Effect of Cavity Size on Supramolecular Stability

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Abstract: We describe the synthesis of a boxlike cyclophane **1**, its complexation with *p*-nitrophenol, the temperature dependence of the ^{1}H NMR spectra of the **1**:*p*-nitrophenol complex, and the effect of solvent on complexation. Cyclophane **1** was designed to test our previous observations on the effect of cavity size and π-hydrogen bonds in stabilizing host–guest complexes in nonpolar solvents. It exhibits an association constant with *p*-nitrophenol in excess of 400 000 M^{-1} in $CDCl_3$. The high stability of the complex is paralleled by slow exchange between free and complexed cyclophane. The axial spinning of the xylene units of the host is slow in the complex but fast in the free host. It is shown that the rate-determining step for xylene spinning is dissociation of the complex. The two guest protons ortho to the nitro group in the phenol are distinct in the complex; their interconversion requires its dissociation. Both K_{assoc} and k_{exch} are dependent on the solvent. Solvents that are "big" (chloroform and tetrachloroethane) exhibit large K_{assoc} values and slow exchange, while "small" solvents (dichloromethane and 1,2-dichloroethane) exhibit both smaller K_{assoc} values and faster exchange. These solvent effects are interpreted in terms of a binding model involving displacement of one intracavity species by another.

Introduction[1]

A number of structural features are commonly used in the design of host molecules:

(1) Hydrophobic complexation, as illustrated by the cyclodextrins, is historically the first and "defining" force in host–guest complex stabilization.[2] Its great importance to biological systems has caused it to be the subject of intense scrutiny. While such complexation was originally ascribed to entropic effects,[3] current thinking is revisionist in ascribing it primarily to enthalpic features of the hydrogen bond and differential solvation of host and guest.[4] A particularly illuminating series of papers by Diederich summarizes the arguments for this viewpoint.[5]

(2) The hydrogen bond has been exploited to great effect in the design of hosts capable of acting primarily[6] in aprotic organic solvents.

(3) Aromatic–aromatic π stacking has been described by Rebek, Hamilton, and many others in building nucleoside binding hosts.[7]

(4) The "lock and key effect", refined as Cram's preorganization concept, has received increasing scrutiny recently.[8,15]

(5) Edge–face aromatic–aromatic interactions have been advanced as a stabilizing force on protein conformations. In favorable cases they exercise a positive effect on complex stability.[9,12d,g,27]

(6) Ion–ion and ion–dipole effects have proven effective in cases studied by Dougherty and others.[10]

(7) Computational tools are increasingly important in this area with respect to both the nature of solvophobic interactions and the origins of host–guest interactions.[11]

Goals and Summary

Our goal was to explore the consequences of constructing a host molecule **1** (Figure 1) that affords, by molecular modeling, an almost perfect fit for an aromatic guest. Our previous work in this area[12] has shown that host **2c** forms stable inclusion complexes in organic solvents with hydrogen bond-donating guests

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(1) Abbreviation: pnp, *p*-nitrophenol.

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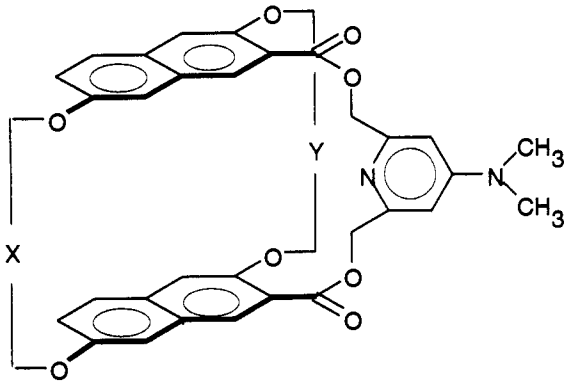


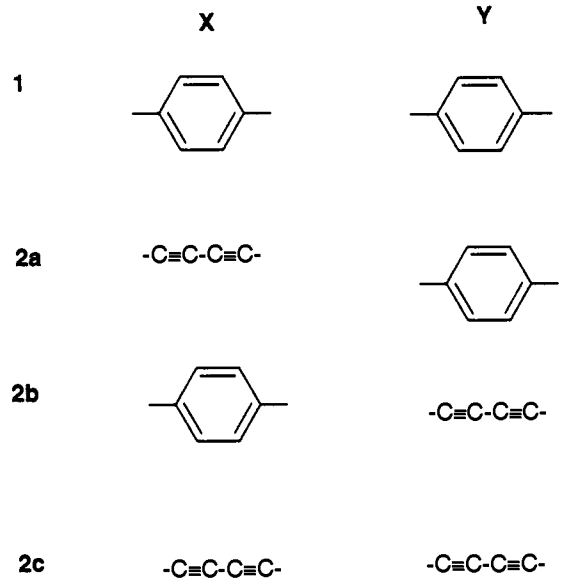
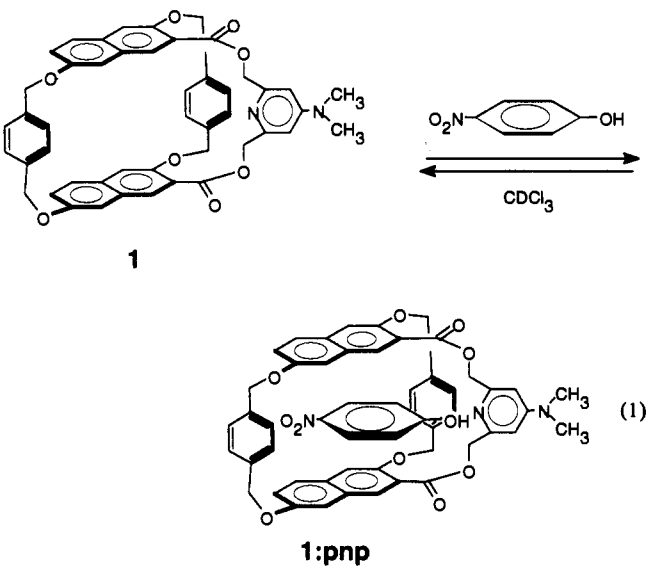


Figure 1. Range of host structures considered.

(e.g., *p*-nitrophenol) with only a single hydrogen bond present. Replacing one of the 2,4-hexadiyne bridges with *p*-xylene units led to hosts **2a** and **2b**, resulting in a major increase in the stability of their *p*-nitrophenol complexes. X-ray and spectroscopic evidence suggests that this increase of stability is due to combination of closer fit and edge–face interaction between the host *p*-xylyl bridge and the perpendicular intercalated guest, primarily the latter. Replacing both bridges X and Y by *p*-xylene spacers offered the possibility of further stabilization by formation of two π-hydrogen bonds (edge–face interactions). Since a *p*-xylene unit is approximately 0.9 Å shorter than a 2,4-hexadiyne unit, the cavity of **1** is appreciably smaller than in **2a–2c**. This could lead to enhanced stabilization of the complex by maximizing van der Waals interactions, but it could also lead to steric destabilization. Corey–Pauling–Koltun (CPK) models indicated and "exact" fit of 1,4-disubstituted benzenes in the cavity. Similarly, molecular mechanics calculations indicated no appreciable steric congestion in the inclusion complex. As we will show below, **1** forms a complex (eq 1) with *p*-nitrophenol[1] of remarkable thermodynamic and kinetic stability; this appears to be due to a combination of both π-hydrogen bonds and steric exclusion of solvent from the cavity. In particular, the remarkable stability of **1**:pnp over similar complexes of **2** need not be explained by invocation of any "special" effects arising from immobilization of the guest.



(1)

(A) Synthesis of 1. The two xylyl and the pyridine bridges of cyclophane **1** were attached to the naphthyl functionality in three separate steps (Scheme 1) by the application of procedures used previously in these laboratories. Etherification of propyl 3,7-dihydroxy-2-naphthoate (**3**) with 0.5 equiv of α,α-dibromo-*p*-xylene (**4**) (K_2CO_3, acetone, 25 °C) at the distal 7-hydroxy substituent gave the xylyl diether **5** in 69% yield. Coupling of the proximal 3-hydroxy substituent of **5** with 1 equiv of dibromide **4** (Cs_2CO_3, DMF, 52 °C) gave the cyclophane dipropyl ester **6** in 21% yield. This cyclization reaction was accompanied by a substantial amount of higher molecular weight material; efforts to improve the yield were unsuccessful. Hydrolysis (LiOH, aqueous THF, 25 °C) of the propyl ester groups of **6** to the corresponding diacid **7** followed by attachment of the third bridge by cyclodialkylation (K_2CO_3, DMF) of **7** with 2,6-bis(bromomethyl)-4-(dimethylamino)pyridine (**8**) afforded cyclophane **1** in 45% yield.

Cyclophanes **1** and **6** have distinctive and readily interpretable NMR spectra (Table 1), similar in many respects to those of the cyclophanes reported previously. Comparison of the NMR spectra of these cyclophanes to those of their acylic precursor **5** indicates that both the naphthyl and the xylyl protons shift upfield upon cyclization, a reflection of the close packing of aromatic residues in the molecule. Cyclophane **6**, with only two xylyl bridges, undergoes free rotation of the various rings, as is evident by the two sharp singlets observed for the methylene protons. When the third bridge is attached as in **1**, a static 3-dimensional molecule is created. The three unique sets of methylene protons

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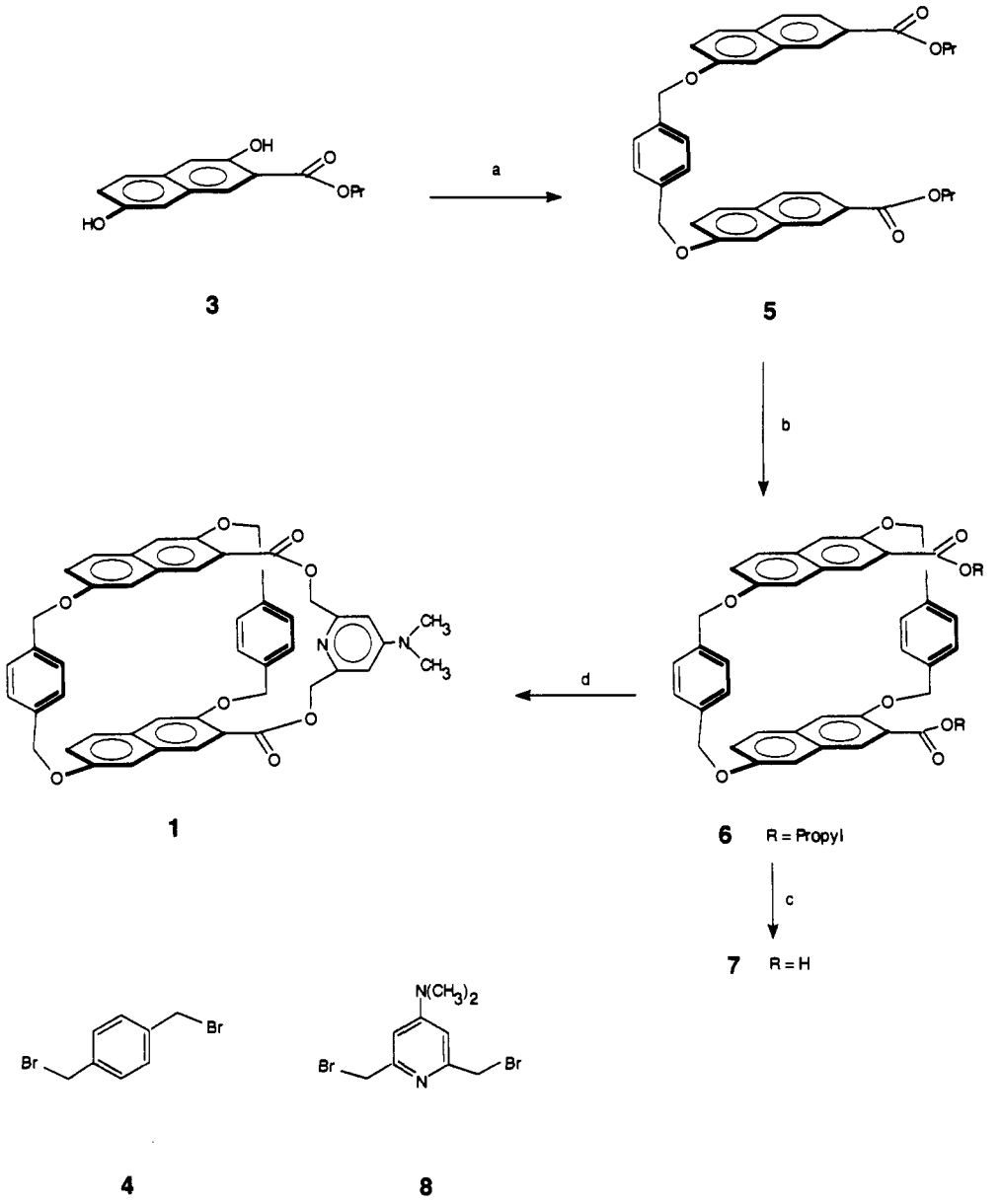
Scheme 1[a]



[a] (a) Dibromide **4**, K_2CO_3, acetone. (b) Dibromide **4**, Cs_2CO_3, DMF, 52 °C. (c) LiOH, aqueous THF. (d) Dibromide **8**, K_2CO_3, DMF.

Table 1. Chemical Shifts of **5**, **6**, and **1**, and **1**:*p*-Nitrophenol[a]

entry[a]	δH_1	δH_4	δH_5	δH_6	δH_8	δxy_d	δxy_p	δpy
5	8.36	7.28	7.62	7.28	7.19	7.53		
6	7.96	6.77	7.12	6.77	7.16	7.30	7.21	
1	8.03	7.06	7.33	7.02	7.0	7.33	6.78	6.87
1:pnp[b]	7.07[c]	6.83	7.08	6.93	6.48	7.53	7.13	6.93

[a] In $CDCl_3$, at 25 °C. [b] One equivalent of *p*-nitrophenol. [c] δ complex for H_1 was calculated to be 7.07 ppm (host is 0.007 M).

in **1** are each diastereotropic pairs, and three distinct AB quartets are observed. In contrast, the sharp singlets observed for the aromatic xylyl protons of **1** suggest that these rings are freely rotating at 25 °C. The signals observed for the aromatic xylyl protons are separated by 0.55 ppm. The assignment of the upfield peak to the xylyl that is shielded by the pyridine ring is consistent with results obtained for **2a** and **2b**. The chemical shift and multiplicity of the remaining naphthyl and pyridyl protons of **1** are unexceptional, other than an appreciable upfield shift relative to previous cyclophanes in this series. The marked upfield shifts of H_4 and H_6 observed in **6** (δ 6.77) are at a normal position in **1** (δ 7.0), suggesting that a parallel alignment of the two naphthalene faces results when the third bridge is in place. This agrees with molecular modeling calculations which show that **6** has several low-energy conformations related by rotation about the naphthalene C_3–C_7 axis. The variable-temperature ^1H NMR spectrum of host **1** was unexceptional (see below).

(B) *p*-Nitrophenol Complex. Major changes occur in the spectrum of host **1** upon addition of 1 equiv of *p*-nitrophenol in $CDCl_3$ at room temperature (Table 1). The spectra of host **1** and its complex are shown in Figures **2a** and **2f**, respectively, and the following points are noted:

(1) The signals of the naphthalene protons of **1** are shifted upfield, with the largest shifts for H_1 and H_8 ($\Delta\delta$ = 0.96 and 0.52 ppm, respectively).

(2) The proton signals of both the distal and the proximal (to the pyridine) xylyl rings become quite broad ($\nu_{1/2}$ 10–20 Hz) and are shifted downfield by 0.2 and 0.35 ppm.

(3) The signals representing the two 3,5 protons of *p*-nitrophenol move upfield to δ 3.4 from their normal position at δ 8.2 (the 2,6 protons of the guest are partially obscured by the 12 host methylene protons at $\delta \sim 5$). This assignment was verified by use of *p*-nitrophenol-3,5-d_2,[13b] which gave a spectrum showing only the

(13) (a) This procedure was worked out by Mr. John Cochran. We would also like to thank him for providing a sample of the dibromide. (b) We thank Mr. Timothy Parrott for a sample of the deuterated phenol.

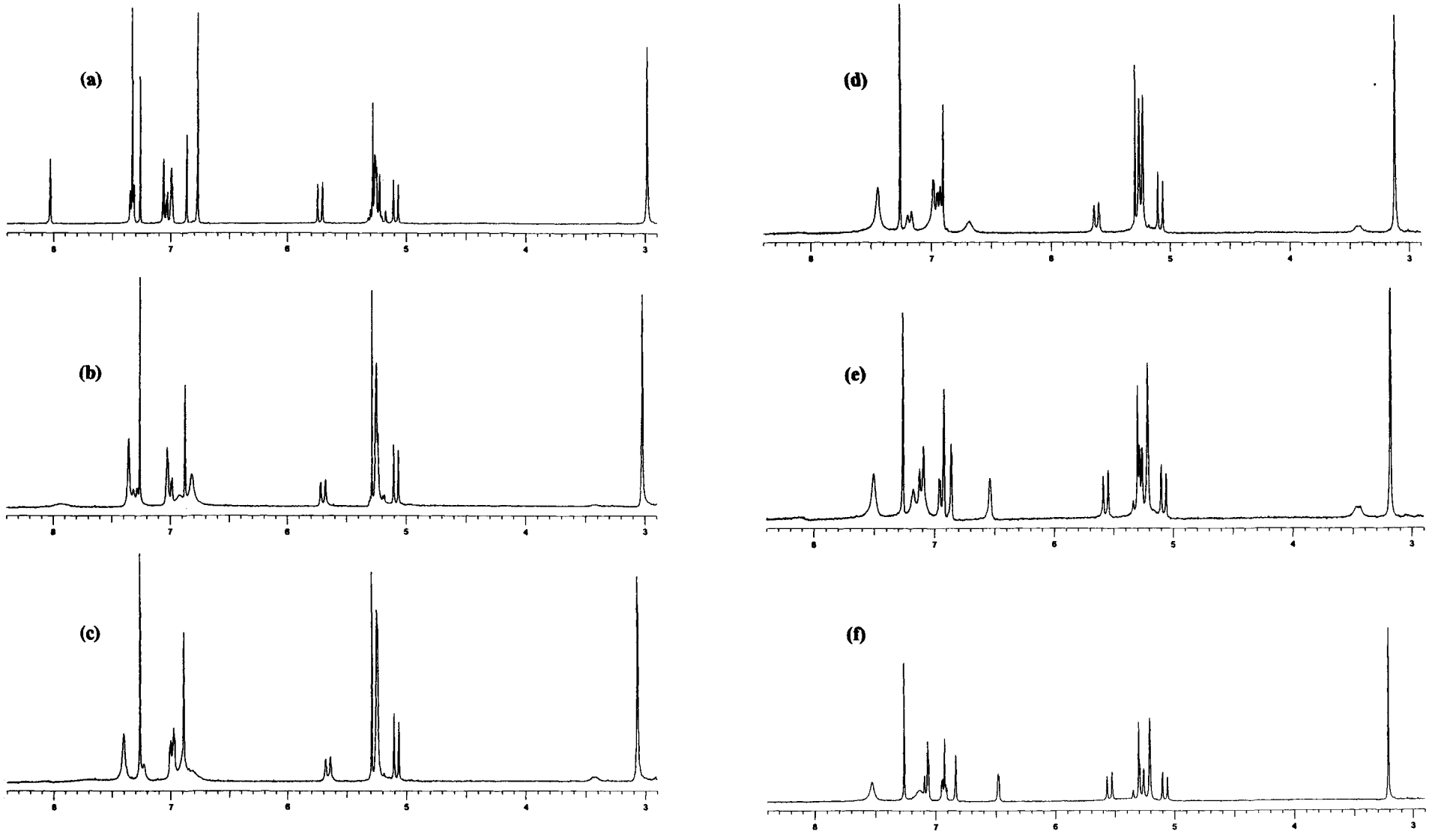


Figure 2. ^{1}H NMR spectra in $CDCl_3$ (host is 0.007 M) at 25 °C: (a) cyclophane **1**; (b–e) **1** and 0.14, 0.34, 0.55, and 0.82 equiv of *p*-nitrophenol, respectively; and (f) **1** and 1.1 equiv of *p*-nitrophenol.

peak at δ 3.4. At 25 °C, H_3 and H_5 of the guest are NMR equivalent (fast exchange).

(4) Both the signals of the methyls of the amino group and those of the aromatic pyridine protons shift downfield, a consequence of the pyridine acting as a hydrogen bond acceptor.

(5) The lower half of the AB quartet of the pyridyl 2,6-methylene protons shifts upfield upon complexation, but the signals of the other methylene protons are unchanged.

These chemical shift changes are consistent with the formation of a host–guest complex between **1** and *p*-nitrophenol (eq 1) with the guest lying in the cavity parallel to the two naphthalene rings (π stacking). The remarkable upfield shift observed for the guest protons and the downfield shift of the xylyl protons suggest that there is also a π-hydrogen bond[9] face–edge interaction between each guest proton and the xylyl rings. Similar results were obtained with CD_2Cl_2 as solvent except that the xylyl protons appeared as sharp singlets in the resulting spectrum. In summary, the NMR spectrum of the **1**:pnp complex fully supports the concept of a highly organized structure dominated by various aromatic–aromatic interactions and held in place by a single hydrogen bond.

(C) Complexation Studies. We have determined the association constant for the interaction of **1** with *p*-nitrophenol using three methods: (1) titration of host with guest in various solvents followed by nonlinear least-squares fitting of the data to binding models; (2) serial dilution of a solution of the complex to the point that dissociation into its components can be observed; and (3) competition between two hosts for a limited amount of guest. Dynamic NMR studies will be described below.

(1) Direct Titration. The NMR titration method, in conjunction with the nonlinear least-squares fit of the data to 1:1 and 1:2 models,[12a] was used to determine the association constants (K_{assoc}) for the formation of the **1**:pnp complex. Titration curves obtained in $CDCl_3$ and CD_2Cl_2 are shown in Figure 3. Only the 1:1 model fits the data. The upfield chemical shift of H_1 or H_8 of host **1** or the downfield shift of the 3,5 protons of *p*-nitrophenol was followed as small increments of guest were added. These protons were chosen because their chemical shifts are most sensitive to complexation, although similar but less accurate calculated best-fit K_{assoc} constants are derived from other protons. This method encounters difficulties when volatile solvents are used and if the association constant is very large ($K_{assoc} > 10\,000$ M^{-1}); it assumes in addition that there is fast exchange of guest between free and bound host.

(a) Solvent Effects. In CD_2Cl_2 (or 1,2-dichloroethane-d_4), all the peaks are easily identified and remain as sharp signals throughout the titration at 21 °C, indicating fast exchange between free and complexed host (see supplemental material). The doublet for the 3,5 protons of *p*-nitrophenol gradually shifts downfield from its initial position at δ 3.6 to 4.3 after 1 equiv of guest is added. Fitting the titration data to a 1:1 model affords a calculated association constant of 26 000 M^{-1} in this solvent (Table 2). NMR titration experiments are subject to numerous inaccuracies, especially when done in volatile solvents. We thus emphasize the approximate nature of the above value and view it as "small" (see below).

The complexation behavior is very different in $CDCl_3$ or tetrachloroethane-d_2. In these solvents the titration data give only minimum estimates for the calculated association constant. Because of the large value of K_{assoc}, the titration curve becomes two intersecting straight lines (Figure 3), and the calculated best-fit K_{assoc} is dominated by small experimental errors. The calculated K_{assoc} is "large" (Table 2), certainly much greater than that in CD_2Cl_2. In contrast to the titration in CD_2Cl_2, slow exchange of the *p*-nitrophenol between free and complexed host **1** results in broad peaks of the host protons (Figure **2a–f**). Since the extent of broadening is dependent upon the chemical shift difference upon complexation, H_1 and H_8 are most affected, and the determination of the chemical shift of these protons is less accurate in these solvents. Peak broadening is at a maximum when 0.5 equiv of guest has been added, since equal amounts of free and complexed host are present. In the spectrum of the **1**:pnp complex (1 equiv of guest), all the signals are sharp except those of the two xylyl groups. Only the spectrum of bound host is observed.

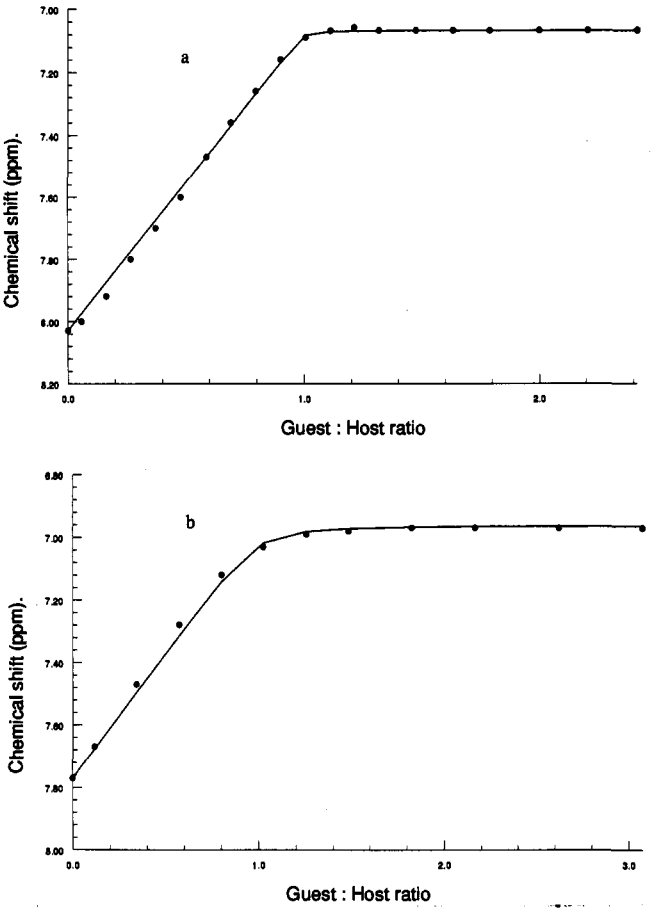


Figure 3. Plot of observed (●) and calculated chemical shift of H_1 of cyclophane **1** upon titration with *p*-nitrophenol. (a) In $CDCl_3$ (0.007 M), the calculated curve used data from the least-squares fit: δH_1 (host) 8.03, δH_1 (complex) 7.07, K_{assoc} = 420 000 M^{-1}, R = 0.017. (b) In CD_2Cl_2 (0.006 M), the least squares fit: δ (host) 7.77, δH_1 (complex) 6.96, K_{assoc} = 26 000 M^1, R = 0.017.

Table 2. Complexation of **1** with *p*-Nitrophenol Determined by Direct Titration and Competitive Complexation[a–c]

entry	solvent	K_{assoc}[a]	K_{rel}[b]	K_{assoc}[c]
1	$CDCl_3$	420 000	2.8	324 000
2	$CDCl_2CDCl_2$	150 000		
3	CD_2Cl_2	26 000	0.8	20 000
4	CD_2ClCD_2Cl	14 000		

[a] These values were determined by nonlinear least-squares reduction of the NMR data using H_1 as the titratable proton. [b] Determined by competitive binding experiments of *p*-nitrophenol with **1b** (see text). [c] Calculated from δ_{obsd} for H_1 or H_8 after serial dilution of the complex.

In $CDCl_3$, the signal for the 3,5 protons of added *p*-nitrophenol does not shift from its initially observed position at δ 3.4 until 1 equiv of the phenol has been added. With excess *p*-nitrophenol present, the signal of the 3,5 protons moves gradually downfield toward δ 8.2, in proportion to the amount of guest added. In contrast, in CD_2Cl_2, a continuous downfield movement of the guest protons occurs, even when small amounts of phenol are added.

In acetonitrile as solvent, binding constants were small. Since chloroform is our reference "solvent of interest", the effect of solvent polarity per se was not pursued.

(b) Association Constants. The values obtained for K_{assoc} for the binding of **1** with *p*-nitrophenol in different solvents are presented in Table 2. The association constants determined by the titration method are extremely large for this type of system.

As noted previously, the values extend beyond the resolution capability of the least-squares analysis and thus should be considered as only approximate. With $CDCl_3$ (or tetrachloroethane-d_2) as solvent, K_{assoc} appears to be extremely large (400 000 M^{-1}), as might be expected for a system in which slow exchange of guest occurs. In CD_2Cl_2 (or dichloroethane-d_4), K_{assoc} is much smaller (20 000 M^{-1}), although still very large for a complex held together by a single hydrogen bond. For each solvent, K_{assoc} appears to be independent of the proton used for the nonlinear least-squares fit calculation. For a solution of host **1** (0.007 M) in $CDCl_3$, the plot of chemical shift versus the guest:host ratio gives a curve with a well-defined break at 1 equiv of *p*-nitrophenol (Figure 3). Visual examination of the corresponding titration curve in CD_2Cl_2 shows a more gradual break at 1 equiv. This observation supports the numerically generated association constants.

(2) Serial Dilution Experiments. The values of K_{assoc} obtained by the titration method were qualitatively confirmed by a set of a serial dilution experiments. For a solution (4.0 mM) in $CDCl_3$ of the **1**:pnp, the fraction (F) of host that is complexed is close to 1.00. When this sample is diluted to 0.066 mM, the fraction complexed drops to $F = 0.81$, and a single point determination of the association constant gives $K_{assoc} = 324\,000\ M^{-1}$. In CD_2Cl_2, a solution of the complex that is 0.4 mM has $F = 0.66$ and $K_{assoc} = 15\,000\ M^{-1}$. Although with extremely dilute solutions one must always consider the possibilities of wall adsorption effects, values of K_{assoc} determined by serial dilution are consistent with those presented in Table 2.

(3) Competition Experiments. We have described[12d] use of competition experiments to determine the relative values of association constants of a series of hosts with a given guest. Application of this method to cyclophane **2a** afforded an association constant for complexation with *p*-nitrophenol of 96 000 M^{-1}, in good agreement with that determined from the direct titration method.[12a] When cyclophanes **1** and **2a**, differing only in the nature of the distal bridge, are allowed to compete for a limited amount of *p*-nitrophenol, it was found that the ratio of complexed **1**:**2a** was 0.8 in CD_2Cl_2 and 2.8 in $CDCl_3$. Although peak broadening in $CDCl_3$ restricted the range of this method, the values obtained for K_{assoc} are comparable to those obtained by the titration method described above and those from the dilution experiments. The quite different behavior in the two solvents in noteworthy.

The experiments described in this section support the idea that host **1** with its double xylyl bridges forms very stable complexes even at high dilution, leading to association constants that are exceptionally large. There appears to be a marked enhancement of the association constant when the solvent is chloroform or tetrachloroethane as compared to dichloromethane or dichloroethane.

(D) Variable-Temperature NMR Studies. The fact that addition of *p*-nitrophenol to solutions of host **1** led first to peak broadening followed by resharpening of the spectra (Figure 2) strongly suggested that exchange broadening phenomena were at work. The unusual stability of the **1**:pnp complex together with this peak broadening effect led us to study the variable-temperature NMR behavior of this system in both $CDCl_3$ and CD_2Cl_2, particularly since there is a paucity of studies of the dynamics of supramolecular complexes. Three sets of experiments were performed over a wide range of temperature: free host **1** (no guest present); **1**:pnp complex (1 equiv of guest); and a 1:1 mixture of free host **1** and **1**:pnp complex (0.5 equiv of guest). The chemical shifts and line widths of the peaks were followed as a function of the sample temperature. Figure 4 shows the variable-temperature spectra of the 1:1 mixture in $CDCl_3$. Because of the complexity of the spectra, no attempt was made to fit the observed spectra with dynamic curve-fitting programs. In the discussion below, only the qualitative and semiquantitative aspects of our observations are treated: we emphasize that our results are *not* of high numerical precision.

Host 1. Other than slow broadening of the dimethylamino methyl proton signals, the spectrum of host **1** in $CDCl_3$ or CD_2Cl_2 was unchanged to –60 °C. Signals due to the two *p*-xylyl bridges behaved similarly and exhibited "free" rotation to the minimum accessible temperature.

1:pnp Complex. In the spectrum of this complex (prepared by the addition of 1.0 equiv of *p*-nitrophenol-2,6-d_2 to **1**), the signals assigned to the two spanning xylyl units are quite broad at room temperature. Upon cooling of the NMR sample, further broadening occurred, followed by resolution into two sharp singlets at –41 °C. This result arises from the slow rotation of the xylyl groups about their 1,4 axis such that the 2,3 and 5,6 protons of each xylyl ring become nonequivalent. Under slow rotation, H_2 and H_3 constitute an enantiotopic pair (as do H_5 and H_6), so only a meta coupling of *ca.* 2 Hz is seen at the low-temperature limit. Other signals were unchanged on lowering the temperature, as is required by the structural model.

Mixture (1:1) of Host 1 and 1:pnp Complex. As shown in Figure 4, the behavior of a 1:1 mixture of unbound host **1** and **1**:pnp complex (prepared by addition of 0.5 equiv of *p*-nitrophenol-2,6-d_2 to **1**) in $CDCl_3$ was followed over a range of temperatures. The temperature-dependent behavior of the individual protons in these spectra are interpreted as involving dynamic exchange between free host **1** and **1**:pnp complex. At the high-temperature limit of 51 °C, a normal spectrum with well-defined peaks and chemical shifts that are expected for a rapidly exchanging mixture of host and complex is observed. At this temperature, the chemical shifts correspond to the weighted average of free and bound **1** in rapid equilibrium. At the low-temperature limit of –41 °C, separate sharp spectra of both free and bound **1** may be observed. Between these temperature extremes, coalescence of the various protons occurs. The spectrum of the 1:1 mixture at –41 °C was compared with that of host **1** and **1**:pnp complex, also at –41 °C. The spectrum of the mixture at this temperature is the superposition of the spectra of free host **1** and **1**:pnp complex. We will now look at the behavior of various protons in this 1:1 mixture.

Naphthyl H_1. The host proton with the greatest chemical shift difference ($\Delta\delta = 0.96$ ppm) upon complexation is the naphthyl H_1. At 51 °C, H_1 appears as a broad singlet at δ 7.53, the weighted averaged at this temperature between free **1** (δ 7.96 at 51 °C) and bound **1** (δ 7.05) present in equal proportion. As the temperature is gradually lowered, the signal continues to broaden until the signal decoalesces at 13 °C (T_c). Below the coalescence temperature, the signal of unbound **1** at δ 8.0–8.2 continues to increase in intensity. Finally at –41 °C, a broad singlet at δ 8.16 ($\nu/2 = 10$ Hz) is observed for H_1 of free host **1**, and a sharp singlet ($\nu/2 = 3$ Hz) at δ 7.09 is observed for H_1 of the **1**:pnp complex. The difference in line width of the two signals is believed to be due to some conformational mobility of the carbonyl groups of the dilactone bridge in the host when it is free of guest and is also observed in the host alone. From the chemical shift difference ($\Delta\nu$) of 264 Hz between free and bound **1** at 13 °C (T_c), one may obtain an exchange rate constant, $k_{exch} = 587\ mol^{-1}$, and $\Delta G^{\ddagger} = 13.1$ kcal/mol.

Naphthyl H_8. This proton behaves similarly to H_1; at 51 °C, H_8 appears as a doublet ($J_{6,8} = 2.6$ hz) at δ 6.75, the average chemical shift of rapidly exchanging free (δ 7.0) and bound **1** (δ 6.5). At 2 °C decoalescence occurs, and a signal due to H_8 of bound **1** develops at δ 6.5 as the temperature is decreased. At –41 °C, peaks due to H_8 of both free and bound **1** appear at of δ 7.03 and 6.51, respectively; $T_c = 2$ °C, $\Delta\delta = 141$ hz, $k_{exch} = 313\ mol^{-1}$, and $\Delta G^{\ddagger} = 12.9$ kcal/mol. The lower coalescence temperature for H_8 than for H_1 arises from the smaller $\Delta\nu$ for the former.

Pyridyl Methylene Protons. At 51 °C, the low-field doublet H_a ($J_{ab} = 11$ hz) of the AB quartet of the pyridyl methylene protons appears at δ 5.59, the average of the doublets of free and bound **1**. Coalescence occurs at 2 °C. As the temperature is lowered to –41 °C, the two doublets of free host **1** at δ 5.84 and

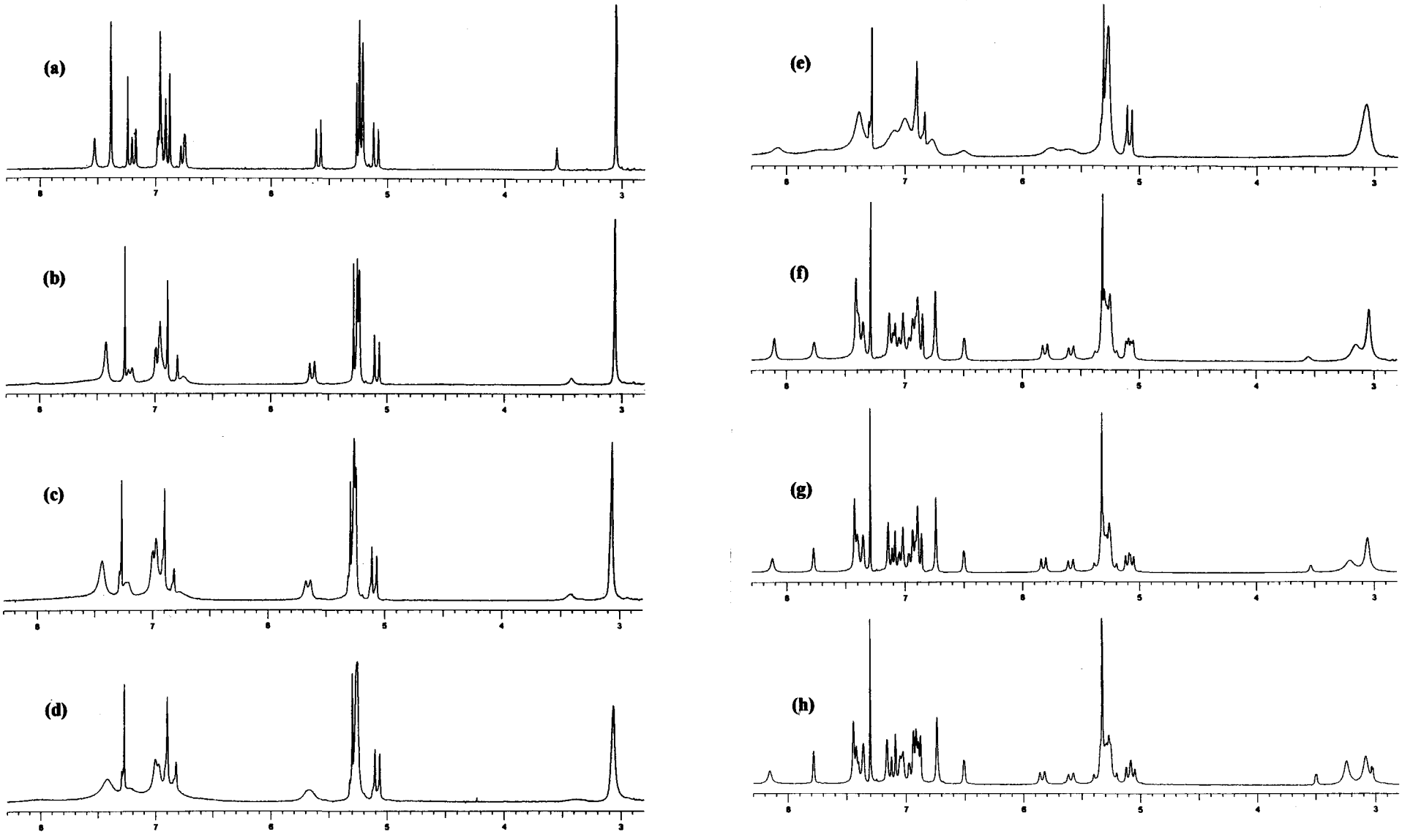


Figure 4. Variable-temperature ^{1}H NMR spectra of a 1:1 mixture of host **1** and **1**:pnp-d_2 complex in $CDCl_3$: (a) 51 °C; (b) 35 °C; (c) 13 °C; (d) 2 °C; (e) −9 °C; (f) −19 °C; (g) −29 °C; and (h) −41 °C.

Table 3. Chemical Shifts and Coalescence Temperatures (T_c) of **1** with 0.5 Equiv of *p*-Nitrophenol-d_2 in $CDCl_3$[h]

proton	δ_o[a]	δ_c[a]	$\Delta\delta$[b]	T_c[c]	k_c[d]	ΔG[e]
H_1	8.18	7.09	264	13	587	13.1
H_8	7.05	6.52	141	2	313	12.9
H_A	5.84	5.59	56	2	124	13.4
NCH_3	3.07	3.27	57	-9	127	12.8
H_{xy}[d]	7.44	7.78	47	2	105	13.5
		7.36	113[f]		251[f]	13.0[f]
H_{xy}[p]	6.74	7.42	105	2	233	13.1
		6.94	111[f]		247[f]	13.0[f]
$H_{3,5}$[g]	8.2	3.50	127	-9	282	12.4
		3.03				

[a] δ_o and δ_c represent the chemical shift (ppm) of free and complexed **1** at -41 °C. [b] Chemical shift difference (Hz) between free and complexed **1** at T_c. [c] Coalescence temperature in °C. Temperatures were determined by a calibration chart (methanol) and are estimated to be ±2°. [d] Calculated rate of exchange (s^{-1}) at T_c. [e] Calculated ΔG (kcal/mol) for exchange of guest between free and bound **1**. [f] Calculated $\Delta\delta$, k_c, and ΔG for rotation of xylyl. [g] Guest protons. [h] For H_1 in CD_2Cl_2, $\Delta\delta$, T_c, k_c, and ΔG are 213 Hz, -15 °C, 282 s^{-1}, and 11.4 kcal/mol, respectively.

bound host at δ 5.59 are observed; T_c = 2 °C, $\Delta\nu$ = 56 hz, k_{exch} = 124 mol^{-1}, and ΔG^* = 13.4 kcal/mol.

Dimethylamino Methyl Protons. The methyl protons of the dimethylamino group of **1** appear as a sharp singlet at δ 3.05 at 51 °C, again corresponding to fast exchange between free and bound **1**. As the temperature is lowered this signal gradually broadens, with coalescence occurring at -9 °C. Signals due to free and bound **1** at δ 3.07 and 3.27 are seen at -41 °C; T_c = -9 °C, $\Delta\nu$ = 57 hz, k_{exch} = 127 mol^{-1}, and ΔG^* = 12.8 kcal/mol.

***p*-Nitrophenol 3,5-Protons**: The temperature dependence of the guest protons in the 1:1 mixture of host **1** and **1**:pnp complex reflects only the different environment of the two protons of the *bound* guest, since this is the only type of guest in the mixture. The rate which is measured, exchange of H_3 and H_5 of *p*-nitrophenol, involves not a spinning of the *p*-nitrophenol unit within the complex but an exchange of guest between two host molecules. At 51 °C, a singlet at δ 3.56 is observed for the 3,5 protons of the guest. As the temperature is lowered, this signal broadens until decoalescence occurs at -9 °C. At -41 °C, two doublets ($J_{3,5}$ = 2.6 hz) appear at δ 3.5 and 3.03. Assuming $\Delta\nu$ = 127 hz at coalescence (T_c = -9 °C), then k_{exch} = 282 mol^{-1} and ΔG^* = 12.4 kcal/mol. It should be noted that *both* H_3 and H_5 are shifted upfield 5 ppm from their position in free *p*-nitrophenol-d_2. This is consistent with the initial hypothesis, and modeling studies that suggest that, in **1**:pnp complex, both H_3 and H_5 are involved in π-hydrogen bonds with the *p*-xylyl bridges. It may be noted that the average chemical shift of the two guest protons is upfield, whereas that of the protons of the complexed host is downfield as the temperature is lowered.

The above experiments are summarized in Table 3. The observations made argue strongly for there being a *single* exchange process involving interconversion of two kinds of host molecules, free and bound **1**, and two kinds of complexed guest protons, H_3 and H_5. The rate of the exchange process (k_{exch}) at T_c depends upon the chemical shift difference ($\Delta\nu$) for a particular proton, but ΔG^* is common to all of the processes examined. In $CDCl_3$, ΔG^* is about 13 kcal/mol. The variation of T_c from one proton to another is a consequence of differences in chemical shift and not due to the occurrence of different processes. Thus the spectra in Figure 4 demonstrate a two-site exchange process between a very stable complex and unbound host.

(E) Variable-Temperature Behavior of the Xylyl Bridges. The behavior of the protons of the *p*-xylyl bridges is more complicated than that of the other protons. A particular xylene (proximal or distal) may exchange between free and bound host, but it may also undergo a spinning about its C_1–C_4 axis wherein H_2–H_6 and H_3–H_5 interconversion is possible. This rate of this rotation of either the proximal or the distal xylyl groups along their 1,4 axes may be meausred, and the following observations can be made.

(1) Distal Xylyl. In $CDCl_3$ at 51 °C (Figure 4), the distal xylyl protons appear as a sharp singlet at δ 7.39, the weighted average of free (δ 7.28) and bound (δ 7.51) host **1**. At 2 °C, decoalescence occurs, and a new peak develops at δ 7.7 as the temperature is lowered further. At -41 °C, the signal for the protons of the distal xylyl group has split into three singlets in the expected ratio 2:1:1 at δ 7.44 (free host) and at δ 7.78 and 7.36 (bound host), respectively. From the chemical shift difference of 113 hz between the two kinds of distal protons ($H_{2,3}$ and $H_{5,6}$) in the bound host **1**, T_c = 2 °C, k_c = 251 mol^{-1}, and ΔG = 13.0 kcal/mol for the rotation process. Using a chemical shift difference of 47 hz for free and bound host at T_c = 2 °C, one may calculate k_{exch} = 105 mol^{-1} and ΔG^* = 13.5 kcal/mol for the exchange process.

(2) Proximal Xylyl. A similar analysis may be applied to the proximal xylyl protons. At 51 °C, a singlet is observed at δ 6.96, the fast exchange weighted average of free (δ 6.8) and bound **1** (δ 7.12). Below the T_c of 2 °C, resolution into three singlets in the ratio of 2:1:1 develops to the low-temperature limit of -41 °C, with δ 6.74 for unbound host and δ 7.42 and 6.94 for bound host **1**. From a chemical shift difference of 111 hz between the two kinds of proximal xylyl protons ($H_{2,3}$ and $H_{5,6}$) of bound host **1**, one calculates at T_c = 2 °C, k_{exch} = 247 mol^{-1}, and ΔG^* = 13.0 kcal/mol for the rotation process. From a chemical shift difference of 105 hz for the xylyl protons exchanging between free and bound host, T_c = 2 °C, k_{exch} = 233 mol^{-1} and ΔG^* = 13.1 kcal/m. We conclude that the rate of xylyl rotation and the rate of exchange process appear to measure the same process. In the absence of guest, the xylyl groups of the host **1** are free to rotate, and sharp singlets are observed for the xylyl protons. In the **1**:pnp complex, rotation is slowed by the presence of guest, and two singlets are observed for each of the nonrotating xylyl rings.

(3) Effect of Excess *p*-Nitrophenol. When the amount of *p*-nitrophenol was increased from 1.0 to 2.0 equiv, the spectrum was unchanged at -41 °C except that in addition to the doublets at δ 3.5 and 3.0 for bound guest, a new peak due to unbound guest appeared at δ 8.2. At this temperature, the peak width of the signals associated with the xylyl groups did not change. This result is consistent with an S_N1-like process in which the guest is expelled from completely bound host in the rate-determining step to give free host **1**, which then may undergo several rotations of the xylyl groups before reassociation to give the complex. The alternative possibility, xylyl rotation without dissociation, is consistent neither with the size of the cavity nor with the fact that dissociation has an activation free energy $\Delta G^* \cong$ 13 kcal/mol.

(F) Replacing $CDCl_3$ with CD_2Cl_2. Results similar to those described above were obtained when CD_2Cl_2 (see supplemental material) was used as the solvent, except that coalescence of the protons occurs at lower temperatures, and therefore ΔG^* is smaller (≈11 kcal/m). At 25 °C, all the peaks of the spectrum are sharp, indicating that rapid exchange is occurring between free and complexed **1** at this temperature. At -25 °C, a typical broadened spectrum in which most of the peaks have coalesced is obtained. Coalescence of H_1 occurs at -15 °C (28 °C lower than in $CDCl_3$). At -55 °C, most of the peaks due to free and complexed **1** may be identified, although the lower temperature required affects the resolution.

(G) Summary of Variable-Temperature NMR Experiments. Complex **1**:pnp exhibits a rather ornate NMR behavior from which a variety of dynamic processes can be extracted. In $CDCl_3$ as solvent, all such processes exhibit a $\Delta G^* \simeq$ 13 kcal/mol, leading to the conclusion that a single underlying process, unimolecular dissociation of the complex, is responsible. The basic exchange of guest between free and complexed **1**, rotation of the xylyl rings and flipping of the bound guest, is similar in CD_2Cl_2 and $CDCl_3$, but coalescence occurs at an appreciably lower temperature in CD_2Cl_2, and $\Delta G^* \cong$ 11 kcal/mol. Both activation energy for dissociation of $\Delta G°$ differ by approximately 1.5–2.0 kcal/mol in the two solvents. Thus the greater thermodyanmic stability of

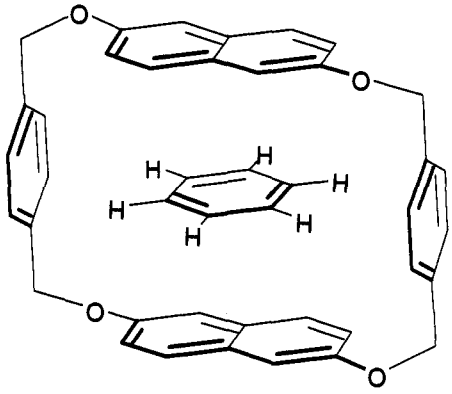


Figure 5. Perspective view of MM2-minimized complex of root cyclophane host and benzene. This figure shows the lack of steric strain on encapsulation of a benzene by the cyclophane host.

1:pnp complex in $CDCl_3$ compared to that in CD_2Cl_2 is paralleled by its greater kinetic stability toward dissociation.

Discussion

Host **1** completes a series of systematically modified cyclophane host molecules capable of complexing hydrogen bond donors in nonpolar media. As the structure of the host changes from **2c** with two diyne connectors to **2a and 2b** with one diyne and one *p*-xylyl to **1** with two *p*-xylyl connectors, the association constant with *p*-nitrophenol increases from ~3600 M^{-1} to >400 000 M^{-1}. Why?

Size of Cavity. Molecular Mechanics. A connecting *p*-xylyl unit is approximately 0.9 Å shorter than a 2,4-hexadiyne unit. Thus there is a more exact "lock and key" fit as we decrease the length of the bridge. The effect is quite pronounced with CPK[14] molecular models; there is a perceptibly "snug" fit of *p*-nitrophenol with **1** and a much looser fit with **2c**. Cram has suggested that snugness of fit, as measured by CPK models, is a desirable attribute of stable complexes.[15] This has been disputed by Collet[16] on the basis of a series of cryptophane-halogenated alkane binding studies. It should be noted that, in the context of the present complexes, snugness of fit in the absence of strain introduction is "good" simply because it maximizes van der Waals contacts. Molecular mechanics calculations (MacroModel V3.5[17]) easily resolve this question in the case of **1**. Using the MM2* force field[18] we find the following (see Figure 5):

(1) The rectangular [2.2.2.2] tetraoxacyclophane (Figure 5) has an energy minimum with naphthalenes parallel to one another. There are several other minima arising from rotation about the naphthalene 2,6 axis. The cavity is 9.77 Å wide and 6.75 Å high.[19] The height is almost exactly that expected (6.84 Å) for minimum energy contact between the π-faces of guest and host.[20]

(2) Placing a benzene molecule in the cavity leads to two minima, one that is centered with C_2 symmetry and the other with the benzene moved perpendicular to the cavity face by ~0.5 Å; the latter is more stable by 0.3 kcal/mol.

(3) Replacing the benzene by a $CHCl_3$ molecule (C–H perpendicular to naphthalenes) led to its prompt ejection from the cavity, resulting in a minimized structure similar to that found earlier[12f] by X-ray.

(4) Placing a benzene molecule in a cone perpendicular to the cavity and ~2 benzene diameters away from the host leads, upon minimization, to its docking to form the intracavity complex (E_{steric} = 38.73 kcal/mol). The same complex is converged upon whenever the benzene is placed (any orientation) less than ~5 molecular diameters away and has an unobstructed approach to the cavity.

(5) Placing the benzene ~10 diameters away prevents its incavitation and gives an E_{steric} of 52.71 kcal/mol (gas-phase ΔE_{steric} = 14 kcal/mol).

Replacing the benzene guest with a *p*-nitrophenol molecule and adding a pyridine bridge to the model produces the **1**:pnp complex. This behaves in an exactly analogous manner, exhibiting spontaneous docking (but only from the back) and substantial stabilization of the complex relative to the two pieces (gas-phase ΔE_{steric} = 19.4 kcal/mol). A stereoscopic view of the final minimized structure is shown in Figure 6 and is in complete agreement with the experiment observations.

One concludes from these molecular mechanics calculations that, for both the base cyclophane and host **1**, attractive cavity–benzene interactions are larger than repulsive ones and that movement of guest into the cavity proceeds with continuously decreasing E_{steric}. Little or no reorganization of the cavity is needed. The same conclusions are reached upon changing the force field from MM2* to Amber* or the starting *syn–anti* conformation of the cyclophane host.

Effect of Guest Immobilization. The idea of immobilization[24e] as a stabilizing factor need not be invoked as the principal source of the structural dependencies observed. In all cases wherein we have obtained X-ray structures of complexes of these hosts with *p*-nitrophenol, the guest benzene ring is in van der Waals contact with the two naphthalene faces of the host. Expansion and shrinking of the cavity of these "rigid" tricyclic hosts is easily achieved by torsion about the axis normal to the naphthalene faces, so the host cavity adjusts itself to the thickness[12] of the aromatic guest. The complex of *p*-nitrophenol and both *dl*- and *meso*-**2c** has the aromatic rings in direct contact. Although we have been unable to obtain X-ray quality crystals of **1**:pnp complex, from the NMR spectra the aromatic rings are clearly in contact here also. The principal argument against an entropy-based immobilization argument, however, is that it is not required by the data.

Face–Face Aromatic Interactions. The importance of π–π interactions between the guest *p*-nitrophenol and the naphthalene faces of host **1** and series **2a–c** is unclear. UV–visible spectral evidence for classical[21] electronic donor–acceptor or π stacking interactions in this series of complexes is absent. Complex **1**:pnp is sufficiently stable that its UV–visible spectrum can be recorded (~10^{-5} M), but there are no bands not attributable to host and *p*-nitrophenol. Diederich[22] and Dougherty[23] have reported modest stabilization of solvophobic complexes by electron-attracting structural modifications. It seems likely that, given the substitution pattern in **1**, any donor–acceptor interactions in **1**:pnp are overshadowed by the effect of the *p*-nitro group on the hydrogen bond to the pyridine and on the π-hydrogen bonds to the spanning xylyl units. This is a vexing issue since the tightening of the cavity on going from **2a** to **1** must lead to both guest immobilization[24] and better π–π interaction. Stabilizing aromatic–aromatic interactions[25] must clearly be present but do not result in excited-state charge-transfer phenomena.[26] Their importance cannot otherwise be evaluated.

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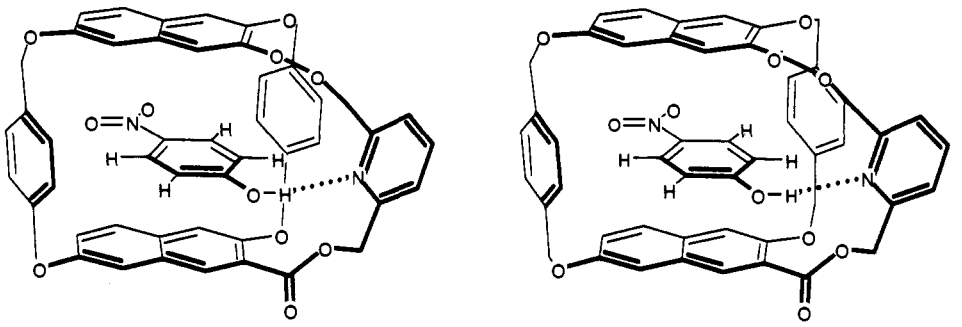

Figure 6. Stereoscopic view of MM2-minimized structure of the **1**:pnp complex.

Edge-Face Aromatic Interactions. In contrast to the above π–π interactions, edge–face interactions, π-hydrogen bonds, seem important in stabilizing the **1**:pnp complex. The ^{1}H NMR spectrum of **1**:pnp shows the two guest protons H_3 and H_5, those ortho to the nitro group, to be at δ 3.5 and 3.0. This upfield shift of approximately 5 ppm is extremely large. Large ring current-induced upfield shifts of protons are generally associated with conformationally rigid molecules wherein a proton is pushed into an aromatic π system by the geometry of a σ framework. The situation is quite different here in that the complex voluntarily assumes a geometry that has a guest proton embedded in a π system. By implication, then, this is a stabilizing interaction. An interaction energy of 1.5–2 kcal mol^{-1} has been suggested by Petsko and Burley;[9] Jorgensen[27] finds 2.3 kcal mol^{-1} (gas phase) from Monte Carlo calculations. On its face, a stabilization energy increment on the order of 1–2 kcal M^{-1} is quite adequate to explain the increase in complex stability as we go from **2c** to **2b** and **2a** to **1**. We have examined binding of *p*-dinitrobenzene by this series of hosts and find only modest K_{assoc} values of 500–1000 M^{-1}. These values are substantial compared to those of guests such as bromobenzene but are unimportant in and of themselves. The significance of this is discussed below.

Hydrogen Bonding. Classical hydrogen bond formation between the phenolic guest and the pyridine bridge of the host is an important feature of these complexes' absolute but not relative stability. The phenol is not uniquely required as a hydrogen bond donor; acylamido and phosphoramido substituents serve equally well in this respect.[28] The *p*-nitro or other resonance sink is important[12b,f] in stabilizing the hydrogen bond, but it also stabilizes the π-hydrogen bond by its acidity enhancing effect.[5c]

Kinetic *vs* Thermodynamic Stability. From equilibrium measurements the stabilization energy of the **1**:pnp complex is approximately 7.6 kcal mol^{-1} at 25 °C in chloroform. The temperature dependence of the NMR spectra produces a common value of activation free energy for interconversion of host and complex of ~13 kcal mol^{-1}, regardless of the proton followed. We view this parallel between kinetic and thermodynamic stability as a confirming feature of the enhanced stability of these complexes.[29] A series of unusually stable dimers termed velcraplexes[30] by Cram *et al.* show similar behavior. The complexes between Hogeberg tetramers and carboxylic acids recently reported by Aoyama[31] are a striking exception to this since they are kinetically stable at room temperature but show only low association constants.

Effect of Solvent Size. Most unusual is the effect of solvent on both kinetic and thermodynamic stability of the **1**:pnp complex. The **1**:pnp complex is approximately 2 kcal mol^{-1} more stable in chloroform and tetrachloroethane than in methylene chloride or dichlorethane. This order is also observed in the kinetics of host–complex exchange, where the difference of ~1.5 kcal mol^{-1} is observed in the $\Delta G^{\ddagger}$ of exchange. The special behavior of tetrachloroethane in peptide complexation by a cavity-based host was observed by Still and co-workers,[32] who suggested that solvent size was responsible. We believe that this effect is at work here for the following reasons:

(1) Chloroform and tetrachloroethane are too large to fit in the cavity of **1** and, in fact, are too large to fit in the cavity of **2a–c**. This follows by examination of CPK molecular models and molecular mechanics calculations discussed above. The cavity in **1** is large enough to accommodate an X–CH_2–Y unit that lies flat parallel to the aromatic faces of the host but not to accommodate a pyramidal HCXYZ unit where X, Y, and Z are carbon or chlorine.

(2) We frequently isolate X-ray quality "naked" host crystals in this series[12f] but only when the cavity is occupied by dichloroethane which exists in a flat *anti* conformation sandwiched between the two naphthalene faces.

(3) Hydrogen bond formation between chloroform and the pyridine is expected and observed.

(4) Association constants determined in benzene or bromobenzene are generally about an order of magnitude smaller than in the other solvents. One may conclude that this is due to occupancy of the cavity by aromatic solvents. The intercalation of benzene or bromobenzene by these hosts is weak,[33] but this is compensated by the bulk solvent.

Still has pointed out[32] that exclusion of solvent from the binding site can lead to a substantial increase in association constant when the cavity binding site is inaccessible to solvent. The host molecules studies by us are clearly not optimal in exploiting this effect, since their cavity is rather shallow and can be partially occupied by the solvent. Nevertheless, major gains in complex stability are observed. One may anticipate that deeper cavities will show this amplification effect to a greater extent.

The question of why we see a solvent size effect on both equilibrium *and* kinetic properties is interesting. We suggest that the kinetic dependence of exchange on solvent size arises from concerted departure of a *p*-nitrophenol molecule from the host cavity and occupancy of the cavity by solvent, if small enough. This second-order process will be faster than the first-order dissociation *unaccompanied* by cavity solvation. The two processes are conceptually related in a manner similar to that of the S_N2 and S_N1 processes.

Conclusions

Host **1** forms a 1:1 supramolecular complex of great stability with *p*-nitrophenol. It is characterized by both thermodynamic and kinetic stability unparalleled for a system possessing a "single" hydrogen bond. On the basis of the above discussion, we conclude the following:

(27) Jorgensen, W. L.; Severence, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768.
(28) Mr. J. L. Cochran, unreported work.
(29) Similar behavior is seen in functionalized derivatives of **2b**: J. Cochran, unpublished.
(30) Cram, D. J.; Choi, H.-J.; Bryant, J. A.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7748.
(31) Kobayashi, K.; Asakawa, Y.; Kikuchi, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1993**, *115*, 2649–2654.
(32) Chapman, K. T.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 3075.
(33) ASIS effects, using mixtures of chlorofom-*d* and benzene, show gradual upfield movement of host protons as the mole fraction of benzene is increased. Association constants calculated are small, ca. 10 M^{-1}, but the chemical shift changes are characteristic of encapsulation of aromatic solvent.

(1) The stability of **1**:pnp complex arises as a consequence of the close fit between functionally complementary host and guest. This natural fit between host and guest results in several stabilizing interactions, especially two π-hydrogen bonds involving the polarized aromatic hydrogens of the guest and the xylyl bridges of the host. Immobilization (spatiotemporal) effects need not be invoked to account for the stability of **1**:pnp.

(2) It is not necessary to rely on tranditional hydrogen bonds to build supramolecular complexes.

(3) Removing solvent from its natural role as a cavity competitor can have major effects on association constants observed. The complex becomes more stable when cavity solvation is eliminated.

(4) Destabilization of unsolvated host relative to complex may have a major effect on the kinetics of complex dissociation. If solvent cannot displace guest, the complex lifetime increases and dissociation rate decreases.

We emphasize that the exceptional nature of the **1**:pnp interaction need *not* be a reflection of any "magic" attractive interactions. Our focus on association constants in the discussion above is justified on the practical grounds of host efficiency, but we must remember that there is an exponential dependence of K_{assoc} on the free energy of complexation $\Delta G°$. Factors such as solvent exclusion and π-hydrogen bonds that are not in themselves sufficient for generation of high-efficiency hosts ($K_{assoc} > \sim 10^4$ M^{-1}) can nonetheless amplify by multiplication the observed binding constants. We suggest the term *affinity amplification* for this effect. Recognition of the role of affinity amplification offers an understanding of the frequently observed role played by host rigidity and guest immobilization in design of high-efficiency hosts for neutral organic guests. There will be a *tendency* for these features to accompany large binding constants simply because of structural consequences of maximizing host–guest contact.

Experimental Section

Dipropyl Ester 5. A mixture containing 16.4 g (0.067 mol) of propyl 3,7-dihydroxy-2-naphthoate (**3**),[12d] 8.2 g (0.031 mol) of α,α'-dibromo-*p*-xylene (**4**), and 27 g (0.27 mol) of potassium carbonate (K_2CO_3) in 200 mL of acetone was stirred for 3 days at 25 °C. The reaction mixture was partitioned between $CHCl_3$ and 5% hydrochloric acid. The $CHCl_3$ layer was washed with saturated bicarbonate and water, dried with Na_2SO_4, evaporated (Roto Vap) at 25 °C, and chromatographed on silica gel to afford 12.7 g (69% yield) of diether **5** as a yellow solid. Crystallization from chloroform–hexane gave yellow needles: mp 194–197 °C; ^{1}H NMR ($CDCl_3$) δ 10.4 (2H, s, OH), 8.36 (2H, s, H_1), 7.62 (2H, d, J = 9 hz, H_5), 7.53 (4H, s, xy), 7.28 (2H, dd, J = 9, 2.4 hz, H_6), 7.28 (2H, s, H_4), 7.19 (2H, d, J = 2.2 hz, H_8), 5.17 (4H, s, CH_2), 4.38 (4H, t, J = 6.6 hz, CH_2), 1.87 (4H, sx, J = 7 hz, CH_2), 1.09 (6H, t, J = 7.5 hz, CH_3); MS m/e 594.2254 (calcd for $C_{36}H_{34}O_8$ m/e 594.2254).

Bis(xylyl)cyclophane Dipropyl Ester 6. A mixture of 1 g (1.68 mmol) of diether **5** and 0.45 g (1.69 mmol) of dibromide **4** in 200 mL of dry dimethylformamide (DMF), was added dropwise to 2.5 g (7.6 mmol) of cesium carbonate in 100 mL of DMF maintained at 52 °C. After the mixture was stirred for 2 days, the DMF was removed by Kugelrohr distillation (60 °C, 1 mmHg), and the semisolid residue was extracted with ethyl acetate to give 0.7 g of yellow oil. Chromatography of this oil on silica gel ($CHCl_3$) afforded 244 mg (21% yield) of diether **6**, which was crystallized from ethyl acetate–hexane: mp 189–191 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (2H, s, H_1), 7.30 (4H, s, xy), 7.21 (4H, s, xy), 7.16 (2H, d, J = 2.6 hz, H_8), 7.12 (2H, d, J 9.5 hz, H_5), 6.77 (2H, s, H_4) and 6.77 (2H, dd, J = 9, 2 hz, H_6), 5.31 (4H, s, xy), 5.20 (4H, s, xy), 4.34 (4H, t, J = 6.6 Hz, CH_2), 1.84 (4H, sx, J = 7 Hz, CH_2), 1.07 (6H, t, J = 7.4 hz, CH_3); MS m/e 696.2724 (calcd for $C_{44}H_{40}O_8$ m/e 696.2723).

Anal. Calcd for $C_{44}H_{40}O_8$: C, 75.84; H, 5.79. Found: C, 75.96; H, 5.72.

Cyclophane 1. (1) Diether **6** was saponified by stirring a mixture of 239 mg (0.34 mmoles) of **6** in 15 mL of tetrahydrofuran (THF) with 337 mg (8 mmol) of $LiOH·H_2O$ in 5 mL of water for 4 days at 25 °C. After separation of the THF by distillation, the residue was acidified at 0 °C and the resulting solid filtered to give 214 mg of acid **7** as a colorless solid. This product was used in the next step without purification.

(2) A mixture containing 162 mg (0.27 mmol) of acid **7**, 91 mg (0.3 mmol) of 2,6-bis(bromomethyl)-4-(dimethylamino)pyridine (0.3 mmol),[13a] and 320 mg (3.2 mmol) of K_2CO_3 in 60 mL of dry DMF was stirred at 25 °C under nitrogen for 4 days. The reaction mixture was partitioned between CH_2Cl_2 and saturated salt. The organic layer was evaporated to afford 351 mg of tan solid. Trituration of this with ethyl acetate and precipitation of the soluble fraction with hexane gave 223 mg of product, which upon chromatography (silica gel, $CHCl_3$–MeOH) afforded 167 mg of colorless solid. Crystallization of this solid from CH_2Cl_2–hexane gave 89 mg (45% yield) of **1** (approximately 1 equiv of CH_2Cl_2 (by NMR and analysis) was present after drying at 25 °C, 1 mmHg): mp > 200 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (2H, s, H_1), 7.33 (4H and 2H, s and d, J = 9 hz, xy and H_5), 7.06 (2H, s, H_4), 7.02 (2H, dd, J = 9, 2.6 hz, H_6) and 7.0 (2H overlapping, H_8), 6.87 (2H, s, py), 6.78 (4H, s, xy), 5.72 and 5.09 (4H, AB J = 10.8 hz, CH_2py), 5.28 (2H, s, CH_2Cl_2), 5.26 (4H, AB q, CH_2), 5.24 (4H, AB q, CH_2), 3.01 (6H, s, NCH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 39.1, 54.0 (CH_2Cl_2), 67.9, 68.4, 69.9, 107.3, 108.8, 110.8, 122.0, 123.5, 126.6, 127.7, 128.2, 128.3, 130.7, 131.5, 136.4, 136.5, 151.8, 153.8, 155.3, 155.5, 165.7; MS m/e 758 (FABS) (calcd $C_{47}H_{38}N_2O_8$ m/e 758.2626).

Anal. Calcd for $C_{47}H_{38}N_2O_8·CH_2Cl_2$: C, 68.32; H, 4.78. Found: C, 68.71: H, 4.81.

Determination of Association Constants. (A) Titration Method. Cyclophane **1** contained approximately 1 equiv of CH_2Cl_2 after being dried *in vacuo* at 23 °C. This is apparent in the titration experiment spectra as a sharp peak at δ 5.3 (see Figure 2). To minimize errors in the titration experiments, the amount of **1** weighed was corrected for the CH_2Cl_2 present and determined by addition of the internal standard mesitylene at the end of the titration. A pulse delay of 15 s was used in the final spectrum. Cyclophane **1** (2–3 mg in 0.5 mL of deuterated solvent) was titrated with appropriate amounts of a standard stock solution of *p*-nitrophenol in the same solvent. At the end of the experiment, the amount of host present was determined by addition of a known quantity of mesitylene. A best fit for the plot of chemical shift versus the guest: host concentration was obtained using the nonlinear least-squares method detailed elsewhere.[12]

(B) Competition Method.[12d] The two cyclophanes to be compared, **1** and **2a**, were combined in the appropriate solvent, and varying amounts of *p*-niotrophenol were added. K_{rel} was calculated (eq 1) from F_1 and F_{2a}, which in turn were obtained from application of eq 2, where δ_0 and $\delta_{complex}$ represent the chemical shifts of the naphthalene H_1 or H_8 proton in the free and bound host.

$$K_{rel} = K_2/K_1 = (1/F_1 - 1)/(1/F_2 - 1) \quad (1)$$

$$F_i = \delta_0 - \delta_{obsd}/\delta_0 - \delta_{complex} \quad (2)$$

(C) Dilution Method. Dilute solutions of the **1**:pnp complex were prepared in $CDCl_3$ or CD_2Cl_2, and their NMR spectra were determined at various concentrations. The fraction (F) of complexed **1** was determined using eq 2. The association constants could be calculated using eqs 3 and 4.

$$K_{assoc} = ([C]/([H_0] - [C]))([G_0] - [C]) \quad (3)$$

$$[C] = F[H_0] \quad (4)$$

Determination of Activation Energy $\Delta G^‡$. The NMR spectra of a 1:1 mixture of **1** and **1**:*p*-nitrophenol-3,5-d_2 complex, prepared from 2–3 mg of **1** and 0.5 equiv of phenol[13b] in $CDCl_3$ or CD_2Cl_2, were obtained over a range of temperatures. Comparison samples were prepared from 2–3 mg of **1** and 0.0, 1.0 and 2.0 equiv of *p*-nitrophenol-d_2. Rate constants (k_c) at coalescence were obtained from eq 5, and $\Delta G^‡$ was obtained by substitution of k_c into the Eyring equation.

$$k_c = (\delta_0 - \delta_{complex})_{Tc}(\pi/\sqrt{2}) \quad (5)$$

Supplementary Material Available: ^{1}H NMR spectra of **1**: pnp at varying ratios in CD_2Cl_2 at 25 °C and **1**: pnp-d_2 in CD_2Cl_2 at varying temperatures (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.