Design of Receptors for Urea Derivatives Based on the Pyrido[3,2-g]indole Subunit

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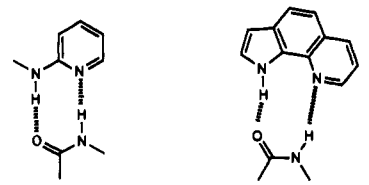
Abstract: The Fischer cyclization of appropriate 8-quinolinylhydrazones was employed to prepare a series of cavity-shaped hosts consisting of a central pyridine ring appended in either the 2,6- or 3,5-positions by two pyrido[3,2-g]indole subunits. The pyridine and pyridoindole moieties were further connected by dimethylene or trimethylene bridges which control the shape of the cavity. Hosts having a dimethylene bridge evidenced a strong affinity for urea derivatives in chloroform or dichloromethane solution. Binding constants were measured by NMR titration, and a structure-binding model was developed involving four strong hydrogen bonds. This model was substantiated by an X-ray analysis of a host-guest complex as well as NOE enhancement between protons on the complex. An X-ray analysis of the trimethylene-bridged host revealed a cavity which was too small to accommodate a urea guest. A decrease in the IR stretching frequency of the urea carbonyl in the complex was taken as a sign of diminished π-character of the C=O bond.

Introduction

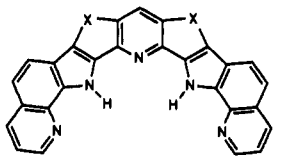
The study of synthetic receptors whose host properties depend on judicious arrangement of hydrogen-bonding sites has received a great deal of recent attention.[2-7] The similarity of such host-guest interactions to those found in naturally occurring enzyme-substrate complexes is not accidental, and an ultimate goal of many of these studies is to better understand and ultimately mimic these very efficient and specific biocatalytic processes.

The 2-aminopyridine subunit or its amide counterpart is a typical component of many host systems. The donor and acceptor groups bear a 1,3-relationship and are capable of forming two parallel hydrogen bonds. This complementarity is particularly well suited for binding with the amide linkages of a guest. The approach has been used to advantage by Hamilton and co-workers in the design of cavities and macrocycles designed to bind barbituates through as many as six hydrogen bonds.[3]

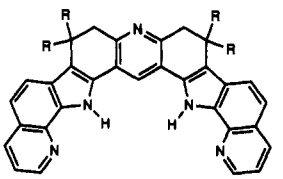
The pyrido[3,2-g]indole subunit has its donor and acceptor groups arranged in a 1,4-fashion. This seemingly less favorable arrangement is somewhat compensated by the five-membered pyrrole ring which ties back the N-H to some extent as well as the rigid, planar conformation of the pyridoindole moiety. The



resulting H-bonded complex involves one more atom in the cycle than its 2-aminopyridine counterpart, and it is not clear how this arrangement will influence the effectiveness of binding. This paper will investigate the pyrido[3,2-g]indole subunit as a component in the receptor systems **1** and **2**, where two of these subunits can act in concert to bind a urea functionality.



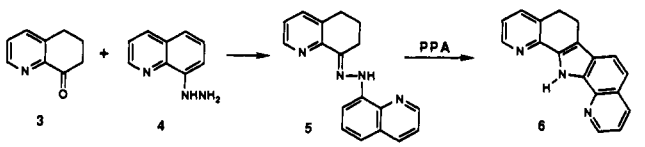
1 a X = H, H
b X = CH_2CH_2
c X = $CH_2CH_2CH_2$



2 a R = CH_3
b R = $(CH_2)_5$

Synthesis of Hosts

In an earlier communication we reported the application of 8-hydrazinoquinoline (**4**) to the Fischer synthesis of pyrido[2,3-g]indoles.[8] The reaction of **4** with 5,6,7,8-tetrahydro-8-quinolone (**3**) provides the corresponding hydrazone **5** in high yield. When



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this material is heated at 100 °C with polyphosphoric acid (PPA),

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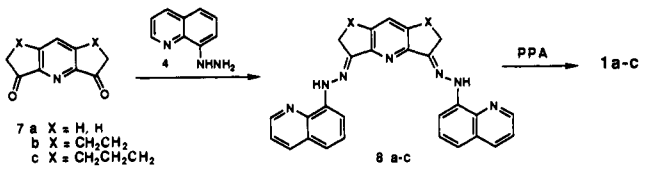
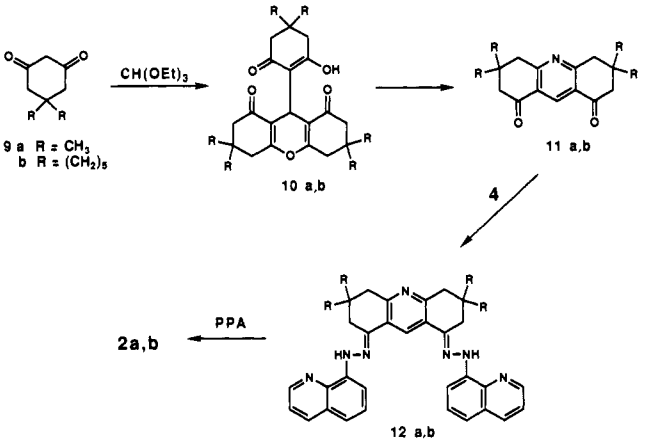
cyclization occurs to provide the pyrido[3,2-*g*]indole **6** in 96% yield. If this methodology is employed in a 2:1 fashion with the pyridyl diketones **7a–c**, the intermediate hydrazones **8a–c** lead directly

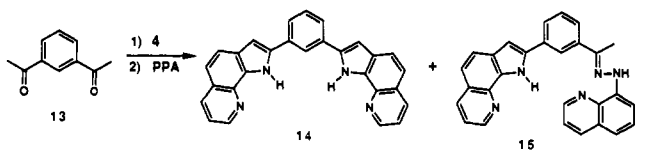


to the desired host systems **1a–c**.[9] It is noteworthy that whereas the hydrazones are usually formed in yields exceeding 90%, **8c** could be obtained in only 29% yield. Similarly we have found that other condensation reactions involving the α-position of 2,3-(pentamethylene)pyridines are unusually sluggish when compared with their tetramethylene counterparts.[10]

Preparation of the hosts **2a,b**, having their central pyridine rings inverted, required the corresponding diketones **11a,b**. These materials can be prepared according to the method of Wolfbeis and Junek from the appropriate 1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthenes **10a,b**, which are, in turn, derived from the reaction of triethyl orthoformate with the appropriate 5,5-dialkyl-1,3-cyclohexanediones **9a,b**.[11]



It would have been of interest to prepare and study the analog of **1a** where the central ring was benzene rather than pyridine. To this end we prepared the bis(quinolinylhydrazone) of *m*-diacetylbenzene (**13**) and cyclized this material with PPA. Along with 31% of the desired bis(pyridoindole) **14**, we obtained 37% of **15**, which had undergone only one cyclization. The solubility of **14** in $CDCl_3$ was insufficient to allow its use in association studies by NMR.



Association Studies

The first observation made with host **1b** was that its addition to a suspension of urea in chloroform caused solubilization of the urea. Due to the poor solubility of urea in chloroform, we were unable to carry out quantitative binding studies but rather proceeded directly to N-substituted urea derivatives which evidenced better solubility. The guests chosen for study were *N,N'*-dimethylurea, *n*-butylurea, imidazolidone, methyl biotin,[12] barbital,[13] and butyrolactam (Chart I). Their binding to **1b** was evaluated

Chart I. Structures of Guest Molecules

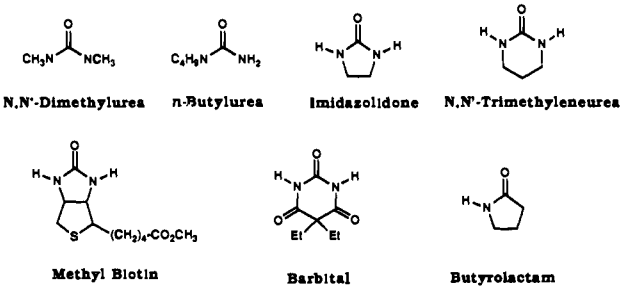


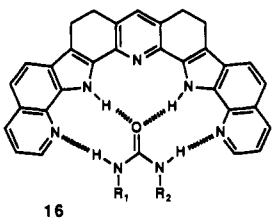
Table I. Association Constants (K_a, L/mol at 18 °C) for Host–Guest Complexation[a]

guest	host **1b**[b,c]	host **2a**[d]
N,N'-dimethylurea	10	118
n-butylurea	65	1190
imidazolidone	2240	13000
N,N'-trimethyleneurea		7950
methyl biotin	2210	9260
barbital	14100	74200
butyrolactam	11	156

[a] Estimated errors are ±30% for K_a values <200 and ±10% for all others. [b] Monitor change in NH resonance in 1:1 $CDCl_3/CD_2Cl_2$. [c] Recalculated values differ slightly from what was reported earlier.[8] [d] Monitor change in CH resonance in $CDCl_3$.

by adding incremental amounts of the guest to a 0.005 M solution of **1b** in 1:1 $CD_2Cl_2/CDCl_3$ at 18 °C. Under these conditions the chemical shift of the NH of **1b** moved downfield over a 2 ppm range. The NMR titration data were analyzed using a linear least squares fitting procedure similar to that described by Wilcox and Cowart,[14] and the calculated association constants are given in Table I. To adjust for any self-association of the host, a dilution study was performed over the range of concentrations studied and an appropriate correction applied to the binding data. The small magnitude of this correction indicated that for **1b** self-association was relatively unimportant. We measure apparent K_a values which do not compensate for self-association of the guest. In chloroform this self-association is normally quite small, a value of 7.0 having been measured for barbital.[15]

The measured K_a values are consistent with the binding model depicted in structure **16**. When $R_1 = R_2 = CH_3$, the binding is relatively weak. It improves for *n*-butylurea, a monosubstituted urea, and presumably would be improved considerably for the parent unsubstituted urea. When the two substituents are con-



strained to an anti-orientation as the result of being included in a bridge, as with imidazolidone, the binding is quite strong. Appendages on the imidazlidone moiety do not inhibit binding, as is seen for methyl biotin, and excellent binding is also observed with barbital. Butyrolactam is an amide analog of imidazolidone in which one of the H-bonding sites has been eliminated. Its binding with **1b** is comparable to that of *N,N'*-dimethylurea, in which three-point binding may also be involved.[16]

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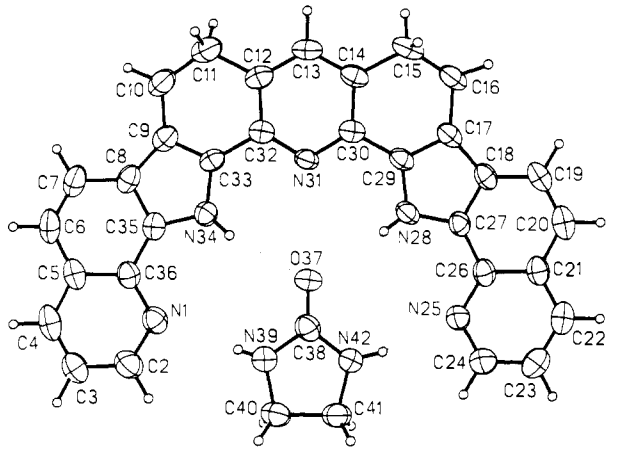
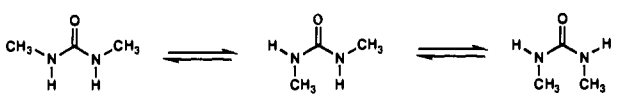


Figure 1. ORTEP drawing of complex of **1b** with imidazolidone showing atomic-numbering scheme.

An interesting conformational question arises for dimethylurea and *n*-butylurea. Rotation about the amide linkage can provide several planar conformers. The situation is illustrated for dimethylurea, whose most favorable conformer would be the syn, syn (**17a**) and least favorable would be the anti, anti (**17c**). Our



17a (*syn, syn*) **17b** (*syn, anti*) **17c** (*anti, anti*)

binding model would require this latter conformation for an optimum fit with the host. The poor association between **1b** and dimethylurea can be explained from two perspectives. The unfavorable 1,3-dimethyl interaction in **17c** can distort the guest sufficiently to disfavor binding using all four H-bonds. Alternatively, complexation may occur through conformer **17a** or **17b**, where only two or three H-bonds could be formed with the host.[16]

Combination of **1b** with 1 equiv of imidazolidone in 4:1 chloroform/dichloromethane followed by solvent evaporation afforded the 1:1 complex, which was sufficiently robust at high concentration to provide a weak but distinct parent ion (M + 1, m/z = 550) in the FAB mass spectrum. The base peak in this spectrum corresponded to the free host. When this complex was recrystallized from benzene, a single crystal was obtained whose analysis by X-ray diffraction, using the data collection and processing parameters given in Table II, afforded the structure shown in Figure 1.

Several important observations can be made regarding the **1b**–imidazolidone complex. The structure is consistent with the binding model given in structure **16**. The host and guest lie essentially in the same plane and form four optimal H-bonds with N1–N39 = 2.94 Å, N34–O37 = 3.09 Å, N28–O37 = 3.03 Å, and N25–N42 = 2.97 Å. All these values are reasonable for effective H-bonding. The only conformational flexibility of the system would be found in the dimethylene bridges of the host, which molecular mechanics predict could impart a dihedral angle of as much as 16° about the central pyridine and attached pyridoindole. The measured dihedral angles are considerably less with C17–C29–C30–C14 = −10.7° and C9–C33–C32–C12 = 7.7°. The opposite signs of these angles indicate a meso conformation for the bound host, which would allow more effective in-plane complexation with imidazolidone.

The role of the central pyridine nitrogen (N31) of host **1b** is noteworthy. A priori one might expect a repulsive interaction between the nitrogen lone pair electrons and the imidazolidone carbonyl oxygen that would disfavor binding. There is sufficient room to replace this nitrogen with a CH, which might be less detrimental. This hypothesis led us to develop the second generation host **2**, which has its central pyridine ring inverted so that a CH points into the cavity. This structural change had several important ramifications. Aside from alleviating the problematic N–O interaction, this internal CH can serve as a sensitive binding probe whose chemical shift can be monitored with more certainty in the NMR titrations.[17] Furthermore, our synthetic approach, which involves the precursor diketone **11a**, incorporates four methyl groups onto the two dimethylene bridges, improving solubility in chloroform so that dichloromethane is no longer required as an NMR cosolvent. Additionally, the NMR pattern of these bridges is now simplified and different conformations of the bridges should be more readily apparent. Lastly, the external nitrogen provides an intriguing site for further functionalization or attachment of the host.

Table II. X-ray Data Collection and Processing Parameters

	1b–imidazolidone	host **1c**
space group	$P2_1$ (monoclinic)	*Pbca* (orthorhombic)
cell constants	a = 13.935 (6) Å	a = 15.384 (6) Å
	b = 6.834 (2) Å	b = 13.372 (5) Å
	c = 15.620 (6) Å	c = 24.648 (10) Å
	β = 116.10 (3)°	
	V = 1336 Å^3	V = 5070 Å^3
molecular formula	$C_{34}H_{27}N_7O$	$C_{33}H_{25}N_5{\cdot}H_2O$
formula weight	549.68	509.65
formula units per cell	Z = 2	Z = 8
density	ρ = 1.37 g·cm^{-3}	ρ = 1.34 g·cm^{-3}
absorption coefficient	μ = 0.81 cm^{-1}	μ = 0.77 cm^{-1}
radiation (Mo Kα)	λ = 0.71073 Å	λ = 0.71073 Å
collection range	4° ≤ 2θ ≤ 55°	4° ≤ 2θ ≤ 40°
scan width	$\Delta\theta$ = 1.20 + (Kα_2 − Kα_1)°	$\Delta\theta$ = 1.20 + (Kα_2 − Kα_1)°
scan speed range	2.0–15.0 deg·min^{-1}	1.5–15.0 deg·min^{-1}
total data collected	3306	2662
independent data, $I > 3\sigma(I)$	1891	1154
total variables	391	342
$R = \sum\|\|F_o\| - \|F_c\|\|/\sum\|F_o\|$	0.043	0.069
$R_w = [\sum w(\|F_o\| - \|F_c\|)^2/\sum w\|F_o\|^2]^{1/2}$	0.028	0.057
weights	$w = \sigma(F)^{-2}$	$w = \sigma(F)^{-2}$
GOF	1.66	2.70

The association constants for complexation of the six guests with **2a** are given in Table I. It is clear that binding with all the guests is stronger than that for **1b**. The improvement is greatest for the poorer binders and somewhat less pronounced for the stronger binders. Two factors could be invoked to explain the more effective binding of barbital as compared with imidazolidone: the ring size of the urea or the acidity of the NH proton. To assess the relative importance of these two effects, we examined the association of *N,N'*-trimethyleneurea[18] with host **2a**. Trimethyleneurea was found to be a considerably less effective binder than barbital and somewhat less effective than imidazolidone, leading to the conclusion that a five-membered-ring guest provides a better fit with **2a** while the increased acidity of barbital dictates its stronger binding.

Figure 2 shows the effect of added imidazolidone on the downfield region of the NMR spectrum of **2a**. It is interesting to note the relative effect of imidazolidone binding on the protons of the host. The central interior proton (H17) is clearly the most affected, moving downfield more than 0.5 ppm and broadening significantly. The changes for H4 and H5 (or H6) are less prominent, since they are more remote from the binding site, while H2 is modestly affected. With **2a** we were also able to compare the validity of monitoring the chemical shift change in NH vs the change in CH and found relatively little difference.

From Figure 1 it appears that the hydrogens attached to C2 of the host and C40 of the imidazolidone guest might be reasonably close to one another. To further probe this proximity in solution, we carried out an NOE experiment on a $CDCl_3$ solution of the **2a**–imidazolidone complex. Irra iation of the imidazolidone

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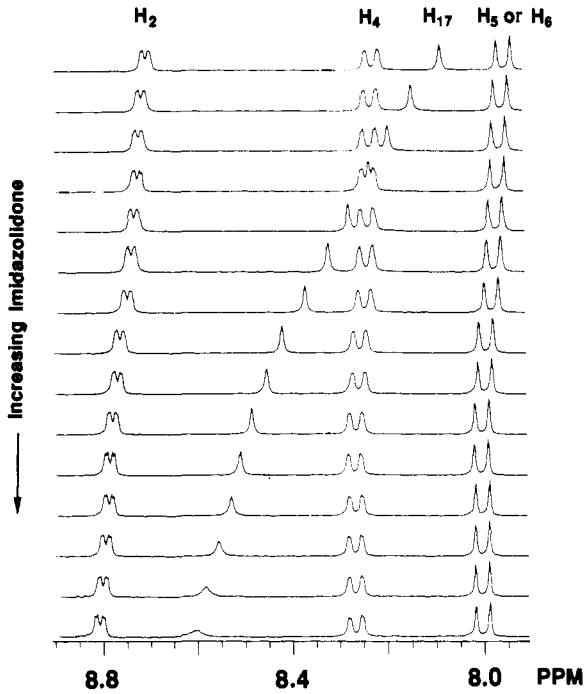


Figure 2. Downfield region of the ^1H NMR spectrum of **2a** in $CDCl_3$ (top spectrum) showing the effect of added increments of imidazolidone.[24]

dimethylene singlet at 3.78 ppm gave a 3% NOE enhancement of the C2-H signal of **2a** at 8.72 ppm. Irradiation in the reverse sense was less definitive. Since the reciprocal of the NOE enhancement is related to the sixth power of the distance between the two protons in question, we can calculate an approximate distance of 3.5 Å between them. This value compares well with the average measured distance between H2 and H40/H40′ of approximately 3.1 Å.

To improve the solubility of host **2a** even further, we prepared the bis(pentamethylene) derivative **2b**. The complex of **2b** with imidazolidone was sufficiently soluble to allow measurement of its ^{13}C NMR. In comparing the carbon spectrum of the free host with that of the complex, we notice relatively small changes with the exception of the signal for the central interior carbon of the host, which shifts downfield from 153.8 to 165.4 ppm upon complexation. The implication is that binding with imidazolidone causes a decrease in electron density at this carbon. This observation would be consistent with an increase in the dipole moment of the central pyridine ring induced by the proximate imidazolidone carbonyl dipole aligned in the same direction.

Another reason for examining a more soluble host such as **2b** was the hope of observing the binding phenomenon at lower temperatures. If complexation could be slowed sufficiently such that the CH being monitored would resolve into separate peaks for the bound and unbound host, one might be able to determine the thermodynamic parameters for this process. A $CDCl_3$ solution of **2b** at −60 °C still showed only one signal for H17 upon addition of imidazolidone.

It was of interest to investigate the influence of preorganization and cavity shape on the binding phenomenon. To address the first point, we examined the unbridged host **1a** and found the chemical shift of its NH to appear at 12.68 ppm. Comparison of this value with one of 10.54 for **1b** and ca. 12.6 ppm as the maximum value for an H-bonded complex of **1b** led us to surmise that the unbridged host was already strongly H-bonded. This premise was borne out by the lack of any change in the NH resonance with added imidazolidone It appeared that the host might be H-bonding with itself and was clear that preorganization is required for effective complexation with a guest.

The issue of shape was addressed by study of the trimethylene-bridged host **1c**, in which the bridging units were lengthened by one carbon. It was expected that such bridging would increase the dihedral angle between the central pyridine and the two pendent pyridoindoles. If these two dihedral angles had the same sign, the molecule would have a C_2 axis and exist as two conformational enantiomers. As such it might be capable of chiral discrimination.

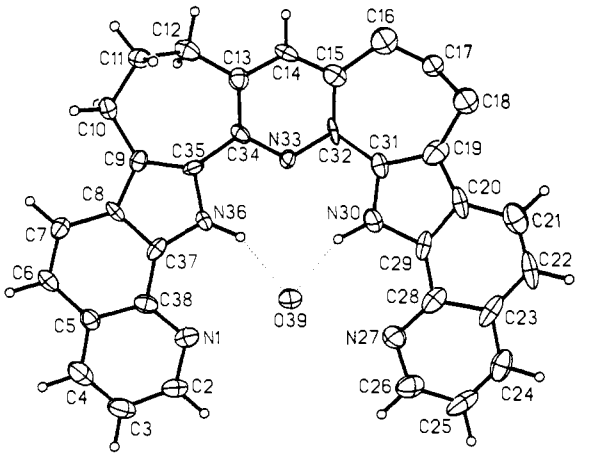
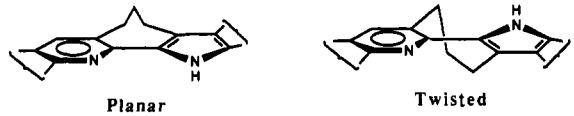


Figure 3. ORTEP drawing of 3,3′:5,3″-bis(trimethylene)-2,6-bis(pyrido[3,2-*g*]indol-2′-yl)pyridine (**1c**) with atomic-numbering scheme. O39 is attributed to a coordinated water molecule.

A recent X-ray analysis of an analogous bis(trimethylene)-bridged terpyridine revealed an overall twist of 79.8° between the peripheral pyridine rings.[19] Examination of the NMR spectrum of **1c** revealed that the indole protons resonate at 12.60 ppm, indicating that these NH functions are already strongly H-bonded, and again we conjectured that perhaps the molecule was H-bonding to itself. If self-binding occurred through the chiral conformation of **1c** and each monomer unit had the same configuration, the resulting hydrogen-bonded polymer would describe either a right- or left-handed helix.

To further investigate this situation, an X-ray crystal analysis of **1c** was carried out, using the data collection and processing parameters given in Table II, to provide the molecular structure shown in Figure 3. Surprisingly, the dihedral angle between the central pyridine ring and its two pendent pyridoindoles is less than 10°, providing an essentially planar host. The C16–C17–C18 bridge was disordered so that in 72% of the molecules this flap was down (C_2 symmetry) and in 28% it was up (C_s symmetry). Since the rest of the molecule was not disordered, the presence of two conformational diastereomers apparently does not influence the actual shape of the cavity. Molecular mechanics calculations for trimethylene-bridged derivatives of 2,2′-bipyridine and 2-(2′-pyridyl)indole support these observations for **1c**. For a trimethylene-bridged biaryl composed of two six-membered rings (bipyridine), the minimum energy conformation is twisted about the central bond, resulting in a dihedral angle of about 45° between the two aryl rings. The same bridge in a biaryl consisting of a five- and a six-membered ring (2-(2′-pyridyl)indole) has two minimum-energy conformations of nearly equal importance. One is twisted, with a calculated dihedral angle of about 41°, and the other is nearly planar, as we observe for **1c**.



Planar Twisted

In terms of cavity shape, the trimethylene bridges force the pyridoindole subunits to pinch in toward one another and considerably restrict the size of the cavity. One can evaluate this effect by considering the angles about C31 and C35. The average of C9–C35–C34 and C19–C31–C32 is 133.1° while the average of N36–C35–C34 and N30–C31–C32 is considerably less at 117.6°. The smaller cavity of **1c** can no longer accommodate a urea guest but instead contains a strongly bound water molecule.

(19) Huang, C.-Y.; Cabell, L. A.; Lynch, V.; Anslyn, E. V. *J. Am. Chem. Soc.* **1992**, *114*, 1900.

The fact that each host molecule contains 1–2 equiv of adventitious water raises the question of what effect such water might have on the association phenomenon. Wilcox has addressed this question for hydrogen-bond-based molecular recognition in chloroform and deduced that observations based on non-hydrogen-bonded protons are less susceptible to errors.[17] This premise lends more credence to results derived from measurements on **2a** as compared with **1b**. It is noteworthy that whether we monitor NH (of the guest) or CH (of the host) for complex formation with **2a**, the values remain relatively invariant.

Hydrogen bonding would be expected to have a profound effect on the carbonyl group of a urea guest. The C=O π-bond should weaken, which would be evidenced by a decrease in the C=O bond IR stretching frequency. Figure 4 depicts the IR band attributed to the C=O of imidazolidone, the pure solid-state **2b**–imidazolidone complex, and a solution containing partially complexed imidazolidone. In the complex the C=O band moves 26 cm^{-1} to lower wavenumber, consistent with less π-character for this bond. An intriguing consequence of polarizing the urea carbonyl group is the concomitant enhancement of its electrophilicity, which should facilitate nucleophilic attack and quite possibly hydrolysis. Current efforts are aimed at maximizing this effect and then evaluating its influence on the hydrolysis of urea.

In summary, we have prepared a cavity-shaped host **1b**, incorporating two pyrido[2,3-*g*]indole subunits attached to a central pyridine, which is a very effective receptor for substituted derivatives of urea. A binding model was developed and substantiated by X-ray analysis which involved four strong hydrogen bonds between the host and guest. This model led to the design of a second generation host **2**, which showed improved binding and solubility. The complexes were well-behaved chemical entities, evidencing a parent ion in the FAB mass spectrum, NOE enhancement between the bound host and guest, and a decrease in the IR carbonyl stretching frequency of the bound urea. Future efforts will be aimed at enhancing the chemical reactivity of urea with the design of a urease mimic as a potential objective.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a General Electric QE-300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C, and chemical shifts are reported in parts per million downfield from Me_4Si. Infrared spectra were obtained on a Perkin Elmer 1330 spectrometer and on an IBM IR/32 spectrometer. FAB mass spectra were obtained on a VG 70-SEQ spectrometer using *m*-nitrobenzyl alcohol as a matrix. Elemental analyses were performed by Canadian Microanalytical Service, Ltd., Delta, BC. It was not possible to completely exclude water from the host molecules. Molecular mechanics calculations were carried out using the programs PC MODEL and MMX from Serena Software, Bloomington, Indiana.

8-Hydrazinoquinoline (4).[20,21] Sulfur dioxide (10 g, 0.156 mol) was dissolved in 80 mL of hydrazine hydrate; 8-hydroxyquinoline (10.16 g, 0.07 mol) was added, and the mixture was stirred at reflux for 7 days. Ethanol (10 mL) was added occasionally to the mixture to dissolve any 8-hydroxyquinoline which had sublimed into the condensor. The mixture was made basic with 100 mL of 2 M NaOH and extracted with $CHCl_3$ (4 × 75 mL). The combined organic layers were washed with 20 mL of brine, dried ($MgSO_4$), and concentrated. The residue solidified in the freezer and was recrystallized from CH_2Cl_2/pentane to yield 8.70 g (78%) of pale-yellow needles: mp 63 °C (lit.[21] mp 63.5–64 °C); ^1H NMR ($CDCl_3$) δ 8.71 (d, 1 H, $J_{2,3}$ = 4.2 Hz, H2), 8.06 (d, 1 H, $J_{3,4}$ = 8.3 Hz, H4), 7.44 (t, 1 H, H6), 7.36 (dd, 1 H, H3), 7.28 (broad s, 1 H, NH), 7.15 (d, 1 H, H5 or H7), 7.05 (d, 1 H, H5 or H7), 3.67 (broad s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 147.3, 137.7, 135.8, 128.4, 127.5, 121.4, 115.9, 105.8, 104.9. Upon exposure to air the 8-hydrazinoquinoline turns rapidly brown. It should be transferred and stored under Ar in the freezer where its shelf life is at least 3 months.

5,6,7,8-Tetrahydro-8-quinolone 8-Quinolinylhydrazone (5). A mixture of 5,6,7,8-tetrahydro-8-quinolone[22] (0.306 g, 2.08 mmol) and 8-hydrazinoquinoline (0.331 g, 2.08 mmol) in absolute EtOH (10 mL) was refluxed for 45 min to provide, after cooling and filtration, 0.54 g (94%) of **5**: mp 220–223 °C; ^1H NMR ($CDCl_3$) δ 9.79 (broad s, NH), 8.73 (d, 1 H, J = 2.7 Hz), 8.62 (d, 1 H, J = 3.6 Hz), 8.10 (d, 1 H, J = 8.2 Hz), 7.95 (d, 1 H, J = 7.5 Hz), 7.52 (t, 1 H, J = 8.0 Hz), 7.44 (d, 1 H, J = 7.5 Hz), 7.38 (dd, 1 H, J = 8.0 Hz), 7.26 (d, 1 H, J = 7.9 Hz), 7.12 (dd, 1 H, J = 5.7, 6.2 Hz), 2.95 (t, 2 H, J = 6.4 Hz, $ArCH_2$), 2.81 (t, 2 H, J = 5.5 Hz, $-CH_2C{=}N-$), 2.33–2.05 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 150.8, 148.5, 147.3, 142.2, 139.8, 137.3, 136.2, 135.9, 134.1, 128.3, 127.9, 122.1, 121.2, 117.4, 109.9, 29.2, 25.3, 21.1; IR (KBr) 3340, 2920, 1570, 1515, 1430, 1385, 1145, 1100, 900 cm^{-1}.

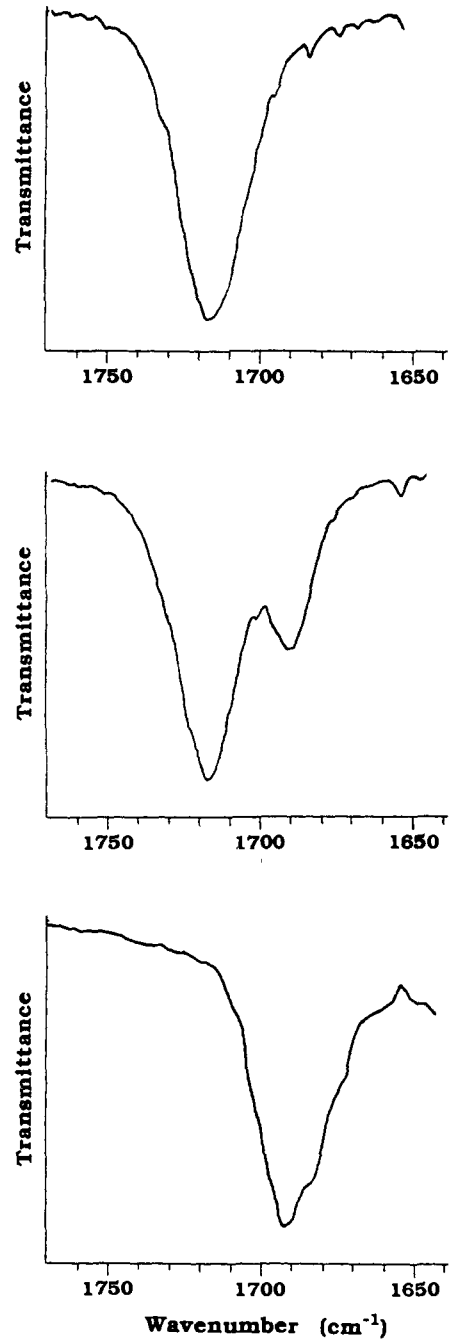


Figure 4. Infrared spectra in the region 1770–1640 cm^{-1} for imidazolidone (0.02 M in CH_2Cl_2, top); imidazolidone (0.022 M) with added host **2a** (0.0048 M in CH_2Cl_2, middle); and the **2a**–imidazolidone complex (KBr, bottom).

3,4-Dihydrodipyrido[2,3-*a*:3,2-*i*]carbazole (6). The hydrazone **5** (0.30 g, 1.00 mmol) was mixed with polyphosphoric acid (3.0 g), and the mixture was heated in a heavy-walled beaker at 100 °C for 2 h. After cooling, the mixture was made basic with 10% NaOH (litmus paper blue) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated to give 0.27 g (96%) of **6**: mp (EtOH) 176–178 °C; ^1H NMR ($CDCl_3$) δ 10.57 (broad s, 1 H, NH), 8.81 (d, 1 H, J = 3.1 Hz), 8.39 (d, 1 H, J = 4.1 Hz), 8.17 (d, 1 H, J = 7.8 Hz), 7.69 (d, 1 H, J = 8.4 Hz), 7.49 (d, 1 H, J = 7.0 Hz), 7.42 (d, 1 H, J = 8.5 Hz), 7.34 (dd, 1 H), 7.04

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(21) Nielsen, P. H.; Dahl, O. *Acta Chem. Scand.* **1966**, *20*, 1113.
(22) Thummel, R. P.; Lefoulon, F.; Cantu, D.; Mahadevan, R. *J. Org. Chem.* **1984**, *49*, 2208.

(dd, 1 H), 3.13 (s, 4 H, $-ArCH_2-$); ^{13}C NMR ($CDCl_3$) δ 148.4 (2 peaks), 148.1, 147.2, 136.1, 136.0, 135.0, 131.2, 125.6, 125.2, 121.3, 119.9, 119.5, 116.8, 96.1, 28.8, 19.6; IR (KBr) 3155, 3055, 2925, 1585, 1415, 1385, 905 cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_3 \cdot 0.2H_2O$: C, 78.66; H, 4.88; N, 15.29. Found: C, 78.77; H, 4.80; N, 15.26.

2,6-Diacetylpyridine Bis(8-quinolinylhydrazone) (8a). A mixture of 2,6-diacetylpyridine (0.9 g, 5.52 mmol) and 8-hydrazinoquinoline (1.75 g, 10.95 mmol) in absolute ethanol (40 mL) was heated at 85 °C for 2 h to give, after cooling and filtration, 2.37 g (94%) of **8a**: mp 291–294 °C; ^1H NMR ($CDCl_3$) δ 9.75 (s, 2 H, NH), 8.80 (dd, J = 1.3, 4.2 Hz, H2′), 8.21 (d, J = 7.8 Hz, H3), 8.15 (d, J = 8.1 Hz, H4′), 7.80 (d, J = 7.5 Hz, H5′), 7.73 (t, J = 7.8 Hz, H4), 7.54 (t, J = 7.9 Hz, H6′), 7.43 (dd, J = 4.3, 8.2 Hz, H3′), 7.29 (d, J = 7.3 Hz, H7′), 2.65 (s, 6 H, CH_3); IR (KBr) 3340, 3030, 2920, 1700 (weak), 1638, 1580, 1520, 1450, 1390, 1185, 1160, 820, 790 cm^{-1}.

1,2,3,4,5,6,7,8-Octahydroacridine-4,5-dione Bis(8-quinolinylhydrazone) (8b). The reaction of 1,2,3,4,5,6,7,8-octahydroacridine-4,5-dione[10] (0.2 g, 0.88 mmol) with 8-hydrazinoquinoline (0.28 g, 1.76 mmol) as described above for **8a** provided 0.43 g (97%) of **8b**: mp 234–236 °C; ^1H NMR ($CDCl_3$) δ 9.91 (broad s, 2 H, NH), 8.77 (d, 2 H, $J_{2',3'}$ = 4.2 Hz, H2′), 8.16 (overlapping t, 4 H, H4′, H5′), 7.65 (t, 2 H, J = 8.0 Hz, H6′), 7.43 (dd, 2 H, $J_{3',4'}$ = 8.3 Hz, H3′), 7.36 (d, 2 H, $J_{6',7'}$ = 8.1 Hz, H7′), 7.26 (s, 1 H, H4′), 2.94 (overlapping t, 8 H, CH_2), 2.32 (quintet, 4 H, CH_2); ^{13}C NMR ($CDCl_3$)[23] δ 147.3, 136.0, 127.9, 121.2, 117.3, 110.2, 96.2, 28.8, 25.0, 21.3; IR (KBr) 3340, 2930, 1570, 1425, 1375, 1145, 1100, 900 cm^{-1}.

α,α'-Dioxo-2,3:5,6-bis(pentamethylene)pyridine Bis(8-quinolinylhydrazone) (8c). A mixture of α,α'-dioxo-2,3:5,6-bis(pentamethylene)-pyridine[10] (0.38 g, 1.6 mmol) with 8-hydrazinoquinoline (0.54 g, 3.38 mmol) in absolute ethanol (20 mL) was heated at 75 °C for 3 h. The reaction mixture was cooled and concentrated, and the residue was purified by chromatography on 10 g of silica gel eluting with CH_2Cl_2 to provide 0.2 g (29%) of the dihydrazone **8c**: mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 9.73 (s, 2 H, NH), 8.75 (dd, 2 H, $J_{2',3'}$ = 4.2 Hz, $J_{2',4'}$ = 1.3 Hz, H2′), 8.11 (dd, 2 H, $J_{3',4'}$ = 8.2 Hz, H4′), 8.0 (d, 2 H, $J_{5',6'}$ = 7.8 Hz, H5′), 7.56 (dd, 2 H, J = 7.8, 5.6 Hz, H6′), 7.40 (dd, 2 H, H3′), 7.27 (dd, 2 H, H7′), 7.23 (s, 1 H, H4), 2.89 (m, 4 H), 2.81 (m, 4 H), 1.91 (broad m, 8 H); ^{13}C NMR ($CDCl_3$) δ 154.1, 148.6, 147.2, 140.5, 137.3, 137.1, 135.9, 133.6, 128.4, 127.8, 121.1, 116.9, 109.8, 29.8, 26.6, 25.7, 21.1; IR (KBr) 3320, 3030, 2910, 1600, 1560, 1505, 1420, 1370, 1125, 1115 cm^{-1}.

2,6-Bis(pyrido[3,2-*g*]indol-2′-yl)pyridine (1a). The dihydrazone **8a** (0.3 g, 1.84 mmol) was mixed with 10.5 g of PPA, and the mixture was heated in a heavy-walled beaker at 160 °C for 3 h. After cooling, the mixture was made basic with 10% NaOH and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with 10% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to give 0.36 g of crude product. This material was recrystallized from CH_2Cl_2 to provide 0.21 g (76%) of **1a**: mp 195.4–195.5 °C; MS *m/e* (relative intensity) 410 (100, M), 166 (53); ^1H NMR ($CDCl_3$) δ 12.65 (s, 2 H, NH), 8.94 (dd, 2 H, J = 4.4, 1.3 Hz, H8′), 8.27 (dd, 2 H, J = 8.1, 1.2 Hz, H6′), 7.81 (d, 2 H, J = 8.6 Hz, H4′ or H5′), 7.78 (t, 1 H, H4), 7.68 (d, 2 H, J = 7.4 Hz, H3), 7.46 (d, 2 H, J = 8.6 Hz, H4′ or H5′), 7.44 (dd, 2 H, H7′), 7.20 (d, 2 H, J = 2.0 Hz, H3′), 2.64 (s, H_2O); ^{13}C NMR (DMSO-d_6) δ 149.8, 147.8, 138.2, 137.6, 137.3, 136.3, 132.0, 127.6, 125.1, 121.7, 119.7, 119.6, 118.0, 102.9; IR (KBr) 3320, 3024, 1590, 1550, 1535, 1440, 1380, 1095, 895, 800, 690 cm^{-1}. Anal. Calcd for $C_{27}H_{17}N_5 \cdot 1.2H_2O$: C, 74.89; H, 4.48; N, 16.18. Found: C, 74.99; H, 4.45; N, 16.26.

3,4,5,6-Tetrahydrobis(pyrido[3,2-*g*]indolo)[2,3-*a*:3′,2′-*j*]acridine (1b). Following the procedure described for **1a**, the reaction of dihydrazone **8b** (0.30 g, 0.59 mmol) with 5.0 g of PPA provided 0.21 g (77%) of **1b**: mp 170–172 °C; ^1H NMR ($CDCl_3/CD_2Cl_2$, 1:1)[24] δ 10.78 (s, 2 H, NH), 8.78 (d, 2 H, H2), 8.16 (d, 2 H, H4), 7.67 (d, 2 H, H5 or H6), 7.38 (d, 2 H, H5 or H6), 7.33 (s, 1 H, H9), 7.30 (dd, 2 H, H3), 3.09 (broad s, 8 H, $-CH_2CH_2-$); ^{13}C NMR ($CDCl_3$) δ 148.5, 145.7, 138.5, 136.1, 134.1, 133.1, 132.2, 129.2, 125.5, 125.4, 119.9, 119.5, 119.4, 116.1, 28.8, 19.8; IR (KBr) 3050, 2940, 1600, 1380, 915, 835 cm^{-1}. Anal. Calcd for $C_{31}H_{21}N_5 \cdot 2.1H_2O$: C, 74.28; H, 5.03; N, 13.98. Found: C, 74.59; H, 5.18; N, 13.59.

3,3′:5,3″-Bis(trimethylene)-2,6-bis(pyrido[3,2-*g*]indol-2′-yl)pyridine (1c). Following the same procedure described for **1a**, the reaction of dihydrazone **8c** (0.10 g, 0.19 mmol) with 4.2 g of PPA provided a solid which was purified by recrystallization from methanol to give 0.05 g (54%) of **1c**: mp > 310 °C; MS *m/e* (relative intensity) 493 (100, M + 1); ^1H NMR ($CDCl_3$)[24] δ 12.60 (s, 2 H, NH), 8.91 (dd, 2 H, J = 4.3, 1.3 Hz, H2), 8.27 (dd, 2 H, J = 8.1, 1.3 Hz, H4), 7.76 (d, 2 H, J = 8.5 Hz, H5 or H6), 7.43 (d, 2 H, J = 8.5 Hz, H5 or H6), 7.41 (m, 2 H, H3), 7.28 (s, 1 H, H10), 3.31 (t, 4 H, H9), 3.08 (m, 4 H, H7), 2.24 (quintet, 4 H, H8); ^{13}C NMR (DMSO-d_6) δ 148.0, 146.7, 139.3, 138.0, 136.7, 133.7, 133.5, 130.8, 127.9, 125.6, 120.2, 120.0, 118.9, 116.4, 33.6, 26.6, 24.9; IR (KBr) 3308, 3020, 2935, 2850, 1640, 1595, 1530, 1440, 1390, 1260, 820, 800, 715 cm^{-1}.[25]

9-(4,4-Dimethyl-2-hydroxy-6-oxo-1-cyclohexenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroxanthene (10a). A mixture of 5,5-dimethyl-1,3-cyclohexanedione (20.0 g, 143 mmol), triethyl orthoformate (12.0 g, 81 mmol), and glacial acetic acid (19 mL) was heated to reflux until a white precipitate formed. After cooling, 5 mL of glacial acetic acid was added, the slurry was filtered, and the residue was washed with water. The filtrate was filtered again, and the combined solid material was recrystallized from EtOH to yield 18.72 g (95%) of **10a** as a white powder: mp 225 °C (lit.[11] mp 224 °C); ^1H NMR ($CDCl_3$) δ 9.87 (s, 1 H, OH), 4.32 (s, 1 H, H9), 2.50 (d, 2 H, J = 17.8 Hz, H2, H7), 2.39 (d, 2 H, H2′, H7′), 2.33 (s, 2 H), 2.26 (s, 4 H, H4, H5), 2.00 (s, 2 H), 1.10 (s, 6 H, CH_3), 1.00 (s, 6 H, CH_3), 0.97 (s, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 198.7, 197.1, 171.9, 165.6, 115.2, 112.9, 51.2, 50.3, 43.0, 40.7, 32.2, 30.7, 29.4, 27.9, 26.9, 21.9.

9-(4,4-(Pentamethylene)-2-hydroxy-6-oxo-1-cyclohexenyl)-1,8-dioxo-3,3:6,6-bis(pentamethylene)-1,2,3,4,5,6,7,8-octahydroxanthene (10b). A mixture of 5,5-(pentamethylene)-1,3-cyclohexanedione[26] (6.0 g, 33.3 mmol), triethyl orthoformate (2.1 g, 14.2 mmol), and glacial acetic acid (6 mL) was treated as described for **10a** to yield 4.02 g (68%) of **10b** as a white powder: mp 208 °C (lit.[11] mp 208 °C); ^1H NMR ($CDCl_3$) δ 9.82 (s, 1 H, OH), 4.25 (s, 1 H, H9), 2.60 (d, 2 H, J = 17.8 Hz), 2.40 (d, 2 H, J = 16.5 Hz), 2.37 (d, 2 H, J = 17.8 Hz), 2.36 (s, 2 H), 2.24 (d, 2 H, J = 16.5 Hz), 2.07 (s, 2 H), 1.42–1.32 (m, 30 H); ^{13}C NMR ($CDCl_3$) δ 198.4, 196.8, 171.3, 165.3, 115.2, 112.9, 48.6, 48.1, 41.2, 38.6, 37.9, 36.3, 35.0 (3 peaks), 33.6, 26.3, 26.1, 21.9, 21.6 (2 peaks).

3,3,6,6-Tetramethyl-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (11a). A mixture of **10a** (1.00 g, 2.4 mmol), ammonium acetate (2.15 g, 28 mmol), and glacial acetic acid (8 mL) was refluxed for 2 h. After cooling to 25 °C, the acetic acid was evaporated and 0.5 M NaOH (40 mL) was added. The mixture was extracted with $CHCl_3$, and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was recrystallized from EtOH to yield 0.55 g (84%) of **11a** as white crystals: mp 144–145 °C (lit.[11] mp 148 °C); ^1H NMR ($CDCl_3$) δ 8.82 (s, 1 H, H9), 3.05 (s, 4 H, H4, H5), 2.57 (s, 4 H, H2, H7), 1.13 (s, 12 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 196.8, 166.4, 133.6, 126.3, 52.0, 46.9, 32.8, 28.3.

3,3:6,6-Bis(pentamethylene)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (11b). A mixture of **10b** (1.00 g, 1.9 mmol), ammonium acetate (2.00 g, 26 mmol), and glacial acetic acid (8 mL) was treated as described for **11a** to provide an oil which was purified by chromatography on 60 g of silica gel, eluting with 7:3 EtOAc/CH_2Cl_2 to yield 0.67 g (100%) of **11b** as a colorless solid: mp 136–137 °C (lit.[11] mp 138 °C); ^1H NMR ($CDCl_3$) δ 8.75 (s, 1 H, H9), 3.13 (s, 4 H, H4, H5), 2.63 (s, 4 H, H2, H7), 1.51–1.44 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 196.7, 166.1, 133.2, 126.7, 50.2, 44.3, 36.6, 35.6, 26.0, 21.5.

3,3,6,6-Tetramethyl-1,2,3,4,5,6,7,8-octahydroacridine 1,8-Bis(8-quinolinylhydrazone) (12a). A mixture of **11a** (0.82 g, 3 mmol), **4** (1.05 g, 6.6 mmol), and three drops of concentrated H_2SO_4 in 50 mL of EtOH was heated on a steam bath for 1 h. After cooling, a solution of 0.8 g of K_2CO_3 in 20 mL of water was added. This solution was diluted with 50 mL of water, and the precipitate was dissolved by adding CH_2Cl_2. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated. The residue was precipitated from EtOH to yield 1.58 g (95%) of **12a** as a yellow solid: mp 301 °C dec; ^1H NMR ($CDCl_3$) δ 9.66 (broad s, 2 H, NH), 9.41 (s, 1 H, H9), 8.80 (dd, 2 H, $J_{2',3'}$ = 4.2 Hz, $J_{2',4'}$ = 1.6 Hz, H2′), 8.15 (dd, 2 H, $J_{3',4'}$ = 8.3 Hz, H4′), 7.95 (dd, 2 H, $J_{6',7'}$ = 7.7 Hz, H7′), 7.61 (t, 2 H, H6′), 7.44 (dd, 2 H, H3′), 7.31 (dd, 2 H, H5′), 2.88 (s, 4 H, H4, H5), 2.67 (s, 4 H, H2, H7), 1.18 (s, 12 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.6, 147.4, 141.4, 140.7, 137.3, 136.1, 128.6, 127.9, 127.3, 126.7, 121.5, 117.1, 108.7, 46.2, 37.7, 31.0, 29.0; IR (KBr) 3440, 2960, 2930, 1575, 1520, 1385, 1240, 1105, 940, 905 cm^{-1}.

3,3:6,6-Bis(pentamethylene)-1,2,3,4,5,6,7,8-octahydroacridine 1,8-Bis(8-quinolinylhydrazone) (12b). A mixture of **11b** (0.46 g, 1.3 mmol), **4** (0.46 g, 2.86 mmol), and three drops of concentrated H_2SO_4 in 30 mL of EtOH was treated as described for **12a**. Workup with $CHCl_3$ in place

(23) Quaternary carbons could not be observed.

(24) The NMR atom-numbering scheme for **1b,c** and **2a,b** designates the quinoline atom as atom one, and each successive nonbridgehead carbon atom on the periphery of the molecule is then numbered sequentially proceeding away from the bay region of the molecule. Atoms identical by symmetry are designated only once.

(25) Insufficient sample available for combustion analysis.

(26) (a) Norris, W. S. G. P.; Thorpe, J. F. *J. Chem. Soc.* **1921**, 1199. (b) Wallach, O. *Liebigs Ann. Chem.* **1912**, *394*, 362.

of CH_2Cl_2 provided 0.69 g (83%) of **12b** as a yellow solid: mp 292 °C dec; ^1H NMR ($CDCl_3$) δ 9.68 (broad s, 2 H, NH), 9.33 (s, 1 H, H9), 8.81 (dd, 2 H, $J_{2',3'}$ = 4.2 Hz, $J_{2',4'}$ = 1.6 Hz, H2'), 8.15 (dd, 2 H, $J_{3',4'}$ = 8.3 Hz, H4'), 7.93 (dd, 2 H, $J_{6',7'}$ = 7.7 Hz, $J_{5',7'}$ = 1.0 Hz, H7'), 7.60 (t, 2 H, H6'), 7.44 (dd, 2 H, H3'), 7.30 (dd, 2 H, $J_{5',6'}$ = 8.1 Hz, H5'), 2.98 (s, 4 H, H4), 2.68 (s, 4 H), 1.58–1.40 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 155.3, 147.5, 141.4, 140.8, 137.3, 136.0, 128.6, 127.9, 127.7, 126.4, 121.4, 117.0, 108.7, 42.7, 37.1, 36.5, 33.7, 26.4, 21.9; IR (KBr) 3440, 2980, 2920, 2860, 1575, 1515, 1380, 1235, 1100, 905 cm^{-1}.

3,4,5,6-Tetrahydro-3,3,6,6-tetramethylbis(pyrido[3,2-*g*]indolo)[2,3-*a*:3',2'-*j*]acridine (2a). A mixture of **12a** (388 mg, 0.7 mmol), PPA (3 g), and toluene (3 mL) was refluxed under N_2 for 4 h. After cooling, the mixture was combined with 20 mL of 15% NaOH. After diluting with 200 mL of H_2O, the aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated to yield 0.35 g of a material which was purified by chromatography on 45 g of SiO_2, eluting with 2:3 ethyl acetate/hexane followed by ethyl acetate. Subsequent recrystallization from ethyl acetate yielded 234 mg (64%) of **2a** as yellow crystals: mp > 300 °C; ^1H NMR ($CDCl_3$)[24] δ 11.18 (broad s, 2 H, NH), 8.73 (dd, 2 H, $J_{2,3}$ = 4.5 Hz, $J_{2,4}$ = 1.5 Hz, H2), 8.59 (s, 1 H, H17), 8.25 (dd, 2 H, $J_{3,4}$ = 8.1 Hz, H4), 7.98 (d, 2 H, $J_{5,6}$ = 8.7 Hz, H5 or H6), 7.44 (d, 2 H, H5 or H6), 7.37 (dd, 2 H, H3), 3.17 (s, 2 H, H8), 2.64 (s, H_2O), 1.59 (s, 12 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 153.8, 147.6, 137.5, 136.9, 132.3, 130.9, 125.0, 124.9, 122.4, 122.3, 121.7, 119.3, 119.2, 118.8, 48.6, 33.9, 29.1; IR (KBr) 3440, 2990, 2930, 2860, 1240, 1110, 910, 635 cm^{-1}. Anal. Calcd for $C_{35}H_{29}N_5 \cdot 1.4H_2O$: C, 77.18; H, 5.84; N, 12.86. Found: C, 77.29; H, 5.56; N, 12.59.

3,3:6,6-Bis(pentamethylene)-3,4,5,6-tetrahydrobis(pyrido[3,2-*g*]indolo)[2,3-*a*:3',2'-*j*]acridine (2b). A mixture of **12b** (380 mg, 0.6 mmol), PPA (4.5 g), P_2O_5 (0.5 g), and toluene (3 mL) was refluxed under N_2 for 4 h. After cooling, 20 mL of 15% NaOH was added and the mixture was diluted with 200 mL of H_2O and extracted with $CHCl_3$. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from EtOAc to yield 260 mg (72%) of **2b** as yellow crystals: mp >300 °C; ^1H NMR ($CDCl_3$)[24] δ 10.87 (broad s, 2 H, NH), 8.66 (dd, 2 H, $J_{2,3}$ = 4.4 Hz, $J_{2,4}$ = 1.4 Hz, H2), 8.14 (dd, 2 H, $J_{3,4}$ = 8.1 Hz, H4), 8.01 (d, 2 H, $J_{5,6}$ = 8.8 Hz, H5 or H6), 7.94 (s, 1 H, H19), 7.36 (d, 2 H, H5 or H6), 7.25 (dd, 2 H, H3), 3.30 (s, 4 H, H8), 2.18–2.07 (m, 4 H), 1.90–1.65 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 153.8, 148.0, 137.9, 136.3, 132.7, 130.6, 124.9, 124.6, 123.5, 122.3, 121.9, 119.4, 119.2, 117.5, 41.1, 37.3, 36.5, 26.3, 22.0; IR (KBr) 3440, 2990, 2920, 2860, 1240, 1105, 905, 635 cm^{-1}. Anal. Calcd for $C_{41}H_{37}N_5 \cdot 1.2H_2O$: C, 79.28; H, 6.35; N, 11.28. Found: C, 79.19; H, 6.27; N, 11.09.

Preparation of Imidazolidone Complexes. Equimolar amounts of **1b** (in CH_2Cl_2) or **2a,b** (in $CHCl_3$) and imidazolidone in the corresponding solvent were combined and warmed on the steam bath. The solvent was then evaporated, and the residue was recrystallized from benzene.

Measurement of Association Constants. A 0.005 M stock solution of the host **1b** (1:1 $CD_2Cl_2/CDCl_3$) and **2a** ($CDCl_3$) was prepared. According to solubility and binding strength, solutions of the guests (0.01–0.5 M) were prepared in $CDCl_3$. Increments of the guest solution were then added to 0.500 mL of the host solution in a 5-mm NMR tube, and the chemical shift change of the host NH or CH resonance was monitored. Strong binders (more dilute) were added in small initial increments (1–2 μL) while weaker binders (more concentrated) were added in larger initial increments (5 μL). A blank run, adding pure $CDCl_3$ to the host solution, was used to correct the data for a small dilution effect. The association constant K_a for each host–guest system was calculated by fitting the mole fraction of bound host with the corrected $\Delta\delta_{NH}$ following the method of Horman and Dreux.[14]

A typical set of NMR titration data is shown in Figure 2. The full data sets for the dilution corrections and all the association measurements are provided with the supplementary material.

X-ray Crystallography. An appropriate crystal was mounted in a random orientation on a Nicolet R3m/V automatic diffractometer. The radiation used was Mo Kα monochromatized by a highly ordered graphite crystal. Final cell constants, as well as other information pertinent to data collection and refinement, are listed in Table II. Intensities were measured using the omega scan technique, with the scan rate depending on the count obtained in rapid prescans of each reflection. Two standard reflections were monitored after every 2 h or every 100 data collected, and these showed no significant variation. In reducing the data, Lorentz and polarization corrections were applied; however, no correction for absorption was made due to the small absorption coefficient.

A. 1b–Imidazolidone. An amber colored fragment having approximate dimensions 0.55 × 0.45 × 0.40 mm was cut from a large plate. The Laue symmetry was determined to be $2/m$, and from the systematic absences noted, the space group was shown to be either $P2_1$ or $P2_1/m$. Analysis of the width of the host molecule and the length of the b axis revealed that the molecule could not be situated on a mirror plane, and so space group $P2_1$ was assumed from the outset. The structure was solved by use of the SHELXTL direct methods program, which revealed the positions of all of the non-hydrogen atoms in the asymmetric unit, consisting of one host and one guest molecule. The usual sequence of isotropic and anisotropic refinement was followed, after which all hydrogens were entered in ideal calculated positions and constrained to riding motion, with a single variable isotropic temperature factor. The four hydrogens attached to nitrogen were eventually allowed to refine freely, although they were constrained to have the same isotropic temperature factor as the other hydrogens. Although the space group is a noncentrosymmetric enantiomorphic one, no attempt was made to determine the absolute configuration of the molecules involved, since there is no significant anomalous scatterer present. After all shift/esd ratios were less than 0.3, convergence was reached at the agreement factors listed in Table II. No unusually high correlations were noted between any of the variables in the last cycle of full-matrix least squares refinement, and the final difference density map showed a maximum peak of about 0.15 e/Å^3. All calculations were made using Nicolet's SHELXTL PLUS (1987) series of crystallographic programs.

B. Host 1c. An orange prismatic block having approximate dimensions 0.50 × 0.24 × 0.16 mm was selected. The Laue symmetry was determined to be *mmm*, and from the systematic absences noted, the space group was shown unambiguously to be *Pbca*. The structure was solved by use of the SHELXTL direct methods program TREF, which revealed the positions of most of the atoms in the molecule. Remaining non-hydrogen atoms were located in subsequent difference Fourier syntheses. The usual sequence of isotropic and anisotropic refinement was followed, after which all hydrogen atoms were entered in ideal calculated positions and constrained to riding motion, with a single variable isotropic temperature factor for all of them. At this point, it was noted that the "thermal motion" of C17 was excessively high, and the largest peak in the difference map was positioned near C17. Therefore it was assumed that the C17 methylene group is actually disordered over two sites. After forcing the two positions to have an equal isotropic temperature factor, the individual site occupancies were determined to be 72% for C17 and 28% for C17'. Since the adjacent C16 and C18 atoms are also involved, they too were refined isotropically. No attempt was made to include hydrogens on any of these three atoms. Hydrogens on the water molecule could also not be located. After all shift/esd ratios were less than 0.1, convergence was reached at the agreement factors listed in Table II. No unusually high correlations were noted between any of the variables in the last cycle of full-matrix least squares refinement, and the final difference density map showed a maximum peak of about 0.4 e/Å^2. All calculations were made using Nicolet's SHELXTL PLUS (1987) series of crystallographic programs.

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Supplementary Material Available: Tables pertinent to the X-ray crystallographic determination of the **1b**–imidazolidone complex and **1c** including atomic coordinates, anisotropic thermal parameters, bond lengths, and bond angles and tables pertaining to dilution corrections for hosts **1b** and **2a** and NMR titration data for seven guests (27 pages); listings of observed and calculated structure factors for the **1b**–imidazolidone complex and **1c** (21 pages). Ordering information is given on any current masthead page.