Host−Guest Chemistry of a Chiral Cyclohexanediamine−Viologen Cyclophane in Solution and in the Solid State

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Two π-accepting viologen substituents were coupled with the chiral barrier (1*R*,2*R*)-(+)-1,2-cyclohexanediamine to synthesize a rigid, C_2-symmetric cyclophane host for aromatic guest molecules. UV−visible spectroscopic titrations show an association constant of 3.3×10^3 M^{-1} with indole, a hydrophobic guest, and constants in the range of 10^1-10^2 M^{-1} for more hydrophilic indole derivatives in water. Tryptophan methyl ester complexes this host in aqueous base with an enantioselectivity ratio of 3.3, and an association constant of 2.0×10^2 M^{-1} for the preferred L-enantiomer. Protonation of tryptophan methyl ester causes both the L- and D-enantiomers to have the same affinity for the host, which is, within experimental error, the same as that of the D-enantiomer in base. The cyclophane host can be intercalated into α-zirconium phosphate, a lamellar solid acid, by first swelling the latter with tetra*n*-butylammonium hydroxide. Because the intercalated cyclophane (layer spacing = 14.7 Å) has a pre-organized binding pocket, indole intercalates from solution to give a 1:1 complex in the solid, with no change in interlamellar spacing. Adsorption isotherms corresponding to indole intercalation and complexation were Langmuirian, in contrast to the strongly cooperative binding found previously for complexation of π-donors with noncyclophane chiral hosts in α-zirconium phosphate.

Introduction

The design of materials for preparative-scale chiral separations remains an important challenge in chemistry today.[1] For new drugs and related products, such as pesticides and fungicides, there is growing pressure to carry out pharmacologic, toxicologic, and clinical studies on single enantiomers. Unfortunately, current methods of resolving or synthesizing optically pure compounds on a preparative scale (grams to kilograms) do not lend themselves to rapid implementation with new substances. Classical resolution techniques, such as derivatization with chiral reagents followed by fractional crystallization and asymmetric syntheses, tend to be idiosyncratic and are therefore not easily adapted to a new compound without time for development.[2] On the other hand, various kinds of chiral solids, such as natural and synthetic polymers,[3] functionalized silica,[4] and imprinted polymers,[5] can act as enantioselective sorbents. Some of these have been used in preparative batchwise and liquid chromatographic enantioseparations,[6] although most are useful primarily on the analytical scale. New materials designed for preparative-scale use should ideally bind a structurally diverse set of analyte molecules with high capacity and enantioselectivity.

An approach to this problem that has been pursued in our laboratory is to use high surface area inorganic materials as supports for chiral host molecules. Lamellar and zeolitic solids have internal surface areas on the order of 1000 m^2/g and have been used extensively as sorbents for achiral molecules. Recently, we showed that α-$Zr(HPO_4)_2 \cdot H_2O$ (α-ZrP), a lamellar solid acid, can be intercalated with the Pirkle-type chiral host **1** and used to resolve the enantiomers of **2** in a batchwise process, on a preparative scale.[7] A problem with α-ZrP intercalation compounds, however, is that they swell upon intercalation of analyte molecules. This expansion constitutes thermodynamic work and therefore leads to a concentration threshold in the binding isotherm of **2**; in addition, the dimensional instability of the material is incompatible with its use as a chromatographic

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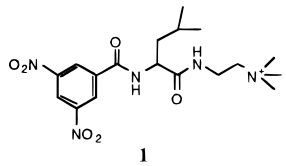
stationary phase. To overcome the problem of layer expansion, viologen cyclophanes **3** and **4**, which have rigid, preorganized binding pockets, were prepared as substitutes for the "floppy" host **1**.[8] Unfortunately, only very strong π-electron donors such as indole and tetramethyphenylenediamine (TMPD) form charge-transfer complexes with **3** and **4**. Since strong π-donor analytes also react with Brønsted acid sites in α-ZrP, it was not possible test the preorganization of **3**−ZrP and **4**−ZrP composites with these analytes.



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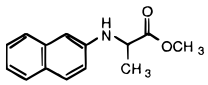

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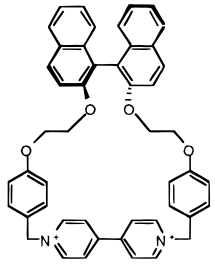

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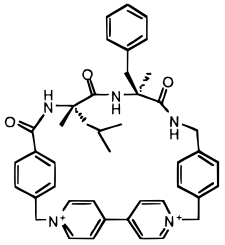

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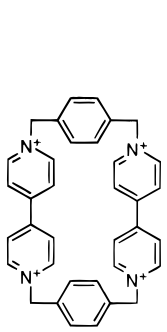
The bipyridium units of cyclophanes **3** and **4** impart π-electron-accepting character, which is useful for binding π-donor guest molecules, and also a positive charge that immobilizes them in the anionic α-ZrP host. **3** is however a poor host, because it also contains a π-donor group (and therefore self-associates), and the binding cavity of **4** is too small and hydrophilic for strong host−guest complexation. A possible approach to eliminating the self-association problem of **3** is to substitute an appropriate non-π-donating chiral barrier for binaphthyl. The strategy described here is to replace the binaphthyl group of **3** with *trans*-1,2-cyclohexanediamine, a popular chiral auxiliary molecule used in asymmetric synthesis,[9] chiral molecular recognition,[10] and chromatography. Still and co-workers have synthesized several related *trans*-1,2- cyclohexanediamine-derived synthetic receptors that have multiple hydrogen-bonding sites.[11] These bowl-shaped hosts show exceptional enantioselectivity toward a variety of amino acid derivatives, with an enantiomeric excess (ee) of 99% for glycine derivatives. Still et al. attributed the high enantioselectivity of these hosts to their well-defined hydrophobic binding cavity and four hydrogen-bonding sites at the appropriate positions. Gasparrini and co-workers have designed *trans*-1,2- cyclohexanediamine-derived chiral chromatographic stationary phases.[12] Of the many analytes tested using analytical-scale columns, amide-based analytes were resolved well, with enantioselectivity ratios as high as 10.[13]

The paraquat cyclophane **5**, designed by Stoddart and co-workers, was used as a starting point for the synthesis of the *trans*-1,2-cyclohexanediamine cyclophane host **6** described here.[14] With two paraquat units, this molecule binds very strongly to π-electron-rich analytes such as indole and catechol. **5** and **6** are nicely preorganized for binding aromatic guests. Recently, cyclophane **7**, a chiral analogue of **5**, has been independently synthesized and characterized by Asakawa et al. Despite the fact that it contains both π-donor and π-acceptor groups, **7** acts as an enantioselective host for tryptophan and tyrosine derivatives in solution.[15]



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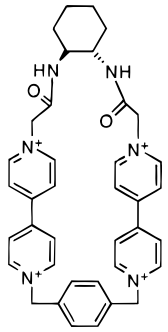

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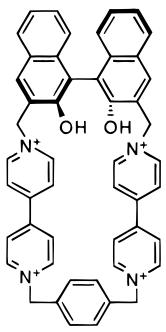

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Apart from the synthesis and characterization of cyclophane **6**, two issues are addressed here that are relevant to the development of intercalation compounds as chiral sorbents: (1) the host−guest chemistry of **6** in solution, including its enantioselectivity, and (2) the intercalation chemistry and intracrystalline molecular recognition properties of cyclophanes **5** and **6**. A critical question in the latter study is whether the cyclophane-intercalated solids are indeed structurally preorganized and how this is reflected in the dimensional stability and binding isotherms of these materials. Ideal cyclophane hosts should exhibit high enantioselectivity for complexation with analytes in solution and should intercalate to give solids that reversibly bind analytes with minimal layer expansion.

Experimental Section

Materials. All synthetic and analytical reagents were used as received from Aldrich and Sigma. Solvents for chromatographic experiments were HPLC grade and were degassed with He for 30 min before use.

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Instrumentation. ^{1}H NMR spectroscopy was carried out using either a Bruker AM-300 or a Bruker AC-E−200 spectrometer. HPLC experiments were performed on a Waters 600E system with a Waters 991 photodiode array detector using a Crownpak CR(+) or Chiralcel OD column from Chiral Technologies Inc. UV−visible spectra were recorded on a Hewlett-Packard 8452A diode array spectrophotometer for solution samples and on a Varian DMS 300 fitted with a diffuse reflectance attachment for solids. Powder X-ray diffraction was done on a Phillips X′Pert MPD diffractometer using monochromatized Cu Kα radiation. Elemental analysis (C,H,N) was performed by Atlantic Microlabs, Inc., Norcross, GA. Polarimetry data were collected on a Perkin-Elmer 343 polarimeter. Mass spectrometry was performed at the Mass Spectrometry Facility at the University of Texas at Austin.

Synthesis. Bromoacetylamide of *trans*-1,2-Cyclohexanediamine. *trans*-1,2-Cyclohexanediamine[16] (0.75 g, 6.57 mmol) and triethylamine (1.33 g, 13.1 mmol) were dissolved in 80 mL of dry CH_2Cl_2. After the reaction mixture was cooled to −76 °C in a dry ice−acetone bath, bromoacetylbromide (2.67 g, 13.2 mmol) was added dropwise to the reaction mixture over 40 min. After the addition was complete, the reaction mixture was stirred for another 3 h and allowed to warm slowly to room temperature. The precipitate was filtered and rinsed with 20 mL of CH_2Cl_2. The combined organic solutions were washed with 3 × 100 mL of 0.1 M HCl and 2 × 100 mL of brine and dried over $MgSO_4$. After removal of the solvents in vacuo, a white solid was obtained and used without further purification. Yield: 1.86 g, 80%. ^{1}H NMR ($CDCl_3$): δ 1.2−2.02 (m, 8H), 3.66 (s, 2H), 3.74 (s, 4H), 6.56 (s, 2H). CIMS: 355 ($(M + 1)^+$).

1,1′-(*trans*-1,2-Cyclohexanediamidebis(methylene)]bis-4,4′-bipyridinium Bis(hexafluorophosphate). The bromoacetylamide of *trans*-1,2-cyclohexanediamine (3.08 g, 8.65 mmol) and 4,4′-dipyridyl (6.75 g, 43.27 mmol) were refluxed in 300 mL of acetonitrile for 2 days. After being cooled to room temperature, the yellow precipitate was filtered, washed with acetonitrile and methylene chloride, and dried in air. The resulting dibromide salt was dissolved in water, filtered to remove any insoluble particles, and precipitated with a concentrated solution of ammonium hexafluorophosphate to afford the hexafluorophosphate salt. The resulting reddish gellike material was washed twice with a small amount of deionized H_2O. After the aqueous solution was decanted, the gellike material was dissolved in a minimum amount of acetone and vacuum-dried to afford a red-colored solid. The compound was used without further purification. Yield: 3.17 g, 83%. ^{1}H NMR (CD_3CN): δ 1.3−1.7 (m, 8H), 3.7 (m, 2H), 5.24 (s, 4H), 7.05 (d, 2H), 8.89 (d, 4H), 8.40 (d, 4H), 8.89−8.92 (dd, 8H). FABMS: 798 (M^+).

Cyclophane 6. 1,1′-(*trans*-1,2-Cyclohexanediamidebis(methylene)]bis-4,4′-bipyridinium bis(hexafluorophosphate) (3.17 g, 3.97 mmol) and α,α′-dibromo-*p*-xylene (1.08, 4.09 mmol) were refluxed in 1.5 L of acetonitrile. After 1 day, an additional 0.44 g (1.67 mmol) of α,α′-dibromo-*p*-xylene was added and reaction mixture was refluxed for two an additional 2 days. After cooling to room temperature, the reaction mixture was air-dried. The resulting solid was dissolved in nitromethane, and the insoluble material was filtered. The filtrate was treated with a concentrated solution of tetraethylammonium chloride in nitromethane, and the precipitate was filtered, washed with nitromethane, and dried in air. The resulting chloride salt of the crude product was run on a 6:3:1 CH_3OH/H_2O/saturated aqueous NH_4Cl silica column. The product fractions were collected and blown dry in air. The resulting solid was dissolved in minimum amount of water, filtered, and treated with a saturated solution of ammonium hexafluorophosphate. The precipitate was filtered, washed with copious amounts of H_2O, and dried in air to afford the PF_6 salt of **6**. Yield: 0.47 g, 0.39 mmol (10%). ^{1}H NMR (CD_3CN): δ 1.2−1.9 (m, overlapped with the solvent peaks), 3.6 (m, 2H), 5.4 (s, 4H), 5.8 (s, 4H), 7.25 (m, 2H), 7.66 (s, 4H), 8.1−8.2 (dd, 8H), 8.8−8.94 (dd, 8H). ^{13}C NMR (MeOD): δ 25.926, 31.632, 53.724, 55.243, 63.633, 128.119, 129.473, 132.322, 138.568, 147.051, 148.839, 152.293, 165.942. Anal. Calcd (found). C, 38.25 (38.17). H, 3.36 (3.63). N, 7.05 (7.34). FABMS: 902 ($(M - 2PF_6)^{2+}$), 1047, ($(M - PF_6)^+$). The PF_6 salt of **6** can be ion-exchanged to the chloride salt by dissolving **6·4PF$_6$** in minimum amount of nitromethane and precipitating it with a concentrated solution of tetraethylammonium chloride in nitromethane. Both racemic cyclophane **6** and its *R* enantiomer were synthesized. The *R* enantiomer of **6·4Cl** had $[\alpha]_D = -41.6$ in H_2O at 25 °C. The chloride salt of **6** was light yellow and was very soluble in H_2O. The PF_6 salt of **6** was very soluble in acetonitrile or acetone.

Tryptophan Methyl Ester. Racemic tryptophan methyl ester hydrochloride was converted to the free amine by dissolving the methyl ester in 0.1 M NaOH and quickly extracting with chloroform. The solvent was then removed by rotary evaporation to give a sticky, light yellow oil. The oil was redissolved in ether and evaporated by vacuum several times to afford a white powder. Anal. Calcd (found). C, 66.0 (65.43). H, 6.42 (6.49). N, 12.84 (12.68). The same procedure was used to convert L-tryptophan methyl ester hydrochloride to L-tryptophan methyl ester and to convert D-tryptophan methyl ester hydrochloride to D-tryptophan methyl ester. Chiral HPLC was used to confirm the optical purity of the individual enantiomers, as described below.

Intercalation of 6 into α-ZrP. In a typical procedure, 0.38 g of **6·4Cl** was dissolved in 6 mL of deionized H_2O. Tetrabutylammonium-intercalated α-ZrP (TBA^+−ZrP) (0.688 g) was added to this solution, and the reaction mixture was stirred at room temperature. After 3 days, the solid was separated from the supernatant solution by centrifugation. The solid was washed with deionized H_2O and centrifuged, and these steps were repeated until no UV absorbance of **6·4Cl** remained in the supernatant. The solid was air-dried (vacuum-drying causes reduction of the viologen cyclophane.)

Solution Binding Studies by UV−Visible Spectroscopy. In a typical experiment, the solubility of the analyte of interest was determined in the solvent used for the binding study. Next, 3 mL of a cyclophane stock solution of the appropriate concentration was used to dissolve a known amount of analyte, so that the maximum solubility of the analyte was reached. The absorbance of the charge-transfer band of the complex was then recorded. If the absorbance was too high to be measured accurately, the concentration of the cyclophane or of the analyte was adjusted so that the final absorbance would be in the appropriate range (≤1.0 absorbance unit). A stock solution of 100 mL of cyclophane of the same concentration was prepared, and 25 mL was used to dissolve a weighed amount of the analyte, so that the desired concentration of the analyte was also reached (analyte stock solution).

Disposable plastic cuvettes were used to monitor the absorbance of charge-transfer complex in the visible region. The solvent was used as the blank. The analyte stock solution (3.0 mL) was first measured to obtain the absorbance of the charge-transfer band (CT band) at λ_{max}. Subsequent data points were collected by mixing appropriate amounts of the two stock solutions, keeping the total volume (and the concentration of cyclophane) constant. A range of analyte concentrations was chosen to cover approximately 20−80% of the saturation region of the binding isotherm.

Binding Studies of the Intercalated Solid with Indole.[17] In a typical experiment, a 5.8 mM stock solution of indole was prepared by dissolving 6.8 mg of indole in 10 mL of deionized H_2O with heating and sonication. A series of indole solutions (0.115−5.89 mM) of 3 mL or more each were then prepared from this stock solution. Each solution (2 mL) was added to 60 mg of intercalated solid. The reaction mixtures were stirred for 3 days and centrifuged. The decanted supernatants were filtered through 0.45 μm filters. The absorbances of the indole solutions at 214 nm before and after interacting with the solid were measured by diluting the solutions to the appropriate concentration range.

Binding Studies of the Intercalated Solid with DL-Tryptophan Methyl Ester and dl-Indole-3-lactic Acid. Very similar procedures were used to evaluate the binding of tryptophan methyl ester and indole-3-lactic acid in the cyclophane-intercalated solids as were used for indole. In the indole

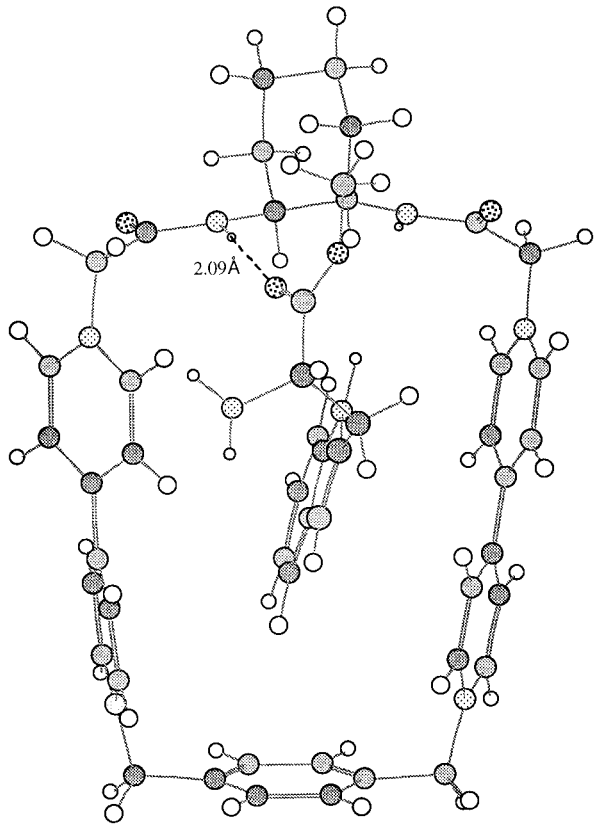

Figure 1. Energy-minimized conformation of the *R,R*-**6**, L-tryptophan methyl ester host−guest complex.

experiments, a series of concentrations was evaluated, keeping the solution volume the same for each concentration. In the tryptophan methyl ester and indole-3-lactic acid experiments, again, a series of concentrations was evaluated (10−80 mM and 0.1−50 mM, respectively.) The only difference was in the quantities and volumes of tryptophan methyl ester and indole-3-lactic acid used in the experiments. A 1:1 molar ratio of cyclophane to analyte was used at each concentration, thus resulting in a different volume at each concentration.

Molecular Modeling. Molecular modeling was used to predict possible structures for the complex of tryptophan methyl ester with **6**. The host and guest were generated using the program Macromodel.[18] Monte Carlo conformational search techniques (MC) in conjunction with the MMFF force field in an aqueous solvation model resulted in the energy-minimized structure of the complex shown in Figure 1.

Chiral HPLC for the Separation of DL-Tryptophan, DL-Tryptophan Methyl Ester, and dl-Indole-3-lactic Acid. To evaluate the usefulness of **6**−ZrP as a preparative-scale chiral stationary phase, an analytical method for the separation of DL-tryptophan, DL-tryptophan methyl ester, and DL-indole-3-lactic acid was developed.

DL-Tryptophan and DL-Tryptophan Methyl Ester. The separation was accomplished using a Chiralcel Crownpak CR-(+) column at 35 °C (constant-temperature bath.) The mobile phase was a mixture of pH 1.5 perchloric acid and methanol (9:1, v/v) with a detection wavelength of 220 nm and a flow rate of 1 mL/min. The tryptophan enantiomers eluted first (10.63 and 13.51 min, $\alpha = 1.27$, $R_s = 1.16$) followed by the tryptophan methyl ester enantiomers (18.43 and 23.29 min, $\alpha = 1.26$, $R_s = 2.03$.)

DL-Indole-3-lactic Acid. The separation was done using a Chiralcel OD at 0 °C (ice bath). The mobile phase was a mixture of hexane, isopropyl alcohol, and formic acid (80:20:1, v/v/v) with a detection wavelength of 280 nm and a flow rate of 1 mL/min. The indole-3-lactic acid enantiomers were not completely baseline resolved (19.86 and 23.80 min, $\alpha = 1.20$, $R_s = 1.06$), but integration did give a 1:1 peak area for the two enantiomers of the racemic mixture.

Results and Discussion

Host−Guest Complexation in Solution. As noted above, cyclophane **6** was designed as a chiral modification of host **5**. **5·4Cl** binds strongly to π-electron-rich amino acids such as tryptophan and tyrosine in both neutral and acidic aqueous media.[14a] In this work, the complexation of *R* **6·4Cl** with the natural amino acids studied by Stoddart et al.[14a] and with other amino acid derivatives (tryptophan methyl ester and DOPA) and related π-electron donors was investigated.

In each experiment, the background absorbance of the cyclophane was measured. A solution of the guest molecule, containing no cyclophane, was prepared at the same concentration as that of the guest stock solution. The absorbance of the guest solution at each dilution was then measured, and the absorbance of the complex at each concentration was determined by difference. The Benesi−Hildebrand equation[19] was used to estimate the association constant, which was refined by the HOSTEST program[20] to optimize the fit to the data. When both enantiomers of a guest molecule were studied, the same cyclophane stock solution was used in order to minimize experimental uncertainties. Also, when the charge-transfer (CT) band overlapped with cyclophane peaks and the absorbance maximum of the CT band could not be located unambiguously, at least two wavelengths were used to monitor the absorbance changes of the complex as a function of guest concentration. In this case the association constants represent the average of values obtained at both wavelengths.

Table 1 shows association constants obtained from UV−visible titrations. Very strong complexation was found between **6·4Cl** and neutral indole in aqueous phosphate buffer at pH 7.0 ($\lambda_{max} = 420$ nm), although the association constant, $(3.3 \pm 0.1) \times 10^3$ M^{-1}, was smaller than that observed with **5·4Cl**, $(7.1 \pm 0.9) \times 10^3$ M^{-1} ($\lambda_{max} = 464$ nm).[21] It is interesting to note the difference in λ_{max} for the CT bands of the two complexes, which reflects more favorable energetics for charge transfer between **5·4Cl** and indole. Very strong complexation was also found in acetonitrile between **6·4PF$_6$** and DL-indole-3-lactic acid, a derivative of indole. The enantiomers of indole-3-lactic acid were not available for individual evaluation, and thus the enantioselectivity could not be determined in this case.

Stronger complexation of **6·4Cl** by amino acid derivatives was found in neutral buffer solutions, relative to

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(17) Duff, D. G.; Ross, S. M. C.; Vaughan, D. H. *J. Chem. Educ.* **1988**, *65*, 815.

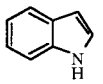
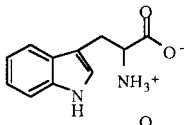
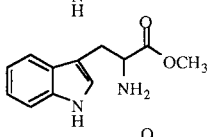
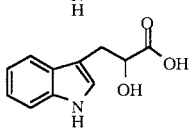
(18) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem*. **1990**, 11, 440.

(19) Connors, K. A. *Binding Constants*; Wiley: New York, 1987; p 148.

(20) Wilcox, C. S.; Glagovich, N. M. *Manual for HOSTEST (v 5.0)*, Craig S. Wilcox and The University of Pittsburgh: Pittsburgh, PA, 1993.

(21) Bernardo, A. R.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1992**, *114*, 10624.

Table 1. Host−Guest Association Constants of 6

Analyte \ K (M^{-1})		Solvent: 1.0 M HCl	0.3 M phosphate buffer, pH 7	aq. NaOH, pH 8.5
			(3.3±0.1) x 10^3	
	*D*-	43±3	263±10	
	L-	41±4	249±13	
	*D*-	65±5	69±6	62±18
	L-	62±5	101±7	210±50
			(1.9±0.3) x 10^3 *	

*binding experiment in acetonitrile, not aqueous media

acidic solutions. This trend, which was also observed by Stoddart and co-workers in their studies of **5·4Cl**,[14a] arises from electrostatic effects associated with protonation of the guest molecule. Zwitterionic tryptophan (at pH 7.0) binds more strongly to the host than the fully protonated form (in 1.0 M HCl). There is no enantioselectivity because the amine group is protonated and is therefore likely to be excluded from the cyclophane binding cavity. The enantioselectivity of tryptophan methyl ester with **6** may be understood as a combination of $\pi-\pi$, hydrogen-bonding, and hydrophobic interactions. Note that the more stable diastereomeric complex (*R*-host, L-amino acid) is the same as that observed by Still and co-workers with other cyclophanes derived from diaminocyclohexyl groups.[22]

Molecular mechanics simulations of the tryptophan methyl ester complex of **6** showed several conformations that differed slightly in energy. The common features of all of these are π-stacking and hydrogen-bonding associations, as illustrated in **Figure 1**. The modeling predicts that the aromatic rings of the tryptophan methyl ester are sandwiched between the bipyridinium rings of **6** for efficient π-stacking. A hydrogen-bonding interaction between the carbonyl group of the guest and an amine group of the host is also apparent. Complexation brings the amine nitrogen atom of the guest close to the positively charged nitrogen atom of the host. This interaction will clearly be unfavorable when both are charged. Taking the pK_a of tryptophan methyl ester (7.3) into consideration, it is interesting to observe the progression of association constants going from the fully protonated to deprotonated forms. A higher enantioselectivity ratio was found at pH 8.5 than at pH 7.0 (3.4 compared to 1.5), where there is a mixture of protonated and deprotonated species.

The molecular modeling results also suggest why **6** binds more strongly to indole, tryptophan, tryptophan methyl ester, and indole-3-lactic acid than it does to tyrosine or DOPA, which are also good π-donors.[23] The preference for indole derivatives is likely due to the electronic distribution in the π-electron rich portion of the indole ring, which roughly overlaps the π-electron poor region (N^+) of the viologen subunits. The π-electron rich subunit of tyrosine and DOPA may not position as well within the cyclophane cavity.

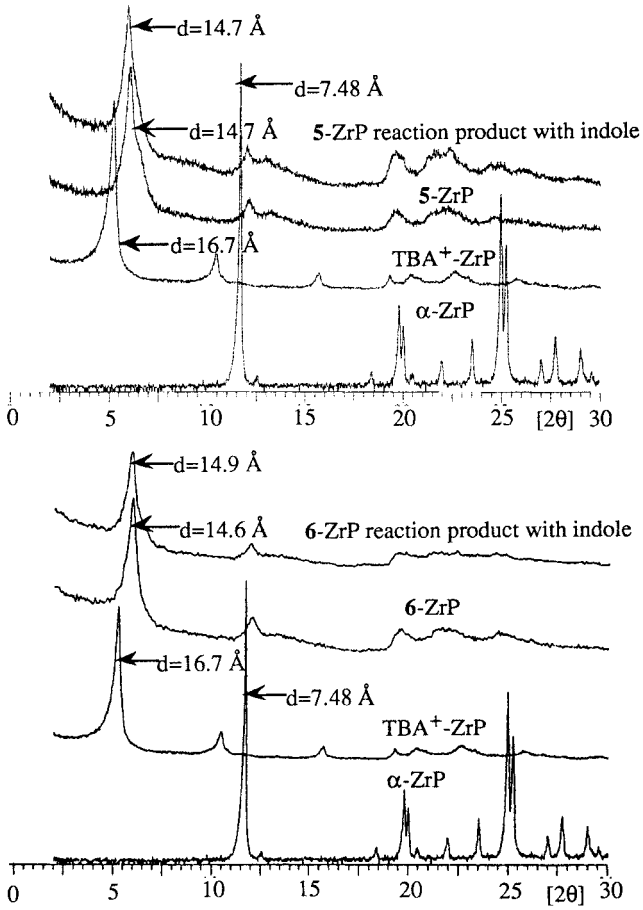


Figure 2. Progression of powder X-ray diffraction patterns for α-ZrP intercalated by cyclophanes **5** (top) and **6** (bottom).

Intercalation of Cyclophane Hosts into α-ZrP. Cyclophanes **5** and **6** were intercalated into crystalline α-ZrP (layer spacing 7.48 Å) in a stepwise fashion by first titrating the solid with 0.5 M aqueous tetrabutylammonium hydroxide (TBA^+OH^-). Depending on the amount of TBA^+OH^- used, one of the two phases (14.7 or 16.7 Å) of TBA^+-intercalated ZrP (TBA^+-ZrP) or a mixture of the two phases was obtained. With the more expanded 16.7 Å phase used in this study, the intercalation compounds of **5** and **6** had interlayer spacings of 14.7 and 14.6 Å, respectively. Figure 2 shows the progression of X-ray powder patterns as the intercalation reaction proceeds. The close correspondence of the interlayer spacings in **5**−ZrP and **6**−ZrP is consistent with the nearly identical van der Waals dimensions of the cyclophanes in the direction parallel to the ring planes and the similar loading of the two compounds in the solid. From this van der Waals dimension (about 6 Å), one would expect a layer spacing of 13−14 Å, given the thickness of the ZrP sheets (7−8 Å). This is in accord with the observed 14.7 Å spacing.

On the basis of elemental analyses, reaction of α-ZrP with TBA^+OH^- gave a composition $Zr((TBA)_{0.244}H_{0.756}$-

(22) Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155.

(23) D- and L-tyrosine, and D- and L-DOPA, had association constants of 10 ± 1 and 11 ± 1 M^{-1}, respectively, with **6** in 1.0 M aqueous HCl. Both compounds are insoluble in neutral or basic aqueous solutions.

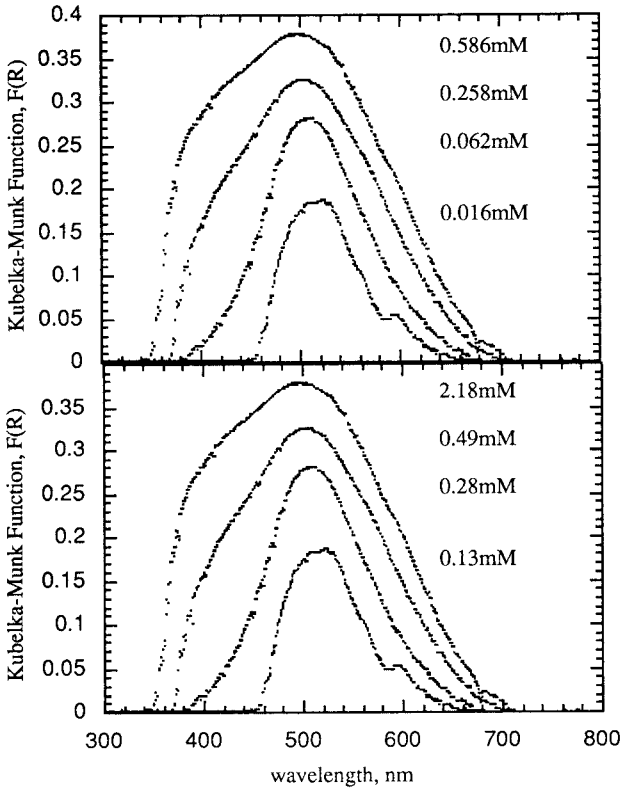


Figure 3. Concentration dependence of the charge-transfer absorbance for indole binding in **5**−ZrP (top) and **6**−ZrP (bottom). Equilibrium solution concentrations of indole are indicated.

$PO_4)_2 \cdot 0.5H_2O$. Because of the large size of the TBA^+ ion, only about $^1/_4$ of the interlamellar protons of α-ZrP are reacted. Exchange with **5** replaces 68% of the TBA^+ ions to give $Zr((TBA)_{0.089}(\mathbf{5})_{0.038}H_{0.756}PO_4)_2 \cdot 2.3H_2O$, and **6** replaces 72% of the TBA^+ ions to give $Zr((TBA)_{0.072}(\mathbf{6})_{0.043}H_{0.756}PO_4)_2 \cdot 2.2H_2O$. Multiple exchanges of TBA^+−ZrP with the cyclophanes does increase this fraction to near unity.

From CPK models, the surface area of cyclophanes **5** or **6** facing the zirconium phosphate sheet is about 160 Å^2. Thus, per proton available for exchange, there should be enough space for a stoichiometry $Zr((cyclophane)_{0.15}H_{0.40}PO_4)_2 \cdot xH_2O$, taking into account the fact that the surface area available per proton exchange site is 24 Å^2. Experimentally, only about $^1/_4$ of this available space is filled by the cyclophanes. One problem is the limited amount of TBA^+ ions available for exchange per proton exchange site. To fully pack the 4^+ charged cyclophanes into the gallery, 0.6 TBA^+ per phosphate group is needed. Experimentally, only 0.24 is available. Smaller quaternary ammonium ions might allow for more complete neutralization of interlamellar protons in the intercalation reaction, thus increasing the number of sites for the intercalation of the charged cyclophanes.

Indole, which binds very strongly to both **5** and **6** in solution, was chosen as a model analyte to study the binding properties of **5**- and **6**-intercalated α-ZrP. When a dilute aqueous solution of indole is mixed with **5**- or **6**-intercalated α-ZrP, the solid immediately acquires the reddish color of the indole CT complex, while the solution remains colorless. Despite this visible evidence of a host−guest complexation reaction, the average interplanar spacing (Figure 2) remains essentially constant for both **5**− and **6**−ZrP. At the highest indole concentration used (5.8 mM), the layer spacing of indole increased slightly, from 14.6 to 14.9 Å. Because the cyclophane binding cavities are preorganized to accommodate the guest, there is essentially no dimensional change in the solid as indole is intercalated.

Using the diffuse reflectance UV−visible spectra of **5**−ZrP and **6**−ZrP as the baseline, the charge-transfer absorbances of the indole-intercalated solids were measured as a function of indole concentration. The diffuse reflectance (R) at each wavelength was then converted to the Kubelka−Munk function $F(R)$, which varies linearly with the quantity of light-absorbing molecules, using eq 1. Figure 3 shows that the CT bands grow in intensity with increasing indole concentration and that the absorbance maxima are 500 and 510 nm for **5**−ZrP and **6**−ZrP, respectively. The red shift in the CT bands relative to aqueous solution (465 and 420 nm, respectively) reflects the highly polar interlamellar environment of α-ZrP.

$$F(R) = \frac{(1 - R)^2}{2R} \tag{1}$$

The solution concentrations of indole at equilibrium (c) and the amount of indole adsorbed into the solid (x) were determined, and binding isotherms were obtained by plotting x vs c. If the binding isotherm is Langmuirian, then eq 2 applies. Here K is the association

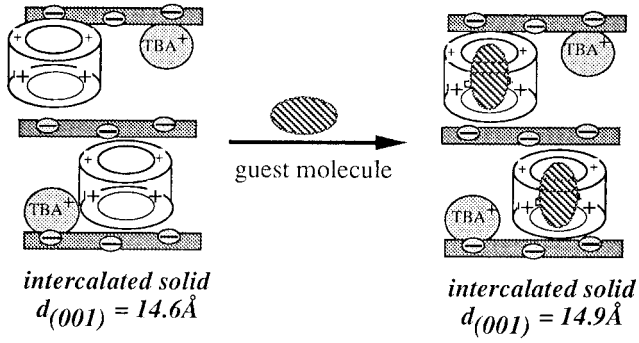
$$x = \frac{x_m K c}{1 + Kc} \tag{2}$$

constant, and x_m is the limiting amount of guest molecule (indole) that can be adsorbed per unit mass of adsorbent (intercalated solid). Rearranging (2) to its double-reciprocal form gives the Langmuir eq 3. K and

$$\frac{1}{x} = \frac{1}{x_m K}\frac{1}{c} + \frac{1}{x_m} \tag{3}$$

x_m can then be obtained from the slope and intercept of the Langmuir plot, $1/x$ vs $1/c$. Figure 4 shows a schematic representation of the binding of an analyte with a cyclophane-intercalated α-ZrP along with the binding isotherms for indole in **5**−ZrP and **6**−ZrP. These plots are very informative as to the nature of the intercalation reaction. In both cases, the adsorption of indole is Langmuirian, and the calculated saturation loading (1.9×10^{-4} mol/g of solid) corresponds to a host:guest stoichiometry of 1.0 ± 0.1. This provides good evidence that the intercalation reaction is driven by interlamellar host−guest complexation, consistent with the observation of CT absorption bands. Also consistent with this interpretation are the equilibrium constants obtained, 1.6×10^3 and 6.7×10^2 M^{-1} for indole in **5**-ZrP and **6**−ZrP, respectively. As in solution, **5** complexes indole somewhat more strongly than **6**.

The intercalation of α-ZrP containing rigid cyclophanes **5** and **6** contrasts markedly with that of α-ZrP containing the conformationally flexible host **1**. The layer spacing of **1**-intercalated ZrP increases from 21.1 to 30.3 Å upon intercalation of **2**.[7] In the case of **1**−ZrP, the thermodynamic work entailed in layer expansion



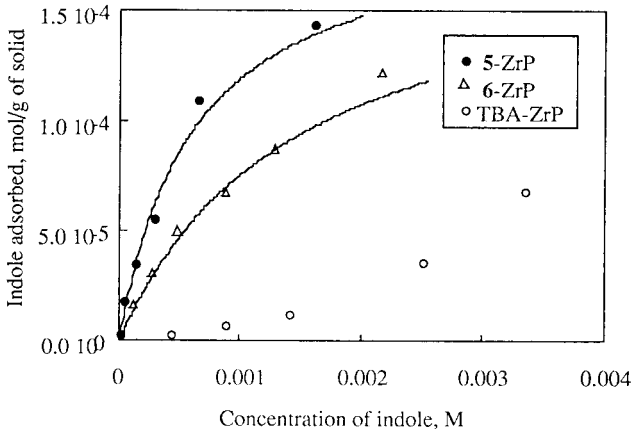


Figure 4. Schematic drawing of the guest intercalation process, and binding isotherms of the cyclophane-intercalated ZrP's with indole. The abcissa represents the concentration of indole at equilibrium.

is reflected in a non-Langmuirian, cooperative binding isotherm. Interestingly, indole itself, in the absence of the cyclophane hosts, intercalates α-ZrP, and this binding isotherm is also shown in Figure 4. The upward curvature in the indole plot indicates strong cooperativity, which suggests that a significant dimensional change occurs in the intercalation reaction. Consistent with this interpretation, the layer spacing expands from 14.8 to 20.0 Å when TBA^+−ZrP is reacted with a saturated solution of indole.

Intercalation of 6-ZrP with Chiral Analytes. Tryptophan Methyl Ester. As noted earlier, **6**·4Cl complexes the neutral form of tryptophan methyl ester with an enantioselectivity ratio of 3.4. Experiments were performed, as with indole, to determine the binding isotherm of tryptophan methyl ester in **6**−ZrP. Tryptophan methyl ester was added to **6**−ZrP at a range of concentrations, and diffuse reflectance UV−visible spectra of the resulting complex were obtained. In contrast to the indole intercalation experiment, the intensity of the charge-transfer bands, as shown in Figure 5, were very similar for all concentrations. By comparing the UV−visible spectra of the solutions before and after complexation, it was determined that each experiment (regardless of concentration) resulted in 1:1 binding of tryptophan methyl ester with the intercalated cyclophane **6**. The charge-transfer band did not diminish after repeated rinsing of the solid, and thus the binding was irreversible. The irreversibility can be understood when one recalls that the guest molecule is a base and α-ZrP is a solid acid. As noted above, only about 30% of the protons in α-ZrP are neutralized in

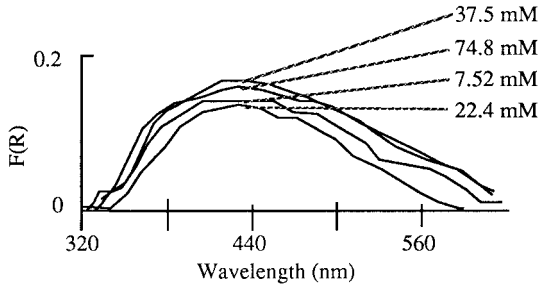
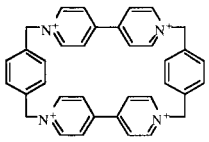
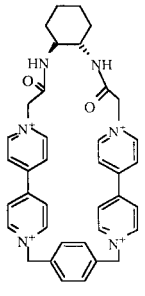
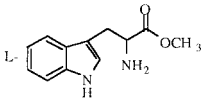
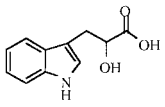


Figure 5. Charge-transfer absorbance for tryptophan methyl ester intercalated into **6**−ZrP. Equilibrium solution concentrations of tryptophan methyl ester are indicated.

Table 2. Comparison of Solution and Intercalation Compound Host−Guest Association Constants

Cyclophane	Analyte	Binding in Solution (M^{-1})	Binding in Solid (M^{-1})
		7100±90	1600±90
		(3.3±0.1) x 10^3	670±20
		210±50	**
		(1.9±0.4) x 10^3	420±60

**Intercalates α-ZrP without cyclophane present

the intercalation reaction with TBA^+OH^-. The Brønsted acid−base reaction imparts a positive charge to tryptophan methyl ester. Once intercalated, it can only be removed by cation exchange (which also removes **6**). Chiral HPLC analysis of the supernatant solutions showed that there was no enantioselectivity in the intercalation/host−guest association reaction. This is consistent with the solution-phase results, which showed that there was no enantioselectivity in the association of protonated tryptophan methyl ester with **6**.

DL-Indole-3-Lactic Acid. Indole-3-lactic acid complexes quite strongly with **6** in acetonitrile solution (Table 1). However, pure enantiomers of indole-3-lactic acid were not available, and so the enantioselectivity of the solution-phase association reaction could not be determined**.** Solid-phase experiments were performed with racemic indole-3-lactic acid, as with tryptophan methyl ester, to determine whether the solid-state complexation reaction was enantioselective. Over the concentration range studied (0.1−50 mM), a progression of increasing CT band intensity was observed with increasing concentration of indole-3-lactic acid. Analysis of the supernatant solutions showed the expected Langmuirian binding (by UV−visible spectroscopy) but no enantioselectivity in the intercalation reaction (by chiral HPLC).

Comparison of Association Constants in Solution and in α-ZrP Intercalation Compounds. As shown in Table 2, association constants in the intercala-

tion compounds are approximately a factor of 5 lower than those of the same host−guest complexes in solution. A reasonable explanation for this effect is electron donation by the negatively charged α-ZrP sheets, which reduces the π-acidity of the cyclophane host. This effect is not observed in the binding of **2** with **1** in α-ZrP, because the quaternary ammonium ion that binds **1** in the solid is relatively remote from the π-accepting dinitrobenzoyl group.

Conclusions

We have synthesized a conformationally rigid, chiral cyclophane **6** containing a 4 Å wide cavity for inclusion of aromatic guests. **6** binds indole and indole derivatives strongly in aqueous and organic media and binds tryptophan methyl ester with an enantioselectivity ratio of 3.4. When this cationic host is intercalated into α-ZrP, the solid is preorganized for intercalation of π-donor guests, and the binding isotherm of indole and indole-3-lactic acid are consequently Langmuirian.

The dimensional stability and high capacity of the cyclophane-intercalated solid could in principle provide a significant advantage for chiral separations, relative to those prepared with "floppy" hosts such as **1**. However, certain problems remain with these materials. Host−guest association constants are significantly lower in the intercalation compounds than in solution, and it is probably advisable to redesign the host so that the π-accepting and positively charged groups are remote from each other. The lack of enantioselectivity in the solid can be attributed to the protonation of basic guests by α-ZrP. Future work in the laboratory will focus on the redesign of these cyclophane hosts and lamellar solids to overcome these problems.

Acknowledgment. We thank Prof. Craig Wilcox of the University of Pittsburgh for providing a copy of the HOSTEST (5.0) program, Dr. Xumu Zhang for use of the Chiralcel OD column, and Dr. Timothy E. Glass for assistance with the molecular mechanics calculations. This work was supported by a grant from the National Institutes of Health (GM 43844). Instrumentation for X-ray diffraction experiments was provided by NSF Grant DMR-9402860.

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