) in 0.5-1.0 mL of DMF and making up the volume to 5 mL with $CDCl_3$. Compounds **6** and **7** were weighed and added directly to the reaction mixture. Compound **8** was weighed in a tared flask and transferred as a solution in $CDCl_3$. Ethanol was added to appropriate reaction mixtures with a graduated pipet. All solutions were shaken thoroughly before use, and no solutions were stored more than 24 h.

Reaction mixtures (minus the substrates) were prepared by adding appropriate amounts of reagents and/or stock solutions to volumetric flasks containing some $CDCl_3$, then making the final volume (2 or 5 mL) with $CDCl_3$ ($CHCl_3$ for runs using EtOH as the nucleophile), and shaking. Runs were initiated by the syringe addition of an aliquot (20 or 50 μL) of ammonium ester stock solution to each volumetric flask so that the initial concentration of ester was 1.0×10^{-4} M. The solutions were shaken thoroughly and partially transferred (using Pasteur pipets) into UV cells (1.00-cm light path, 1 or 2.5 mL total volume). These cells were equilibrated and maintained at 24 °C in cell holders which were immersed in a constant-temperature water bath. The cells were fitted with Teflon-brand stoppers.

Absorbances A_t were measured periodically at 350 nm with a Beckman DU quartz spectrometer equipped with a Guilford digital readout, thereby monitoring the formation of p-nitrophenol. Endpoints (A_∞) were noted at 5-8 half-lives and were stable within experimental error. Initial absorbance readings were in the range 0.050-0.200 units, whereas A_∞ was typically 0.300-0.600 units. Table II and its footnotes record the conditions of the runs and the k_1 (and k_2 values where appropriate) values obtained.

Determination of Association Constants and Free Energies of Complexation. The standard method for determining K_a and $-\Delta G°$ values previously reported[6] was applied to hosts **3** and **5** binding Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates. Because of the strongly binding character of these compounds, 0.001 M solutions of host and guest in $CDCl_3$ and D_2O were used, respectively. The limited supply of host **4** allowed only values for Rb^+ and $CH_3NH_3^+$ to be determined. Two values were obtained and averaged for each K_a, once the range was established by preliminary measurements. Deviations between aqueous- and organic-phase determinations of $-\Delta G_a$ ranged from 0.0 to 0.5 kcal/mol, the larger values always being observed at the upper end of the scale in the organic layer or lower end of the scale in the water layer, where errors are greatly magnified. Equilibration of the guest between the two layers was essentially instantaneous on the human time scale. Table I records the K_a and $-\Delta G°$ values for **3**-**5**, as well as values for **8**, **9**, **11**, and **23** obtained earlier, which are listed for comparison purposes.

Registry No. 5, 91084-72-9; **6**, 91084-73-0; **7**, 91084-74-1; **8**, 91084-75-2; **9**, 91084-76-3; **10**, 91084-77-4; **11**, 91084-78-5; **14**, 91084-79-6; **16**, 91084-81-0; **17**, 91084-80-9; **18**, 91084-82-1; **23**, 67191-44-0; **24**, 91084-83-2; **25**, 91084-84-3; **26**, 91084-85-4; **28**, 91084-86-5; **29**, 91084-87-6; **30**, 91084-88-7; **31**, 91084-89-8; **32**, 91084-90-1; **33**, 91110-52-0; 2-bromo-4-methylphenol, 6627-55-0.

Communications to the Editor

Application of Circular Dichroic Spectroscopy for Determination of Chiral Organization of H-Bonded Alcohols

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Chiral molecules possessing two or more π-electron chromophores located in chiral positions in respect to each other show intramolecular CD exciton coupling effects.[1] We now report on *intermolecular* CD exciton coupling effects exhibited in nonprotic solvents, at low temperatures by hydroxylated chiral molecules possessing only one π-electron chromophore, pointing to their chiral organization in solution.

Circular dichroic spectra of transoid dienes **1** and **2** derived from *trans*-vitamin D_3 (**3**) and vitamin D_3 (**4**), which possess planar diene chromophores, exhibit at room temperature in the region 220-260 nm low-intensity structured Cotton effects. The peaks appear at the same wavelengths as the UV absorption maxima,[2] which doesn't change by lowering the temperature. However, in isopentane/methylcyclohexane (IP/MCH) solution at ca. -100 °C the CD of these dienes changes drastically giving rise to split Cotton effects: negative at 264 and 253 nm, and positive at 250, 242, and 232 nm, whose amplitude increases with lowering temperature and with increased concentration.[3] The shape of the components of these bisignate effects (Figure 1) equidistant from the compounds UV band center, and each possessing vibrational structure, indicates that they originate from exciton coupling.[1] These effects disappear on addition of isopropyl alcohol and do not appear in the acetylated and benzoylated derivatives, showing

(1) "Circular Dichroic Spectroscopy—Excitation Coupling in Organic Stereochemistry"; Harada, N., Nakanishi, K., Eds.; University Science Books: New York, 1983; pp 1-46.

(2) Duraisamy, M., Walborsky, H. M. *J. Am. Chem. Soc.* **1983**, *105*, 3264.

(3) Only Cotton effects due to the long-wavelength π-π* transition exhibit a clear bisignate effect.

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