# Concave Functionality: Design Criteria for Nonaqueous Binding Sites

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**Abstract:** The synthesis and phenol-binding properties of cyclophane hosts **1a** and **1b** are described. A sliding scale method for determining binding constants of the hosts is described. Host **1a** with *p*-nitrophenol has a binding constant of ca. 96 000 $M^{-1}$. The significance of this result with respect to the design of sites capable of molecular recognition is discussed.

Since the conceptually pioneering work of Stetter and Roos[1] and Cramer[2] host–guest complexation of neutral organic guest molecules has become an area of intense interest. Early work focussed on hydrophobic complexation, typical hosts being the cyclodextrins[2] with water as the solvent. More recently complexation of neutral guests in *organic* solvents has attracted attention.[3]

With the abandonment of hydrophobic forces, the question arises as to what forces should replace them in order to design a receiving site capable of high guest specificity and affinity. Mechanical enclosure of guests has been exploited by Cram and co-workers in the study of carcerands.[4] Diederich[5] has shown that there is a continuum of behavior of solvents via a vis their ability to support apolar complexation, ranging from water at one extreme to carbon disulfide at the other. Thus the "hydrophobic"–"organic solvent" dichotomy is seen to accommodate gradations. Ion pairing effects have been shown to be appreciable in a number of cases. Stauffer and Dougherty[6] have demonstrated this in the binding of a tetraanionic host with ammonium guests. Schmidchen has studied some interesting tetrahedral hosts with ammonium vertices that are anion binders.[7] Lehn and co-workers have synthesized several ionic hosts capable of binding charge-complementary guests in organic solvents.[8] The ability of hydrogen bonds to serve as a guest binding force is crucial to the development of hosts capable of high recognition and binding ability. Rebek et al.[3c,9a,b] have studied a series of cleft hosts bearing different hydrogen bonding functionalities. Still[10] has examined a novel bicyclic imidazole-binding host and discovered an exceptionally interesting role of solvent size in guest complexation. Hamilton has exploited the hydrogen bond in devising a barbiturate binding host.[11] Kelly[12] has synthesized a nucleophilic

condensation catalyst of singular beauty based on guest recognition by a hydrogen bonding network.

Finally, we have previously reported the synthesis[13] of the extraordinarily efficient hosts **2a** and **2b**, which bind acidic phenols with a high degree of electronic and stereochemical specificity in nonpolar organic solvents. Their properties are attributed to the combination of a concave functional group capable of serving as a hydrogen bond acceptor and a rigid host, resulting in temporal fixation[14] of the guest at the hydrogen binding site. We now report the preparation and guest-complexation behavior of cyclophanes **1a** and **1b**.

**Design.** Two design criteria were applied in selecting these hosts. (1) We wished to decrease the naphthalene–naphthalene dimension of the cavity from the value of ~4.6 Å in the previously reported **2a** and **2b**.[13] This would ensure a tighter fit of aromatic guests
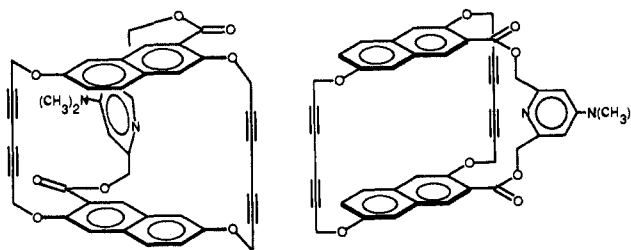
**2a**　　　　　　**2b**

and is consistent with the X-ray results which show that complexation by **2** is accompanied by a "screwing down" of the host, presumably to maximize $\pi-\pi$ overlap between host and guest. The C1–C6 distances of several spacer groups (those groups connecting the naphthalene units) were calculated by molecular mechanics, using the program MacroModel.[15] The C1–C6 distance of 2,4-hexadiyne is 6.77 Å; that of (*E,E*)-2,4-hexadiene (s-trans) is 6.37 Å and s-cis is 6.08 Å. For comparison, the *p*-xylene distance is 5.86 Å, but that a *m*-xylene is only 5.07 Å. By virtue of these calculations a *p*-xylyl spacer was chosen. This results (by molecular mechanics) in a decrease of the naphthalene-naphthalene distance in the uncomplexed host from 7.58 Å in **2b** to 6.88 Å in **1**. (2) Replacing a hexadiyne spacer by a *p*-xylene group also results in a face-edge aromatic–aromatic interaction upon complexation of an aromatic guest. Petsko[16] and Karlstrom[17] have

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(2) Cramer, F. *Angew. Chem.* **1981**, *73*, 49.

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(13) Sheridan, R. E.; Whitlock, H. W. *J. Am. Chem. Soc.* **1988**, *110*, 4071–4073. Sheridan, R. E.; Whitlock, H. W. *J. Am. Chem. Soc.* **1986**, *108*, 7210–7211.

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(16) Burley, S. K.; Petsko, G. *Science (Washington, D.C.)* **1985**, *229*, 23. Burley, S. K.; Petsko, G. *J. Am. Chem. Soc.* **1986**, *108*, 7995–8001.

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**Table I.** Chemical Shifts (ppm) of Uncyclized (**6a,b**) and Cyclized (**1a,b**) Hosts and of Complexes with 1 Equiv of p-Nitrophenol (PNP)[a]

| entry | host | δH$_1$ | δH$_4$ | δH$_5$ | δH$_6$ | δH$_8$ | δ$_{Xyl}$ | δH$_{Py3}$ | δH$_{Py4}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 6a | 8.31 | 7.31 | 7.73 | 7.25 | 7.32 | 7.17 | 6.63 | |
| 2 | 1a | 7.87 | 7.15 | 7.46 | 7.00 | 7.03 | 7.00 | 6.81 | |
| 3 | 1a-PNP | 7.17[b] | 6.97 | 7.22 | 6.86 | 6.61 | 7.19 | 6.92 | |
| 4 | 6b | 8.40 | 7.3 | 7.71 | 7.3 | 7.3 | 7.10 | 7.5 | 7.5 |
| 5 | 1b | 8.11 | 7.19 | 7.47 | 7.04 | 7.01 | 6.85 | 7.71 | 7.86 |
| 6 | 1b-PNP | 7.34[c] | 6.97 | 7.22 | 6.92 | 6.60 | 7.09 | 7.87 | 8.12 |

[a] Entries 1–3 in CD$_2$Cl$_2$, 4–6 in CDCl$_3$. [b] δ-Complex for H$_1$ was calculated to be 7.09 (host is 0.005 M). [c] δ-Complex is calculated to be 7.25 (host is 0.004 M).

suggested a stabilizing effect of approximately 2 kcal for this type of interaction from statistical examination of a number of protein X-ray structures. We hypothesized that a similar effect would be operative here, resulting in further stabilization of the complexes of **1**.
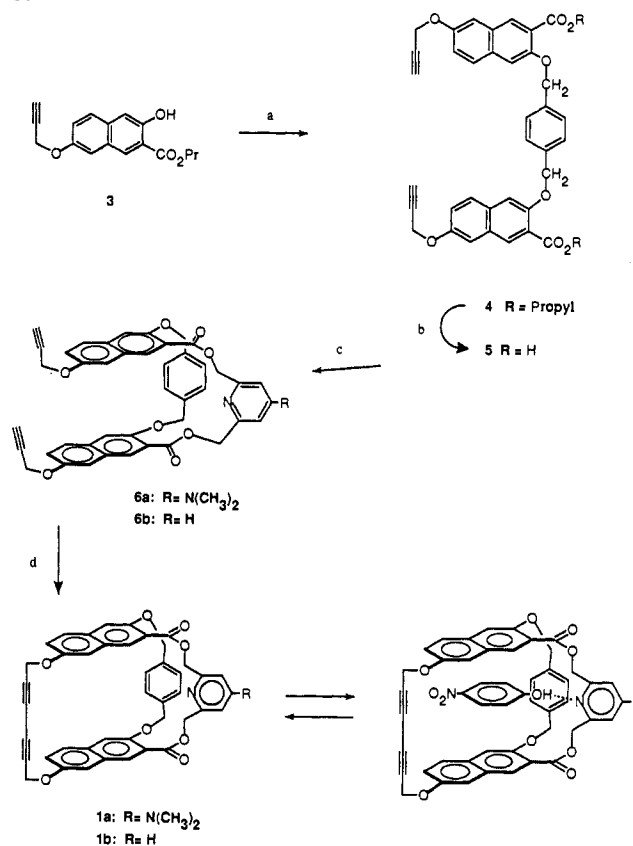
**Synthesis.** Cyclophanes **1a** and **1b** are of modest complexity, each containing 108 distinct rings, the largest of which possesses 39 atoms. Nonetheless, by attaching the three different bridging groups sequentially to the functional groups of the naphthalene ring system, the unambiguous synthesis of *meso* cyclophanes **1a** and **1b** is achieved in a straightforward manner. Furthermore, the difficulties previously encountered in the separation of *meso* and *dl* isomers (e.g. **2a** and **2b**)[13] are eliminated.

The cyclophanes **1a** and **1b** were synthesized from commercially available 3,7-dihydroxynaphthoic acid as shown in Scheme I. Esterification (propyl bromide, KHCO$_3$, DMF, 70 °C) of the acid gave the corresponding propyl ester in 70% yield. Propargylation of this ester with a limiting amount of reactant (1.1 equiv of propargyl bromide, K$_2$CO$_3$, acetone, 56 °C) afforded the mono-propargyl ether **3**, in 49% yield. When ether **3** was treated with 0.5 equiv of α,α'-dibromoxylene (K$_2$CO$_3$, DMF), xylylene diether **4** was obtained in 73% yield. Acid **5**, obtained in 84% yield by hydrolysis of **4** (LiOH, aqueous THF), was esterified with Mit-sunobu[20] conditions (triphenylphosphine, diethyl azodicarboxylate, THF) with the appropriate pyridinedimethanol (0.5 equiv) to give the precyclophanes **6a** and **6b** in 54 and 58% yield, respectively. The final step involving the Cu$^+$-catalyzed coupling to the pre-cyclophanes **6a** and **6b** with high-dilution conditions (copper acetate, pyridine, 40 °C) proceeded in low yield. By the nature of the synthesis, **1a** and **1b** are the *meso* diastereoisomers corresponding to **2b**, isolated as the minor isomer in the previously described synthesis. Both **1a** and **1b** were isolated as high-melting solids soluble in the usual organic solvents and were characterized by their NMR and mass spectra.

**Structure.** In the initial absence of X-ray crystallographic structures for **1a** or **1b**, we relied upon spectroscopic and molecular mechanics modeling studies to infer salient structural features of these substances. In particular, comparison of **1a,b** with the well-characterized **2b**[13] permits the drawing of structural conclusions with some degree of confidence. As discussed below, these conclusions are supported by the X-ray structure of the **1a**-p-nitrophenol complex.

The conformation of the 21-membered ring in monocyclic[18] **6a,b** was not explored computationally, but since only four tetrahedral carbons are present, it is probably flexible without a well-defined conformation. The methylene protons appear as singlets in the NMR spectrum as is required from their time-averaged enantiotopic relationship. Precyclophane **6a,b** is certainly not flat since perceptible shifts of the various aromatic protons are observed on closure of the first ring (**5 → 6**).

Closure of the second host ring by copper-mediated coupling of the acetylene groups (**6a → 1a** and **6b → 1b**) resulted in changes in the NMR spectra that were generally consistent with those observed in the synthesis of **2a** and **2b**.[13] Upfield shifts of the

(18) By "Monocyclic" we refer to the presence of a single ring *excluding* the aromatic groups. These are viewed as simple components of the overall structure. The divalent groups connecting the naphthalene rings are referred to as "spacers".

(19) Miller, S. P.; Whitlock, H. W. *J. Am. Chem. Soc.* **1984**, *106*, 1492–1494.
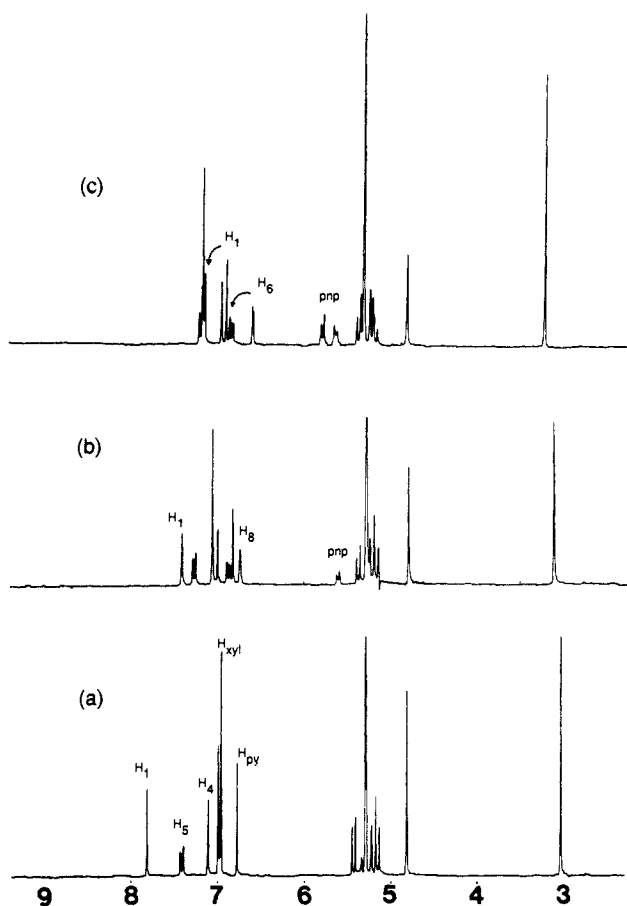
(20) Mitsunobu, O. *Synthesis* **1981**, 1–28.

**Scheme I[a]**



[a] (a) C$_6$H$_4$(CH$_2$Br)$_2$, K$_2$CO$_3$, DMF. (b) KOH, CH$_3$OH, 65 °C. (c) (4R)-Pyridine-2,6-diol, (C$_6$H$_5$)$_3$P, (NCOOEt)$_2$, THF. (d) Cu(OAc)$_2$, pyridine, 40 °C.

naphthyl and xylyl protons occurred, and well-defined AB quartets were observed (Figure 1a; Table I) for the diastereotopic protons of the xylyl and pyridyl-CH$_2$ groups. The methylene protons of the hexadiyne, although diastereotopic, were not separated from one another in the spectrum of **1a**. Of particular interest was the observation of substantial *downfield* shifts of the pyridine protons on closure of the second host ring, as the conformation of this ring is of importance in hydrogen bonding to incavitated phenolic guests. We suggest that this downfield shift arises from population (not exclusive) of a conformation wherein C$_4$ of the pyridine bridge is near the xylene unit and approximately in its plane. This idea is supported by molecular modeling to be discussed below and is important, since this conformation has the pyridine nitrogen *away* from the xylene spacer and hence pointing toward the host's cavity. In CD$_2$Cl$_2$ or CDCl$_3$, ring current effects on the various host protons are minimal due to the rigid spacers. In aromatic solvents (pyridine-d$_5$, bromobenzene-d$_5$), the naphthalene protons are shifted upfield by 0.3–0.8 ppm in a manner strikingly similar to that exhibited by the host–guest complexes. In mixtures of the solvents dichloromethane-d$_2$ and bromobenzene-d$_5$ the C$_1$ proton of **1b** moved from 8.1 to 7.3 ppm as the mole fraction of the aromatic solvent approached unity. The solvent is bound weakly, however, as an association constant (C$_6$H$_5$Br) of only ~500 M$^{-1}$ was determined. Competitive occupancy of the host's cavity by

Figure 1. Proton NMR spectra in $CD_2Cl_2$ (host is 0.006 M): (a) cyclophane 1a; (b) 1a and 0.5 equiv of p-nitrophenol; (c) 1a and 1.0 equiv of p-nitrophenol.

solvent was noted previously.[19] We find that the association constant of a phenolic guest in bromobenzene-$d_5$ is comparable to that determined in "noncompeting" solvents such as chloroform and dichloromethane. The value should be less in bromobenzene, but due to the small changes in chemical shift, we are unable to determine the constant accurately. Still et al.[10] have recently

reported substantial effects of solvent occupation of a host cavity on the binding of imidazole. That we see minimal solvent occupancy effects is primarily due to the fact that all of our cases of complexation involve competition of the guest with solvent, and none of our solvents interact strongly with the cavity. It seems clear that the "structure" of these hosts involves a facile and transient solvation of the cavity.

**Molecular Modeling.** Comparison of the structures of 1 and 2b suggests that their geometries are quite similar except for differences arising from the different spacer groups. Stereoviews of energy-minimized 1 and 2b are presented in Figure 2. In both cases the two naphthalene rings are tipped at an angle of approximately 30°. This is reflected in the naphthalene–naphthalene distances measured between the atoms carrying the three bridges. The point of closest naphthalene–naphthalene approach is C2–C2′, the site of the pyridine bridge, 6.65 Å for 2b and 6.25 Å for 1. The C3–C3′ distances are 7.58 Å for 2b and 6.88 Å for 1. At the distal connecting sites, C7–C7′, with the diyne bridge in each case, the distances are 7.84 Å in 2b and 7.67 Å in 1. The fact that these two distances are not the same points up one of the advantages of molecular modeling over the use of molecular models. The effect of shortening the spacer at one end of the host is not simply a tipping of the rings about some fixed axis but is a more global conformational change involving a number of sites. The xylene constitutes a face of the cavity.

We have shown by X-ray analyses that in the cases of both 2a and 2b the two naphthalene rings are parallel.[13] In these cases, however, the cavity is occupied by a molecule of either 1,2-dichloroethane or p-nitrophenol. One may infer from these results that, while the cavity in these structures is maintained by the presence of the rigid spacers, it is still rather flexible.

The question of the conformation of the pyridine bridge is of crucial importance in the ability of 1a and 1b to bind phenols. One may envisage several limiting conformations of this bridge: the ester carbonyl groups may lie on the same (cis) or opposite (trans) sides of the mean plane of the pyridine-containing ring and may point either toward (endo) or away from (exo) the xylylene spacer. Host 2a adopts the trans-endo and host 2b the cis-endo conformation regardless of the guest, ethylene dichloride, or p-nitrophenol. The pyridine nitrogen may point either toward or away from the cavity; the former orientation is the desired one. We will refer to these as "normal" and "flip" conformations, respectively. These are all energy minima; intermediate starting
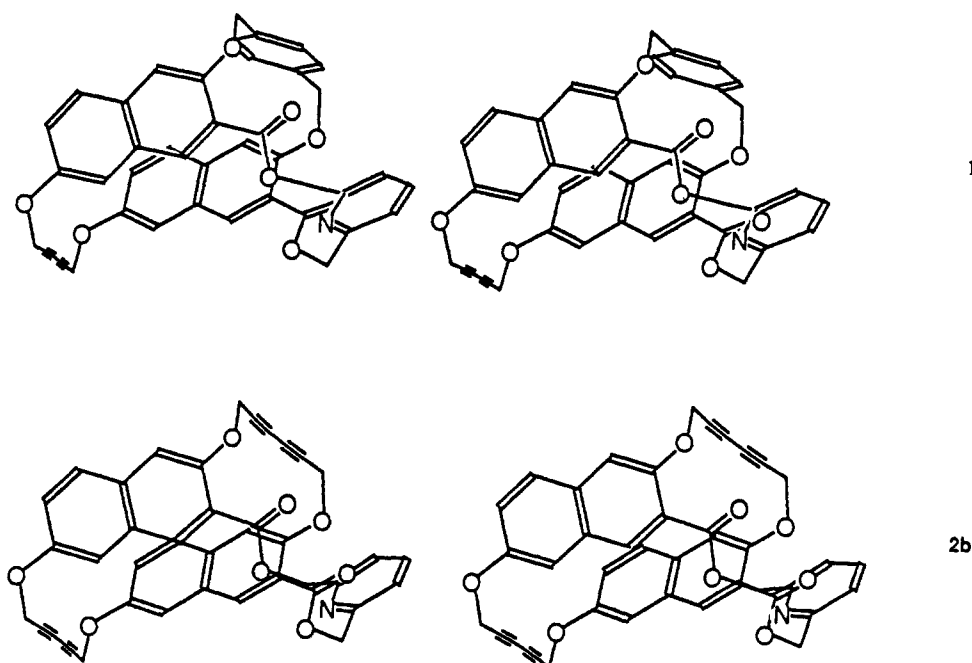


1

2b

Figure 2. Stereoviews of (a) cyclophane 1 and (b) cyclophane 2b after minimization.

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Keq=23949, δ(1:1)=7.087

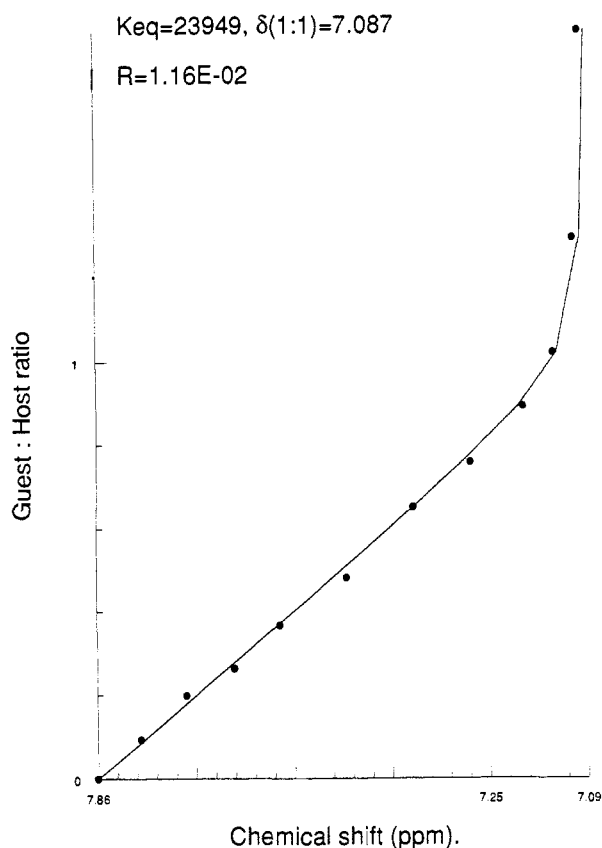R=1.16E-02



Chemical shift (ppm).

**Figure 3.** Plot of observed and calculated chemical shift of $H_1$ of **1a**. The ordinate is the molar ratio of p-nitrophenol:host **1a**. The abscissa is the observed chemical shift. The initial concentration of **1a** was 0.005 M in $CD_2Cl_2$. Experimental values are shown as filled circles. The calculated curve used data from the nonlinear least-squares fit: $\delta H_1$(host) = 7.87, $\delta H_1$(complex) = 7.09, $K_{assoc}$ = 24 000 $M^{-1}$, $R$ = 0.012.

conformations relax on minimization toward one or the other, but basically the situation is one of a broad shallow energy well containing both normal and flip, cis and trans, endo and exo forms.

To summarize our molecular modeling studies, **1** and **2** should have similar conformations but with a smaller naphthalene-naphthalene distance in **1**. In one sense these hosts are rigid, but not nearly as rigid as molecular models would suggest. We suggest that the rather remarkable binding properties of **1a** described below arise from a combination of the rigid cavity together with a somewhat flexible bridge.

**Binding Studies.** In contrast with the facile but weak binding of neutral solvents by the cavity of **1a**, acidic phenols are bound quite tightly. Xylylene host **1a** shows phenol recognition properties much more pronounced than those exhibited by diyne spacer hosts **2a** and **2b**. Titration of a $CD_2Cl_2$ solution of **1a** with p-nitrophenol results in substantial upfield shifts of both the guest and host protons (Table I; Figure 1). While nonlinear least-squares[21,22] modeling of the NMR titration experiments affords a $K_{assoc}$ of 24 000 $M^{-1}$, at a concentration of 0.006 M (Figure 3) the host is effectively saturated upon the addition of 1 equiv of phenol.

A difficulty encountered in the determination of association constants by the nonliner least-squares method from titration data is that unreliable results are obtained for association constants with values greater than ca. 10 000 $M^{-1}$. The problem arises from an apparent discontinuity in the titration curves at 1 equiv of guest in the plot of δ vs added guest; the computed association constant deviates from infinity only by virtue of experimental scatter in

(21) The program NLSQ was written using the SIMPLEX algorithm according to ref 22. Program NLSQ handles several complexation cases and has an attached PostScript and graphical user interface that produces plots interactively. The source (Turbo C) is available from the authors on request.

(22) Noggle, J. H. *Physical Chemistry on a Microcomputer*; Little Brown & Co.: Boston, 1985; pp 145–165.

**Table II.** Complexation of Cyclophane Hosts with p-Nitrophenol[a]

| entry | host | $K_{assoc}$[b] | $K_{rel}$[c] | $K_{assoc}$[d] |
|---|---|---|---|---|
| 1 | **2a**-*dl* | 6000 | 1.0 | 6 000 |
| 2 | **2b**-*meso* | 14000 | 3.8 | 22 800 |
| 3 | **1a** | 24000 | 16.0[e] | 96 000 |
| 4 | **1b** | 9800 | 2.6 | 47 000 |
| 5 | **1a** | 7000[f] | | |

[a] Entries 3 and 5 are in $CD_2Cl_2$; the others are in $CDCl_3$. [b] These values were determined by nonlinear least-squares data reduction of NMR titration experiments. [c] $K_{rel}$ is determined by competitive binding experiments as described in the text. [d] Calculated from $K_{rel}$ assuming the value of entry 1 to be 6000 $M^{-1}$ (ref 13 and 23). [e] $K_{rel}$ of **1a/2b** is 4.3. [f] Guest is 6-nitro-2-naphthol.
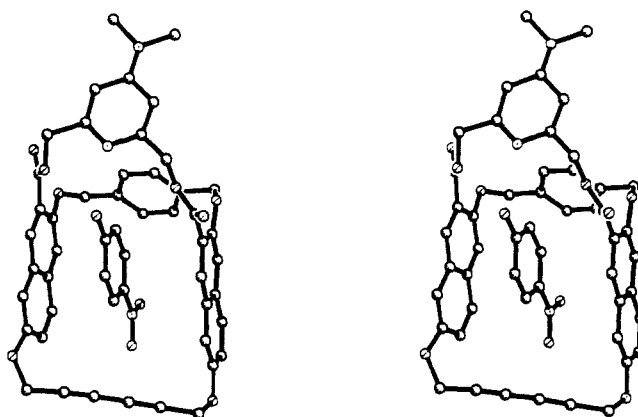


**Figure 4.** Stereoview of cyclophane 1-p-nitrophenol single-crystal X-ray structure. The sample was crystallized from 1,2-dichloroethane.

the data. Rather than work at lower concentrations we have devised a competitive method for determining association constants. An additional advantage of this method is that an exact measurement of the host and guest concentrations is not required. When two hosts are presented with a limiting amount of guest, $K_{rel}$ may be determined as shown in eq 1 and 2, where $K_2/K_1$ is

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

$$F_i = \delta_o - \delta_{obsd}/\delta_o - \delta_{complex} \qquad (2)$$

the ratio of the association constants for the two hosts and $F_i$ is the fraction of host i that is bound. $F_i$ may be determined if one knows the chemical shift of the observed proton in the uncomplexed host *and* in the host–guest complex. Application of this method has permitted us to develop a sliding scale for the association constants, using host **2a** as a standard.

Noting the usual *caveats* associated with equations of this form, we have studied several of the hosts prepared in these laboratories with the following conclusions (Table II). Host **2a**-*dl*, with an association constant of 6000 $M^{-1}$ determined by the titration method, is assigned a value of unity. By substitution into eq 1, xylylene host **1a** (R = $NMe_2$), in competition with the standard host **2a** for p-nitrophenol, has $K_{rel}$ = 16. Therefore, host **1a** has a calculated association constant ($K_{assoc}$, column 5) of ~96 000 $M^{-1}$. This value is considerably higher than that obtained by the direct titration method ($K_{assoc}$ = 24 000, column 3). Xylylene host **1b** (R = H) is also a better host than **2a** with a $K_{rel}$ of 2.6, leading to a calculated $K_{assoc}$ of 47 000.

The effect of the increased basicity of the 4-dimethylamino group on the pyridine bridge causes a marked increase in the value of association constants. This enhancement is also seen in derivatives of **2** with different substituents at $C_4$ of the pyridine bridge.[23] The dominant structural feature in these compounds affecting $K_{assoc}$ is that of the xylylene bridge.

(23) Karen Neder, unpublished observations. The authors thank Ms. Neder for the revised determinations of the association constant for **2a**.

**Structure of Phenol Complexes of 1.** A single-crystal X-ray structure of the **1a**-*p*-nitrophenol host–guest complex is shown in Figure 4.[24] Except for the detailed conformation of the pyridine bridge, it is **exactly** as predicted by MM calculations: the two naphthalene rings are now parallel; the phenol is hydrogen bonded to the (dimethylamino)pyridine nitrogen; the guest makes a Petsko face–edge contact with the *p*-xylylene bridge. Molecular modeling reproduces this structure, the steric energy decreasing by 9 kcal on insertion of the guest into the cavity. The major difference between this complex and those of **2a** and **2b** lies in the trans endo–exo conformation of the ester carbonyl groups. The large (∼2 ppm) upfield shifts of the guest protons in the solution NMR spectrum of the complex are consistent with the X-ray structure. That the carbonyl groups adopt a trans arrangement rather than cis as was found for **2b**-*meso*-*p*-nitrophenol complex is attributed to their role in conformational adjusting of the pyridine bridge to accommodate the guest within the cavity.

## Conclusions

We have demonstrated that replacement of a 2,4-hexadiyne spacer in the previously studied hosts **2a,b** with a *p*-xylylene spacer results in a substantial enhancement of guest binding properties. This enhancement arises from two effects. The naphthalene–naphthalene distance in **1** corresponds to a better fit by the guest than in **2a** or **2b**. It was observed[13] that complexation of **2a** was accompanied by a slight decrease in the naphthalene–naphthalene distance of the host, presumably to maximize host–guest contact. This is not necessary in **1a,b** as the average cavity height is smaller before complexation. Second, X-ray, molecular modeling, and NMR shifts argue convincingly for the importance of an attractive guest–xylylene interaction as shown in Figure 4. We cannot at present factor the stability gain in the phenol complexes into these two features; both are probably important.

There are several features of the remarkable stability of these host–guest complexes that we still do not understand. The role of conformational flexibility in the pyridine bridge is unclear. Our feeling is that, given the inability to design and synthesize a host that is an *exact* match for the desired host, some flexibility may compensate for inexact design of the host. As observed previously for **2a** and **2b**, the present hosts do *not* complex aromatic carboxylic acids. This fact is not accommodated by our present model of complexation, but it may simply arise from the preference by carboxylic acids for a cisoid HO—C=O conformation.

The principal goals of this work were achieved. We now feel confident that, within a relatively limited structural context, we understand structural features present in these hosts that are responsible for their complexation of guests in nonaqueous media: (1) A rigid cavity is required to immobilize the guest relative to the coordinate frame of the host. The closer the fit (greater the immobilization) the better. (2) A concave functional group[13] is required to serve as a binding force for the guest. Our present hosts employ a single hydrogen bond and seem to harvest a substantial fraction of the strength of the hydrogen bond (∼7–10 kcal) in binding the guest. Menger's hypothesis of temporal interactions[14] is a convenient framework for thinking about the synergistic effect of cavity rigidity and concave functionality in these cyclophanes. (3) Face–edge and possibly face–face interactions may fruitfully be employed in design of hosts accepting aromatic guests. The increase in chemical malleability associated with replacement of diyne by aromatic spacing units has obvious desirable features.

## Experimental Section

**Propyl 3,7-Dihydroxy-2-naphthoate.** A stirred mixture containing 22.6 g (0.11 M) of 3,7-dihydroxy-2-naphthoic acid (Aldrich Chemical Co.), 11 mL (0.12 M) of propyl bromide, and 18 g of potassium bicarbonate in 114 mL of dimethylformamide was heated at 70 °C for 19 h. Workup from ethyl acetate–water and crystallization from chloroform–hexane afforded the desired propyl ester in 70% yield: mp 134–35 °C; *m/e*

246.0892 (Calcd for $C_{14}H_{14}O_4$, 246.0891); δ (CDCl$_3$) 10.44 (1 H, s, OH), 8.3 (1 H, s, H$_1$), 7.6 (1 H, d, *J* = 9 Hz, H$_5$), 7.27 (1 H, s, H$_4$), 7.15 (1 H, dd, *J* = 9, 2.5 Hz, H$_6$), 7.14 (1 H, s, H$_8$), 5.3 (1 H, br s, OH), 4.37 (2 H, tr, *J* = 7 Hz, OCH$_2$), 1.87 (2 H, sx *J* = 7 Hz, CH$_2$), 1.07 (3 H, tr, *J* = 7 Hz, CH$_3$).

**Propyl 3-Hydroxy-7-(propargyloxy)-2-naphthoate (3).** A suspension of 40 g (0.16 M) of the propyl ester, 14 mL (0.18 M) of 97% propargyl bromide, and 24 g of potassium carbonate in 200 mL of acetone was heated under reflux (nitrogen) for 20 h. Workup followed by crystallization from chloroform–hexane gave 23 g (49% yield) of propyl 3-hydroxy-7-(propargyloxy)-2-naphthoate (3) as colorless needles: 97–99 °C; *m/e* 284.1048 (Calcd for $C_{17}H_{16}O_4$, 284.1049); δ (CDCl$_3$) 10.42 (1 H, s, OH), 8.38 (1 H, s, H$_1$), 7.6 (1 H, d, *J* = 9 Hz, H$_5$), 7.2–7.3 (3 H, m, H$_{4,6,8}$), 4.78 (2 H, d, CH$_2$C≡C), 4.38 (2 H, tr, *J* = 7 Hz, CH$_2$), 2.57 (1 H, tr, *J* = 2.5 Hz, CH), 1.87 (2 H, sx, *J* = 7 Hz, CH$_2$), 1.09 (3 H, tr, *J* = 7 Hz, CH$_3$).

**Xylylene Diether (4: R = Propyl).** A mixture containing 5.0 g (17.6 mM) of propyl ester **3**, 2.3 g (8.8 mM) of α,α'-dibromo-*p*-xylene, and 12 g of potassium carbonate in 20 mL of dimethylformamide was stirred for 24 h at 25 °C. Workup from chloroform–water, followed by crystallization from chloroform, gave 4.3 g (73% yield) of the propyl ester **4** as colorless crystals: mp 147–9 °C; *m/e* 670.2552 (Calcd for $C_{42}$-$H_{38}O_8$, 670.2564); δ (CDCl$_3$) 8.23 (2 H, s, H$_1$), 7.63 (2 H, d, *J* = 9 Hz, H$_5$), 7.56 (4 H, s, xylyl), 7.2–7.25 (6 H, m, H$_{4,6,8}$), 5.25 (4 H, s, xylyl-CH$_2$), 4.79 (4 H, d, *J* = 2.4 Hz, CH$_2$C≡C), 4.32 (4 H, tr, *J* = 7 Hz, OCH$_2$), 2.55 (2 H, tr, *J* = 2.4 Hz, C≡CH), 1.77 (4 H, sx, *J* = 7 Hz, CH$_2$), 0.98 (6 H, tr, *J* = 7 Hz, CH$_3$).

**Xylylene Diether (5: R = H).** A mixture containing 4.3 g (6.4 mM) of propyl ester **4** and 1.4 g (25.7 mM) of potassium hydroxide in 12 mL of methanol was heated under reflux for 4 h. Acidification with dilute hydrochloric acid gave, after filtration and drying, 3.4 g (84% yield) of acid **5**, as a pale yellow solid: mp >215 °C dec; *m/e* 586.1628 (Calcd for $C_{36}H_{26}O_8$, 586.1626); δ (CDCl$_3$–DMSO-$d_6$) 8.12 (2 H, s, H$_1$), 7.7 (2 H, d, *J* = 9 Hz, H$_5$), 7.59 (4 H, s, xylyl), 7.34 (2 H, s, H$_4$), 7.3 (2 H, d, *J* = 2.6 Hz, H$_8$), 7.21 (2 H, dd, *J* = 9, 2 Hz, H$_6$), 5.27 (4 H, s, CH$_2$-xylyl), 4.82 (4 H, d, *J* = 2 Hz, CH$_2$C≡C), 3.0 (2 H, tr, *J* = 2 Hz, C≡CH).

**Precyclophane 6a.** To a stirred mixture containing 7.1 g (12.1 mM) of diacid **5**, 1.96 g (10.8 mM) of 4-(dimethylamino)-2,6-pyridinedimethanol, 5.7 g (21.7 mM) of triphenylphosphine, and 220 mL of tetrahydrofuran (THF) at 25 °C was added dropwise 3.6 mL of diethyl azodicarboxylate. After 2 days the solvent was evaporated, and the resulting solid was triturated with ethanol to give 4.3 g (58% yield) of precyclophane **6a**, as a colorless solid. A small sample crystallized from pyridine had mp >220 °C dec: *m/e* 732.2472 (Calcd for $C_{45}H_{36}N_2O_8$, 732.2470); δ (CD$_2$Cl$_2$) 8.31 (2 H, s, H$_1$), 7.73 (2 H, d, *J* = 9 Hz, H$_5$), 7.31 (2 H, s, H$_4$), 7.32 (2 H, d, *J* = 2.5 Hz, H$_8$), 7.225 (2 H, dd, *J* = 9, 2.3 Hz, H$_6$), 7.17 (4 H, s, xylyl-H), 6.63 (2 H, s, py-H), 5.39 (4 H, s, py-CH$_2$), 5.12 (4 H, s, xylyl-CH$_2$), 4.81 (4 H, d, *J* = 2.5 Hz, CH$_2$Cl≡C), 2.78 (6 H, s, NMe$_2$), 2.6 (2 H, tr, *J* = 2.5 Hz, C≡CH).

**Cyclophane 1a.** A solution containing 1.4 g (1.91 mM) of precyclophane **6a** in 220 mL of pyridine was added dropwise over a period of 2 h to a solution containing 5.8 g (29 mM) of copper acetate in 80 mL of pyridine maintained at a temperature of 45 °C. After 3 h, the pyridine was separated by distillation under reduced pressure and the residue was extracted with methylene chloride. The combined extracts after washing with water were chromatographed on silica gel, using methylene chloride as eluent, to afford 184 mg of crude product. Crystallization from methylene chloride–hexane gave 123 mg (7% yield) of cyclophane **1a**: mp >220 °C dec; *m/e* (FABS) 730 (Calcd for $C_{45}H_{34}N_2O_8$, 730.23); δ (CD$_2$Cl$_2$) 7.87 (2 H, s, H$_1$), 7.46 (2 H, d, *J* = 9.5 Hz, H$_5$), 7.15 (2 H, s, H$_4$), 7.03 (2 H, br s, H$_8$), 7.00 (6 H, s and m, xylyl and H$_6$), 6.81 (2 H, s, py-H), 5.35 (4 H, ABq, *J* = 12 Hz, py-CH$_2$), 5.31 (4 H, ABq, *J* = 15 Hz, xylyl-CH$_2$), 4.83 (4 H, s, CH$_2$C≡C), 3.02 (6 H, s, NMe$_2$).

Anal. Calcd for $C_{45}H_{34}N_2O_8$·0.5CH$_2$Cl$_2$: C, 70.67; H, 4.51. Found: C, 71.00; H, 4.13.

**Precyclophane 6b.** To a suspension containing 1.28 g (2.2 mM) of diacid **5**, 0.31 g (2.2 mM) of 2,6-pyridinedimethanol (Aldrich Chemical Co.), and 1.15 g (4.4 mM) of triphenylphosphine in 25 mL of THF was added dropwise 0.7 mL of diethyl azodicarboxylate. The clear solution that resulted was allowed to stir for 3 days. After separation of the solvent, the residue was triturated with ethanol and then crystallized from CH$_2$Cl$_2$–hexane to give 0.8 g (54% yield) of precyclophane **6b**: mp 247 °C dec; *m/e* 689.2047 (Calcd for $C_{43}H_{31}NO_8$, 689.2048); δ (CDCl$_3$) 8.40 (2 H, s, H$_1$), 7.71 (2 H, d, *J* = 9 Hz, H$_5$), 7.5 (3 H, m, py-H$_{3,4,5}$), 7.3 (6 H, m, H$_{4,6,8}$), 7.10 (4 H, s, xylyl), 5.59 (4 H, s, py-CH$_2$), 5.10 (4 H, s, CH$_2$-xylyl), 4.83 (4 H, d, *J* = 2.5 Hz, CH$_2$C≡C), 2.58 (2 H, tr, 2.5 Hz, C≡CH).

**Cyclophane 1b.** To a solution of 2.7 g (13.6 mM) of copper acetate in 43 mL of pyridine at 40 °C was added dropwise over a period of 2 h

0.65 g (0.94 mM) of precyclophane **6b** in 43 mL of pyridine. After standing overnight, the solvent was separated by distillation in vacuo. The residue obtained was taken up in $CH_2Cl_2$ and washed with water. The organic concentrate was chromatographed on silica gel with $CH_2Cl_2$ as eluent to give 79 mg of a pale yellow solid. Crystallization from $CH_2Cl_2$ afforded 41 mg (6% yield) of cyclophane **1b**: mp >250 °C; *m/e* 687.1893 (Calcd for $C_{43}H_{29}NO_8$, 687.1893); δ (CDCl₃) 8.11 (2 H, s, H₁), 7.86 (1 H, tr, *J* = 8 Hz, py-H₄), 7.71 (2 H, d, *J* = 8 Hz, py-H₃,₅), 7.47 (2 H, d, *J* = 9 Hz, H₅), 7.19 (2 H, s, H₄), 7.04 (2 H, dd, 9, 2.4 Hz, H₆), 7.01 (2 H, s, H₈), 6.85 (4 H, s, xylyl), 5.5 (4 H, AB q, *J* = 11 Hz, py-CH₂), 5.31 (4 H, s, CH₂-xylyl), 4.84 (4 H, s, CH₂C≡C).

**Determination of Association Constants. (A) Titration Method.** The cyclophane (1–2 mg in 0.5 mL of deuterated solvent) was titrated with appropriate amounts of a stock solution of *p*-nitrophenol in the same solvent. By integration of the NMR spectrum, the number of equivalents of phenol was determined. At the conclusion of the experiment, a known quantity of dichloroethane was added to determine the host concentration. A best fit for the plot of chemical shift of the H₁ naphthalene proton versus the guest–host concentrations was obtained with a nonlinear least-squares method.

**(B) Competition Method.** The two cyclophanes to be compared (1–2 mg each) were dissolved in 0.5 mL of $CD_2Cl_2$ and varying amounts of *p*-nitrophenol were added. From comparison of the observed upfield chemical shift ($\delta_0 - \delta_{obsd}$) of the naphthalene H₁ proton to that of the chemical shift of the complex ($\delta_0 - \delta_{complex}$), $F_1$ and $F_2$ were obtained, and $K_{rel}$ was calculated (eq 1). The chemical shift of H₁ in the complexes was assumed to be that which is observed when the guest–host ratio is large.

# Benzylchlorocarbene: Kinetics Parameters for 1,2-H Migration, UV Absorption Spectrum, and Mechanism for Addition to Alkenes†

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**Abstract:** Laser flash photolysis (LFP) of 3-benzyl-3-chlorodiazirine, **1**, in isooctane, produces benzylchlorocarbene which reacts with pyridine to form an ylide or undergoes 1,2-H migration to form the (*Z*)- and (*E*)-β-chlorostyrenes. The rate for the 1,2-H migration is determined by plotting the pseudo-first-order rate constants for the growth of the ylide vs [pyridine] and extrapolating to [pyridine] = 0. From such measurements, performed at various temperatures, the kinetic parameters $E_i$ = 4.5 kcal/mol and $A_i$ = $10^{11.1}$ s⁻¹ are obtained. LFP of **1** in the absence of pyridine produces a transient absorption (280–330 nm) assigned to benzylchlorocarbene. Monitoring the carbene decay directly at 310 nm over the same temperature range gives similar values: $E_i$ = 4.8 kcal/mol and $A_i$ = $10^{11.3}$ s⁻¹. Three independent methods—LFP, products ratios (*Z/E* and cyclopropane/chlorostyrenes)—yield a single value, (6.2 ± 0.2) $10^8$ M⁻¹ s⁻¹ for $k_t$, the rate constant for the addition of benzylchlorocarbene to tetramethylethylene. These results are consistent with a mechanism involving the formation of a complex between benzylchlorocarbene and tetramethylethylene.

The most common rearrangement reaction of alkyl-substituted carbenes is the migration of a hydrogen atom to the carbene center which affords an alkene. Theoretical calculations have deduced

$$R-CH-\ddot{C}-X \longrightarrow R-CH=CHX$$
$$\quad\quad |$$
$$\quad\quad H$$
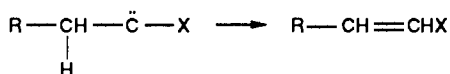
energy barriers to this rearrangement ranging from 0 to 27 kcal/mol.[1-6] The original zero value,[2] obtained by the semiempirical MINDO method, was considered unreliable due to the known deficiency of MINDO in favoring cyclic structures. Ab initio methods gave large values,[1,4] but more sophisticated calculations, involving polarized functions and correlation effects, reduced the value of the energy barrier to 2.1 kcal/mol.[5]

Experimentally, work on 1-aryl-2-diazopropanes[7] and examination of the vibrational structure of vinylidene photoelectron spectrum[8] has produced evidence of a definite barrier for 1,2-H migration, even though no value was assigned. Recently, the products derived from the thermolysis of 4-diazirinopentanoic acid gave an estimate of 1.1 ± 1 kcal/mol for the height of the barrier to 1,2-H shift in a dialkylcarbene.[9] By examining the competition between inter- and intramolecular reactions of halocarbenes, Liu and Subramanian[10,11] estimated the barrier to be 6.4 and 4.7 kcal/mol in Ph–CH₂–C̈–Cl and Ph–CH₂–C̈–Br, respectively. Although the estimated values may have errors of ±2 kcal/mol,

this latter work provides a valuable beginning for further insight into factors which control the intramolecular rearrangement.

Direct measurement, by laser flash photolysis, of the rate of H migration as a function of temperature seems quite difficult in the case of benzyl- and alkylhalocarbenes because, unlike arylhalocarbenes which are easily detected,[12] these species do not absorb with a high extinction coefficient in an easily accessible part of the spectrum. The "pyridine probe" technique[13] presents

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