JOC The Journal of Organic Chemistry

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Synthetic Hosts for Molecular Recognition of Ureas[||]

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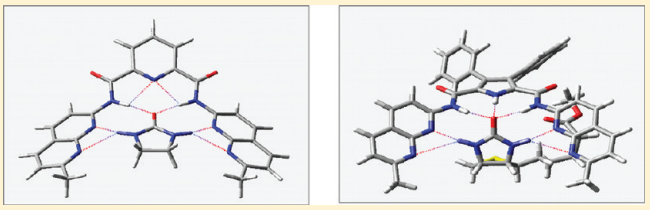
Supporting Information

ABSTRACT: Four hosts (**7**−**10**) containing 2,6-bisamidopyridine- and 2,5-bisamidopyrrole-bearing pyridyl or 1,8-naphthyridyl groups have been prepared and their structures studied by a combination of multinuclear NMR spectroscopy and X-ray crystallography. Their behavior in molecular recognition of urea derivatives, including (+)-biotin methyl ester, has been approached by molecular modeling (Monte Carlo conformational search, AMBER force field). The minimum energy values for the complexes are correlated with the experimental binding energies determined by means of ^{1}H NMR titrations.



INTRODUCTION

In all the supramolecular situations described as host−guest chemistry, collections of molecules are glued together by weak forces, predominantly hydrogen bonds (HB).[1,2] The complementariness is so relevant that the definition of the host and the guest is somewhat arbitrary (usually the hosts are larger than the guests). Ureas are compounds rich in HBs, both donor and acceptor,[3,4] and so there are many host−guest compounds held together by HBs belonging, in part, to ureas. From this very large number of complexes involving ureas, those with urea in the host (ureas as receptors) are more abundant than those where the urea is the guest (molecular recognition of ureas).

Our interest lies in this last topic, and between 2004 and 2010 we have published six papers dealing with the molecular recognition of biologically relevant ureas, including drugs.[5−10] Host design for ureas and related binding compounds usually includes amide N−H as hydrogen bond donors (HBD, in red) as well as nitrogen atoms of basic heterocycles such as pyridines and naphthyridines as hydrogen bond acceptors (HBA, in blue).

The first three hosts used (Chart 1)[5,6] were Thummel's host **1**, based on the acidity of indolic N−H in lieu of amides N−H;[11] and hosts **2** and **3** were previously reported by Goswami et al.[12,13] Many other hosts for ureas recognition were described in chronological order by Goswami;[14,15] by Gozin;[16] by Gale;[17] by Boyer;[18] by Ghosh and Sen;[19,20] Goswami;[21] by Yatsimirsky;[22] by Roesky;[23] and by Ghosh.[24] Some hosts were prepared by Ghosh specifically for biotin salt,[25] while related pyridine-based oligoamides were prepared by Gunnlaugsson as DNA-targeting supramolecular binders.[26]

Bearing this in mind, hosts **4**−**6** were prepared (Chart 2). The first one **4** contains, in addition to Goswami's host **2**, a pyridine nitrogen[6] whereas hosts **5** and **6** explore the advantages of trimerization of the "amide−pyridine" and "amide−naphthyridine" motifs.[7]

In the present work we report the synthesis and molecular recognition properties of four hosts: *N*,*N*′-bis(6-methylpyridin-2-yl)-2,6-pyridinedicarboxamide (**7**),[27] *N*,*N*′-bis(7-methyl-1,8-naphthyridin-2-yl)-2,6-pyridinedicarboxamide (**8**), *N*,*N*′-bis(6-methylpyridin-2-yl)-3,4-diphenyl-1*H*-pyrrole-2,5-dicarboxamide (**9**), and *N*,*N*′-bis(7-methyl-1,8-naphthyridin-2-yl)-3,4-diphenyl-1*H*-pyrrole-2,5-dicarboxamide (**10**) (Chart 3). As we will explain later on, the host properties of compound **7** cannot be measured.

These hosts are structurally related to previously reported ones. For instance, **7** is the dechlorinated analogue of **4** and the **7**/**8** pair is just Goswami's **2**/**3** pair where the central benzene has been replaced by a pyridine ring. Some structures loosely related to **7** and **8** have been reported (**11**,[22] **12**,[26] and **13**,[18] Chart 4), whereas pyrrolic hosts **9** and **10** have been inspired by the pioneering work of Gale et al. (**14**,[28] **15**,[29] and **16**,[30] Chart 5).

Our goal has two avenues, the first one is the study of the binding changes when the central core shifts from pyridine (hosts **7** and **8**) to pyrrole (hosts **9** and **10**). The second one tries to improve the binding constants by replacing the picoline arms (hosts **7** and **9**) by naphthyridines (hosts **8** and **10**). The two accepting nitrogens of each naphthyridine will give rise to extra HBs and consequently stabilize the formed complexes.

RESULTS AND DISCUSSION

The binding properties of receptors **7**−**10** (Chart 3) have been studied with the four guests (**17**−**20**) depicted in Chart 6.

Received: June 8, 2011
Published: July 08, 2011

Chart 1. Hosts 1−3

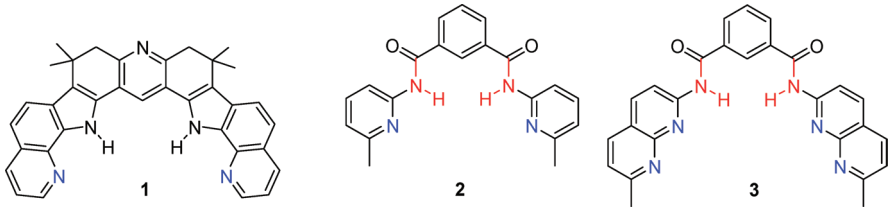


Chart 2. Hosts 4−6

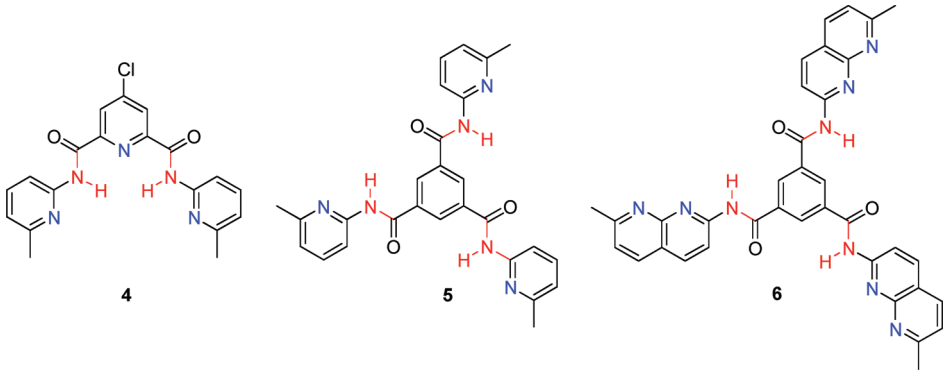
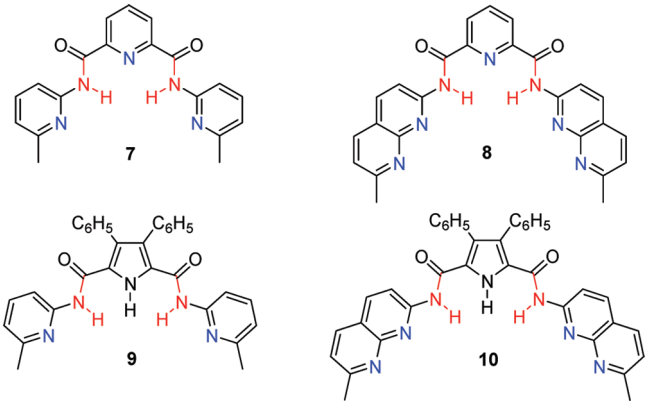


Chart 3. Hosts 7−10



As shown in Charts 1 and 2 above, only Thummel used the HB acidity of the indolic NH instead of the hydrogen bond donor capability of amides.[11] In order to take advantage of both effects, hosts **9** and **10** were designed. They combine both amide and pyrrole NH hydrogen bond donor motifs. Thus, the four hosts of Chart 3 should allow determination, by comparison with hosts **2** and **3**, of the best option: to replace a benzene with a pyridine, adding one more HBA site, or to replace a benzene by a pyrrole, adding one more HBD site.

Molecular Modeling. All complexes have been modeled using Monte Carlo conformational search with the AMBER force field. This procedure affords the most probable conformation of the complex and allows us to get useful information about the binding mode of the guest. The structure of the complexes is created from minimum energy conformations of hosts and guests, obtained from Monte Carlo conformational searches. The interaction energy for the complex is obtained using eq 1.

$$E_{interaction} = E_{min}\,(complex) - E_{min}\,(host) - E_{min}\,(guest) \quad (1)$$

Minimum energy values for complexes are gathered in Table 1, and the minimum energy conformations for hosts **7**−**10** are shown in Figure 1. In all cases the formation of two intramolecular hydrogen bonds is responsible for the most stable conformation. Hosts **7** and **8** show a syn−syn conformation that allows the preorganization of the two amide hydrogen atoms inward for optimal guest binding. However, in hosts **9** and **10** the formation of two intramolecular hydrogen bonds between the pyrrolic NH and amide CO groups determine the preferred anti−anti conformation.

The interaction modes (Figure 2) for the complexes with (+)-biotin methyl ester (**17**), 2-imidazolidone (**18**), and *N*,*N*′-trimethylenurea (**19**) are much alike and in accordance with the usual binding mode for this kind of compounds through the urea moiety. Attention must be paid to the case of barbital (**20**) as it uses only the carbonyl group with all hosts (see Supporting Information). The main reason for that particular behavior is that **20**, a voluminous guest due to the ethyl groups in position 5, sterically hinders the urea binding into the hosts cleft (see **8**:**20** and **10**:**20** in Figure 2); it was already reported by us in other complexes.[6] In all cases the hosts are in the syn−syn conformation, and selected parameters for the intermolecular hydrogen bonds involved in host−guest binding are given in the Supporting Information.

Hosts **8** and **10**, bearing naphthyridine units, give rise to more stable complexes than those formed by hosts **7** and **9**, containing pyridine moieties, due to the formation of bifurcated hydrogen

dx.doi.org/10.1021/jo201191x |*J. Org. Chem.* 2011, 76, 6780–6788

Chart 4. Hosts 11−13

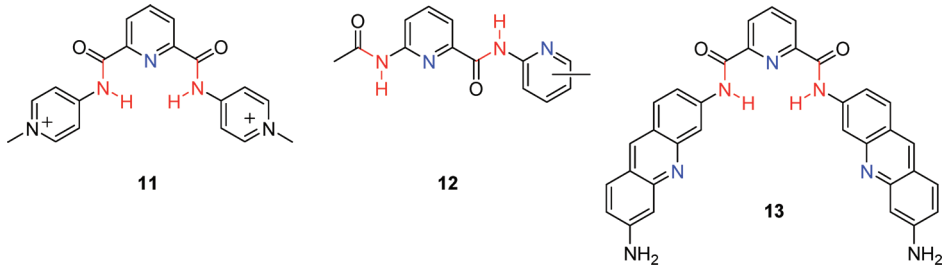


Chart 5. Hosts 14−16

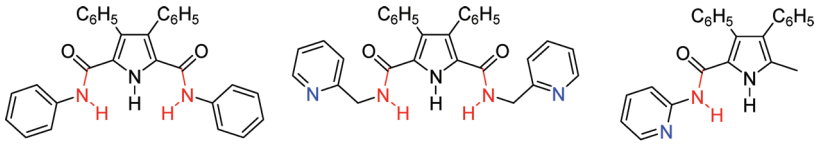


Chart 6. The Four Guests Studied in the Present Work

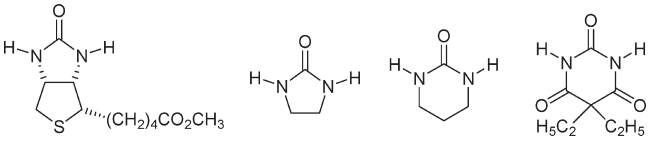


Table 1. Interaction Energy Values: E_{min} (kJ mol^{-1}) for the Complexes of Hosts 7−10 with the Studied Guests

guest	7	8	9	10
biotin methyl ester (**17**)	68.0	70.5	64.8	72.0
2-imidazolidone (**18**)	51.7	57.5	43.7	52.1
N,*N*′-trimethyleneurea (**19**)	57.7	59.5	46.2	54.8
barbital (**20**)	74.8	108.5	59.1	90.9

bonds between the NH urea groups and the N1′/N8′ naphthyridine nitrogens (see **8**:**18** and **10**:**17** in Figure 2).

On the other hand, in the complexes formed by hosts **9** and **10** the additional hydrogen bond arising from the pyrrolic NH compensates energetically for the necessary conformational change in the receptor (from anti−anti to syn−syn) to bind guests.

Syntheses and Structural Characterization of Hosts 7−10: NMR and X-ray Crystallography. Hosts **7** and **8** were synthesized according to Scheme 1, starting from 2,6-pyridinedicarbonyl dichloride that was reacted with 2 equiv of either 2-amino-6-methylpyridine or 2-amino-7-methyl-1,8-naphthyridine and 4 equiv of triethylamine at room temperature.

Our attempts to prepare hosts **9** and **10** using 3,4-diphenyl-1*H*-pyrrole-2,5-dicarbonyl dichloride in similar conditions failed, due to the inherent instability of the pyrrole dichloride and to the formation by self-condensation of dimeric species.[31] However when the dichloride was slowly added at 0 °C over an excess of the corresponding amine (8 equiv), the pure hosts could be obtained in moderate yields.

A complete characterization of all hosts was carried out by NMR spectroscopy in $CDCl_3$ as solvent (see Supporting Information). For symmetry reasons, besides the isochronous atoms in the central bisamido ring: pyridine (C2/C6 and C3/C5) and pyrrole (C2/C5 and C3/C4), these molecules show equivalent methylpyridinyl, methylnaphthyridinyl, and phenyl groups. Full assignment of protons and carbons was achieved by careful analysis of the chemical shift values, multiplicity of the signals and the coupling constants magnitude, and gs-COSY, gs-HMQC, and gs-HMBC bidimensional experiments.

The deshielded proton signals at 10.99 and 11.40 ppm of hosts **7** and **8** containing the 2,6-bisamidopyridine central core correspond to the NH amide protons involved in an intramolecular hydrogen bond with the pyridine nitrogen atom, showing a preference for the syn−syn conformation. However, in hosts **9** and **10** the deshielded NH pyrrole signals at 10.44 and 10.54 ppm, and the upfield amide NH signals at 7.97 and 8.37 ppm, indicate the preferred anti−anti conformation, with formation of two intramolecular hydrogen bonds between the NH pyrrole and the CO amide groups. These results are in agreement with the predicted minimum energy conformations (Figure 1) discussed in Molecular Modeling.

Finally, the ^{15}N NMR chemical shifts were assigned using gs-HMQC and gs-HMBC (^{1}H−^{15}N) correlation experiments that also allowed us to measure the $^{1}J_{NH}$ coupling constant of the amide nitrogen (see Experimental Section). The pyridine N1 in **7** and **8** and the naphthyridine N1′ in **8** and **10** could not be detected under the aforementioned conditions, so we proceeded to record the 1D spectra with an inverse gated ^{1}H decoupling technique. Due to the insolubility of compound **8**, either in $CDCl_3$ or in DMSO-d_6, no signal was observed in this experiment.

Crystals of sufficient quality for X-ray diffraction were obtained only for two hosts: **8** ($C_{25}H_{19}N_7O_2$) from chloroform, and **10** ($C_{36}H_{27}N_7O_2 \cdot SOC_2H_6 \cdot {}^{1}/_{2}H_2O$) from dimethyl sulfoxide (all trials to crystallize **10** in chloroform or other solvents were unsuccessful), and both compounds crystallize in the *C*2/*c*

dx.doi.org/10.1021/jo201191x |*J. Org. Chem.* 2011, 76, 6780–6788

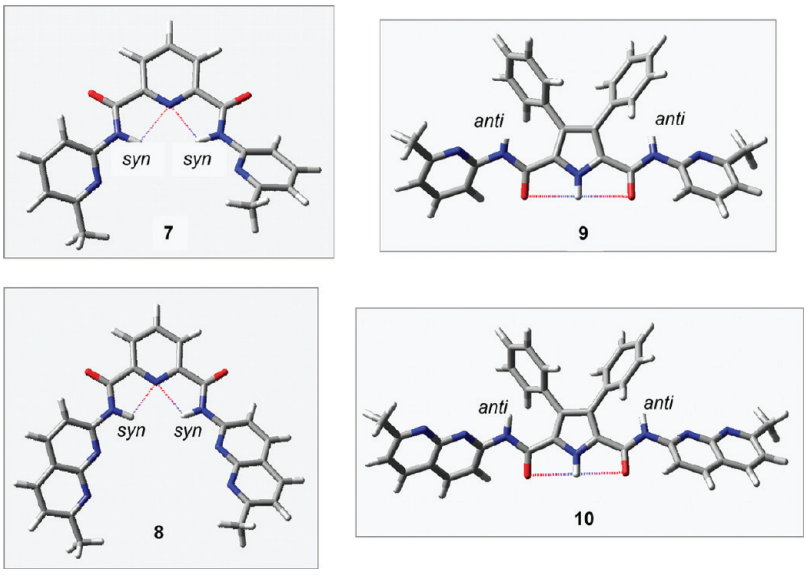


Figure 1. The minimum energy conformations of hosts: syn−syn in **7** and **8**, anti−anti in **9** and **10**.

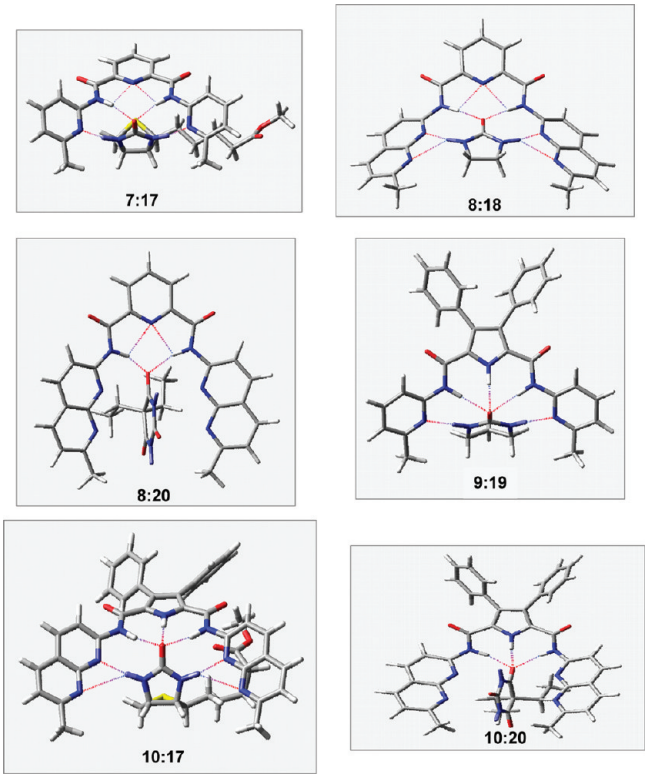
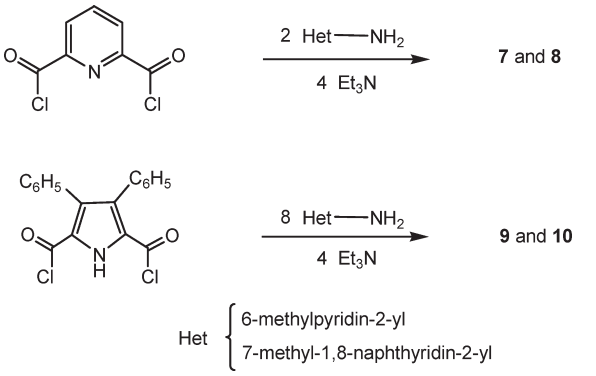


Figure 2. The minimum energy conformations of some complexes where all hosts are in the syn−syn conformation.

monoclinic space group (see Experimental Section and Supporting Information for the ORTEP views).

Compound **8** contains a 2-fold axis, and there is only a half molecule in the asymmetric unit. The molecule, presenting a syn−syn conformation, is not planar, with a dihedral angle of 18.8(1)° between the pyridine unit and the best least-squares plane N2···C9 (naphthyridine moieties). For **10**, one crystallographic nonplanar independent molecule and a dimethyl

Scheme 1. Synthesis of hosts 7−10



sulfoxide molecule bonded by hydrogen bonds were identified in the structural determination; this compound crystallizes with a half water molecule, and the geometry (anti−syn conformation) appears to be different from that found in solution and predicted in the Monte Carlo conformational search.

Molecular modeling of the complex formed by **10** with dimethyl sulfoxide resulted in a minimum energy conformation of −29.7 kJ mol^{-1} in which the solvent (DMSO) locates into the cleft of the host in a syn−syn conformation as in the other complexes. However the anti−syn conformation found in the solid state is only 4.4 kJ mol^{-1} higher in energy, and the inclusion of a half molecule of water and packing forces compensate for it, accounting for the experimental geometry (See Figure 3 for both conformations).

In both compounds the molecules are held together by normal van der Waals forces expanding into columns along the crystallographic *a* axis in **8** (Figure 4) and *c* axis in **10** (Figure 5). Selected bond distances and angles as well as hydrogen bonds (HBs) are given in the Supporting Information.

Binding Constant Quantification. Experimental versus Theoretical Data. ^{1}H NMR titrations in $CDCl_3$ at 300 K have been performed to quantify the interactions between hosts **7**−**10**

dx.doi.org/10.1021/jo201191x |*J. Org. Chem.* 2011, 76, 6780–6788

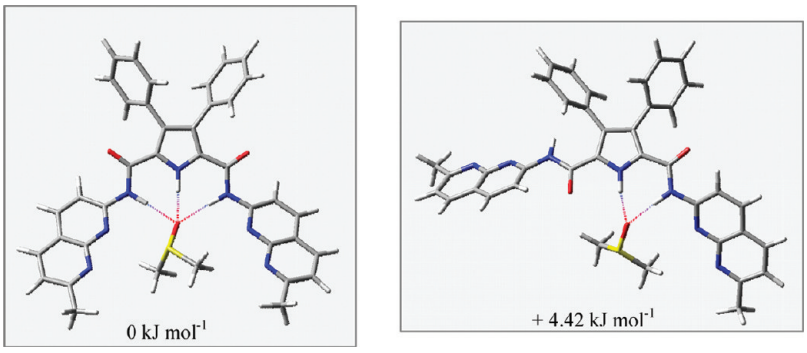


Figure 3. The minimum energy conformations of complex **10**:DMSO.

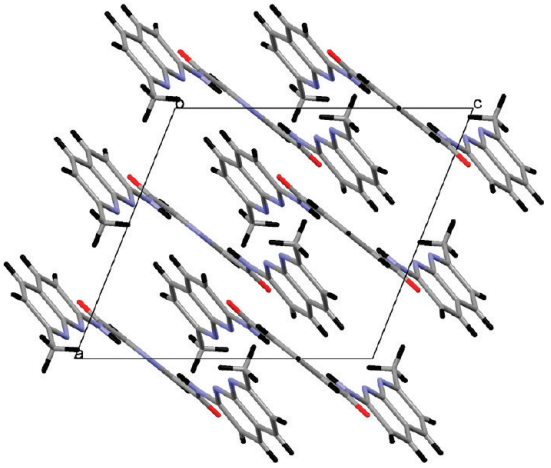


Figure 4. Part of the crystal structure of **8** showing the packing along the crystallographic *b* axis.

and biotin methyl ester (**17**), 2-imidazolidone (**18**), *N*,*N*′-trimethylenurea (**19**), and barbital (**20**) as guests. The host–guest binding constants (K_b) have been measured using the Chemical Induced Shifts (CIS) on the NH signal of the amide groups for hosts **7** and **8**, and on two independent signals, NH proton in the pyrrole nucleus and NH signal of the amide groups for hosts **9**–**10**.[6]

As we have previously proved, a careful determination of the best concentrations of host and guest must be carried out to measure the binding constants with the lowest error.[5] All the titrations have been performed in such a way that the saturation fractions of both host and guest are between 20% and 80%, avoiding situations where the chemical induced shifts, of the monitored protons, are zero. Under these conditions, a soft titration curve, with no linear behavior, is obtained and the data are nonlinearly fitted by the use of the appropriate software, obtaining curves like the one shown in Figure 6.

At this point a special comment needs to be made concerning the measurement of binding constants in the case of host **7**. All our assays afforded erratic values that are not useful. The fact that this host presents a particular affinity for water[27] gave rise, even applying extreme dryness manipulation conditions, to a short-range of CIS unable to provide reliable values of K_b, neither by direct titrations nor by competitive ones. Therefore, we will continue our discussion using the already measured[6] binding constant of 4-chloro-*N*,*N*′-bis(6-methylpyridin-2-yl)-2,6-pyridinedicarboxamide (**4**), the chlorinated analogue of **7**.

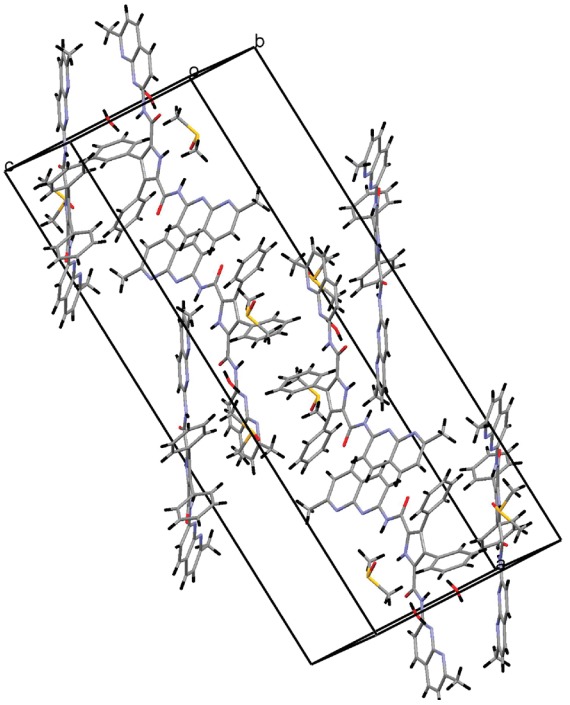


Figure 5. Part of the crystal structure of **10** showing the packing in the unit cell.

The experimental binding constants K_b (M^{-1}) with the four guests **17**–**20** measured for complexes of host **8** plus the already measured binding constants of **4** are gathered in Table 2, and those with hosts **9** and **10** in Table 3.

In our previous papers we found a quite good correlation between experimental binding constants and predicted interaction energies, and because of that we are confident that this is a correct approximation to the study of these systems.[5−7]

If data of Tables 1, 2, and 3 are compared, the correlation matrix shows that there are no good linear relationships. In general, the compound that behaves differently is barbital (**20**) which is the most structurally distinct. The interaction energies of guests **18** and **19** are related [$E_{min}(\mathbf{18}) = (0.92 \pm 0.21)E_{min}(\mathbf{19})$, $n = 4$, $R^2 = 0.90$] as are the energy changes but much worse [$\Delta G(\mathbf{18}) = (0.70 \pm 0.33)\Delta G(\mathbf{19})$, $n = 4$, $R^2 = 0.69$]. Both series of points are represented in Figure 7.

If quantitatively the results are not as good as expected, qualitatively and in a simplified way, both E_{min} and ΔG indicates

dx.doi.org/10.1021/jo201191x |*J. Org. Chem.* 2011, 76, 6780–6788

that the best host for biotin methyl ester is **10** (naphthyridine-pyrrole) followed by **8** (naphthyridine-pyridine). For the three other guests while E_{min} accounts for **8** followed by **10**, ΔG indicates the contrary. In conclusion, in the studied hosts the binding properties of those bearing naphthyridine are better than those containing pyridine, but pyrrole and pyridine central cores are comparable.

The hosts we describe here are difficult to compare with the previous ones because the data for the binding constants were in some cases determined in different conditions (host **3** labeled * in Figure 8).[5,6] From the present work it results that host **10** (pyrrole/naphthyridine) is the best we have found, followed by **8** (pyridine/naphthyridine) or **4** (pyridine/pyridine).

There are two possible strategies when preparing hosts for ureas: (i) either a flexible universal host that recognizes a family of related ureas but with poor selectivity for any of them, or (ii) a preordained host specific for a given urea derivative. Future improvements are expected in both directions.

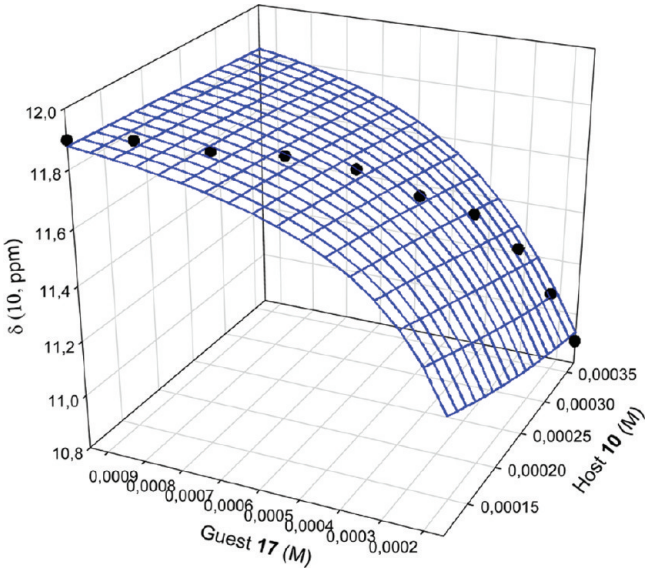


Figure 6. Titration curve for the complex **10**:**17**.

Table 2. Experimental Binding Constants K_b (M^{-1}) and Free Energy Changes ΔG (kJ mol^{-1}) at 300 K for the Complexes of Hosts 4 and 8

guest	K_b(4)	ΔG(4)	K_b(8)	ΔG(8)
17	3600 ± 640	−20.4	3429 ± 300	−20.3
18	141 ± 25	−12.3	655 ± 112	−16.2
19	100 ± 18	−11.5	276 ± 46	−14.0
20	274 ± 74	−14.0	438 ± 50	−15.2

EXPERIMENTAL SECTION

General Methods. Melting points for compounds **7**−**10** were determined by DSC. Thermograms (sample size 0.003−0.0010 g) were recorded at the scanning rate of 5.0 °C min^{-1}.

Materials. The four guests are commercially available: biotin methyl ester (methylbiotin, **17**) (>99%, dried under vacuum), 2-imidazolidone (**18**) (96%, recrystallized from ethyl acetate), *N*,*N*′- trimethyleneurea (**19**) (>98%, recrystallized from ethyl acetate), and barbital (**20**) (>99%). The starting reagents were obtained from commercial suppliers and used as received without further purification. Solvents were purified and dried with use of standard procedures.

Synthesis of *N*,*N*′-Bis(6-methylpyridin-2-yl)-2,6-pyridinedicarboxamide (7). A mixture of 2,6-pyridinedicarboxylic acid (1 g, 5.98 mmol) and oxalyl chloride (15 mL) was heated at 40 °C until a clear solution was obtained. After cooling, the excess of oxalyl chloride was eliminated under reduced pressure, yielding 2,6-pyridinedicarbonyl dichloride as a brown solid, which was recrystallized from hexane. Then, the dichloride (1.55 g, 6.56 mmol) in 20 mL of dry $CHCl_3$ was added to a solution of 2-amino-6-methylpyridine (1.63 g, 15.09 mmol) and triethylamine (3.05 g, 30.176 mmol) in 25 mL of dry $CHCl_3$. The reaction mixture was stirred for 4 h at room temperature, after which the solvent was removed under reduced pressure. The resulting solid was recrystallized from methanol to give pure **7** (1.48 g, 65% yield): mp 234.2 °C (lit.[27] 234−235 °C); ^{1}H NMR ($CDCl_3$) δ (ppm) 10.99 (s, 2 H, CONH), 8.51 (d, 2 H, J = 7.7, H-3,5), 8.32 (d, 2 H, J = 8.2 Hz, H-3′), 8.14 (t,1 H, J = 7.7, H-4), 7.69 (t, 2 H, J = 7.8 Hz, H-4′), 6.99 (d, 2 H, J = 7.5, H-5′), 2.57 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 161.7 (CO), 156.9 (C6′), 150.4 (C2′), 148.2 (C2), 139.4(C4), 138.9 (C4′), 125,7(C3/C5), 119.6 (C5′), 111.3(C3′), 24.0 (CH_3); ^{15}N NMR ($CDCl_3$) δ (ppm) −90.2 (N1), −103.7 (N1′), −248.3 ($^1J_{NH}$ = 90 Hz, HNCO).

Synthesis of 2-Amino-7-methyl-1,8-naphthyridine. 2,6-Diaminopyridine (4.20 g, 38.5 mmol) was dissolved in 31 mL of H_3PO_4 and heated at 90 °C under argon atmosphere. Then, 5.67 mL (90%, 38.5 mmol) of 3-oxobutanal dimethyl acetal from a pressure-

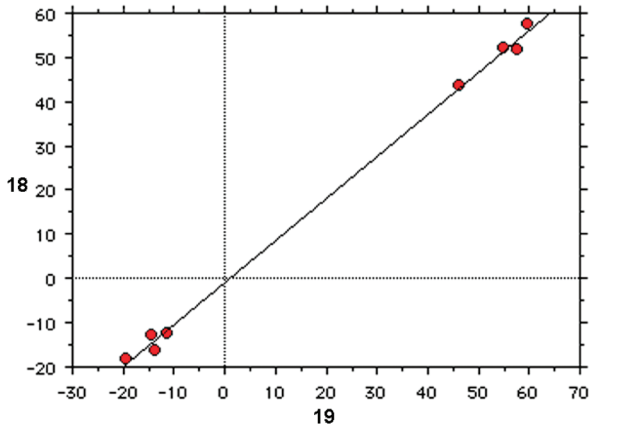


Figure 7. Plot of the energies of guests **18** and **19**. The trendline corresponds to $E_{min}(\Delta G)$(**18**) = 0.95 $E_{min}(\Delta G)$(**19**), n = 8, R^2 = 0.998.

Table 3. Experimental Binding Constants K_b (M^{-1}) and Free Energy Changes ΔG (kJ mol^{-1}) at 300 K for the Complexes of Hosts 9 and 10

guest	K_b(**9**) NH amide	K_b(**9**) NH pyrrole	average K_b(**9**)	ΔG(**9**)	K_b(**10**) NH amide	K_b(**10**) NH pyrrole	average K_b(**10**)	ΔG(**10**)
17	171 ± 17	145 ± 13	158	−12.6	9717 ± 1382	9148 ± 1243	9432	−22.8
18	171 ± 24	166 ± 22	168	−12.8	1447 ± 139	1400 ± 139	1423	−18.1
19	341 ± 72	336 ± 72	338	−14.5	2427 ± 111	2338 ± 131	2382	−19.4
20	–	101 ± 24	101	−11.5	468 ± 137	517 ± 55	492	−15.5

dx.doi.org/10.1021/jo201191x |*J. Org. Chem.* 2011, 76, 6780–6788

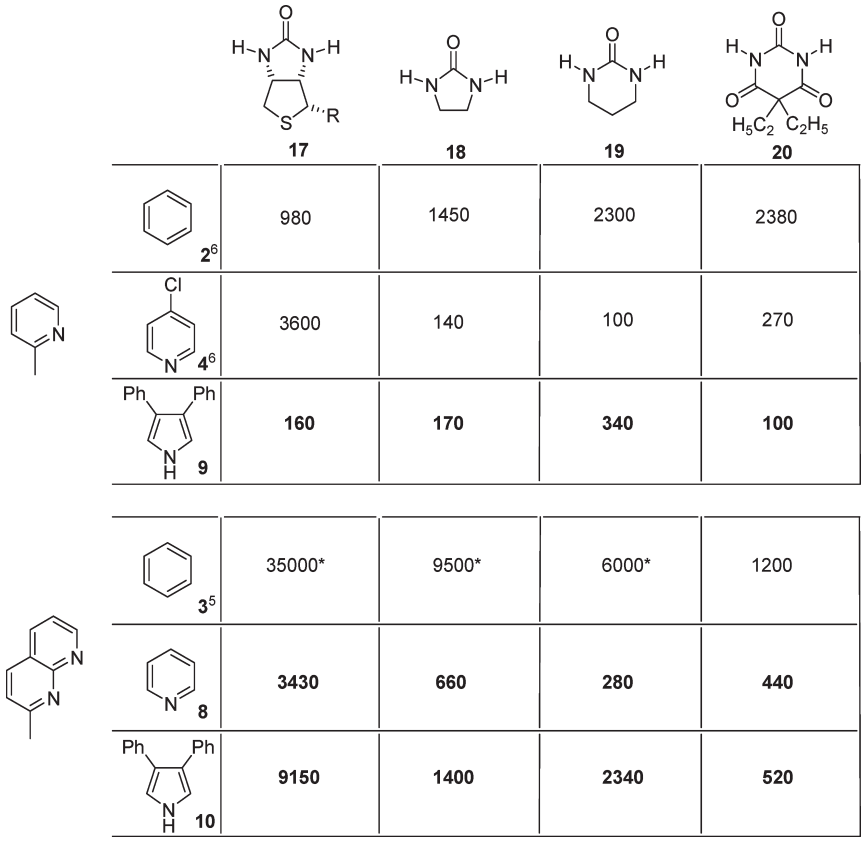


Figure 8. K_b values determined in this work (bold) and in our previous publications.

compensated addition funnel was slowly added and the mixture heated to 115 °C for 3.5 h. After cooling and adding ice, ammonia solution was added to pH 8.5 to 9.0. Precipitated salts were removed and the aqueous solution extracted with $CHCl_3$ (5 × 100 mL). The organic phase was dried over SO_4Na_2 and then the $CHCl_3$ removed in a rotary evaporator. The brown solid obtained was purified by column chromatography on neutral alumina (CH_2Cl_2/CH_3OH 98:2), yielding 3.53 g of 2-amino-7-methyl-1,8-naphthyridine (57.5%): mp 176.9 [lit.[32] 175−185 °C (crude), 217−218 °C (toluene)]; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.80 (d, 1 H, $^3J_{6\text{-H}}$ = 8.0 Hz, 5-H), 7.78 (d, 1 H, $^3J_{3\text{-H}}$ = 8.6 Hz, 4-H), 7.05 (d, 1 H, 6-H), 6.70 (d, 1 H, 3-H), 5.11 (sa, 2 H, NH_2), 2.66 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 162.0 (C7), 159.5 (C2), 156.2 (C8a), 137.9 (C4), 136.1 (C5), 118.8 (C6), 115.3 (C4a), 111.4 (C3), 25.3 (CH_3).

Synthesis of *N*,*N*′-Bis(7-methyl-1,8-naphthyridin-2-yl)-2,6-pyridinedicarboxamide (8). Diacid dichloride (1 g, 4.90 mmol) dissolved in 20 mL of dry CH_2Cl_2 was slowly added to a solution of 2-amino-7-methyl-1,8-naphthyridine (1.57 g, 9.86 mmol) and Et_3N (1.98 g, 19.6 mmol) in 100 mL of CH_2Cl_2 under inert atmosphere. The mixture was stirred overnight at room temperature and then washed twice with 1 M HCl. The organic phase was dried over SO_4Na_2, and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH 98:2), yielding 220 mg of host **8** (10%): mp 352.8 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 11.40 (br s, 2 H, CONH), 8.74 (d, 2 H, $^3J_{4'\text{-H}}$ = 8.7 Hz, 3′-H), 8.57 (d, 2 H, $^3J_{4\text{-H}}$ = 7.7 Hz, 3,5-H), 8.26 (d, 2 H, 4′-H), 8.21 (t, 1 H, 4-H), 8.07 (d, 2 H, $^3J_{6'\text{-H}}$ = 8.4 Hz, 5′-H), 7.33 (d, 2 H, 6′-H), 2.83 (s, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 163.6 (C7′), 162.5 (CO), 154.4 (C8a′), 153.2 (C2′), 148.8 (C2/C6), 139.6 (C4), 139.4 (C4′), 136.4 (C5′), 126.1 (C3/C5), 122.0 (C6′), 118.8 (C4a′), 114.5 (C3′), 25.55 (CH_3); ^{15}N NMR ($CDCl_3$) δ (ppm) −79.4 (N8′), −245.6 ($^1J_{NH}$ = 89.5 Hz, HNCO); Anal. Calcd for $C_{25}H_{19}N_7O_2$ 1.2 H_2O: C, 63.74; H, 4.58; N, 20.81; Found: C, 63.70; H, 4.69; N, 21.15.

Synthesis of 3,4-Diphenyl-1*H*-pyrrole-2,5-dicarbonyl Dichloride. First, the corresponding 2,5-dicarboxylic acid was prepared according to the Steglich et al. procedure[33] described for related pyrroles: to a solution of phenylpyruvic acid (2.12 g, 12.9 mmol, 1.0 equiv) in dry THF (120 mL) under argon at 78 °C was added dropwise with stirring 10.3 mL of nBuLi (2.5 M in hexane, 25.75 mmol, 2.0 equiv). After the mixtrue was stirred for an additional 25 min, a solution of iodine (1.64 mg, 6.45 mmol, 0.5 equiv) in 20 mL of THF was added dropwise. The mixture was heated to room temperature, and a slow stream of ammonia was passed through for 10 min. After saturation with ammonia, 0.70 mL (6.43 mmol, 0.5 equiv) of $TiCl_4$ in 20 mL of dry hexane was added, leading to a suspension of brown color which in a period of 24 h evolved to pale yellow. The reaction was poured into 150 mL of 2 N NaOH, and the aqueous phase was washed with ethyl acetate (2 × 50 mL). The pH was adjusted to 4 with HCl, and the aqueous phase was extracted with ethyl acetate (4 × 150 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and evaporated under vacuum. The crude was washed with 1 mL of MeOH previously cooled in a refrigerator, resulting in 3,4-diphenyl-1*H*-pyrrole-2,5-dicarboxylic acid (466 mg, 20%): mp 249.3 °C (melt) and 270.3 °C (decomp) [lit.[34] 273−293 °C (decomp)].

Diacid dichloride was obtained by reaction of 3,4-diphenyl-1*H*-pyrrole-2,5-dicarboxylic acid (326 mg, 1.06 mmol) with 8.5 mL of thionyl chloride at reflux overnight. The reaction was allowed to cool, and removing the excess of thionyl chloride under reduced pressure afforded 3,4-diphenyl-1*H*-pyrrole-2,5-dicarbonyl dichloride as a beige solid (320 mg, 87.6%): ^{1}H NMR ($CDCl_3$) δ (ppm) 10.01 (br s, 1 H, 1-NH), 7.25 (m, 6 H, *m*-H, *p*-H), 7.10 (m, 4 H, *o*-H); ^{13}C NMR ($CDCl_3$) δ (ppm) 156.0 (CO), 135.8 (C_{ipso}), 130.5 (C3/C4), 130.3 (C*o*), 128.3 (C*p*), 127.9 (C*m*), 125.1 (C2/C5).

Synthesis of *N*,*N*′-Bis(6-methylpyridin-2-yl)-3,4-diphenyl-1*H*-pyrrole-2,5-dicarboxamide (9). A solution of 3,4-diphenyl-

dx.doi.org/10.1021/jo201191x |*J. Org. Chem.* 2011, 76, 6780–6788

Table 4. Crystal Data and Structure Refinement for Hosts 8 and 10

crystal data	8	10
CCDC Number	812043	812044
empirical formula	$C_{25}H_{19}N_7O_2$	$2[(C_{36}H_{27}N_7O_2)(SOC_2H_6)\cdot{}^1/_2H_2O]$
formula weight	449.47	1353.56
wavelength (Å)	0.71073	0.71073
crystal system	monoclinic	monoclinic
space group	*C*2/*c*	*C*2/*c*
a (Å)	10.594(1)	37.009(2)
b (Å)	19.501(2)	13.0987849
c (Å)	11.647(1)	14.0975(5)
β (deg)	111.836(2)	95.401(3)
volume (Å^3)	2233.7(4)	6803.7(4)
Z	4	4
density (calculated) (mg/m^3)	1.337	1.321
absorption coefficient (mm^{-1})	0.090	0.146
F(000)	936	2840
θ range (deg)	2.09 to 25.0	2.61 to 25.0
index ranges	−12/−23/−13 to 12/23/12	−32/−13/−15 to 44/15/16
reflections collected	8525	15263
independent reflections	1949 [*R*(int) = 0.0530]	5999[*R*(int) = 0.0219]
data/restraints/parameters	1949/0/155	5999/0/447
$R^a[I > 2\sigma(I)]$ (ref obsd)	0.0409 (960)	0.0535 (3892)
Rw_F^b (all data)	0.1301	0.1688

^{a} $\Sigma||F_o| - |F_c||/\Sigma|F_o|$. ^{b} $\{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

1*H*-pyrrole-2,5-dicarbonyl dichloride (320 mg, 0.93 mmol) in THF (13 mL) was slowly added (for 1 h) to a solution of the 2-amino-6-methylpyridine (805 mg, 7.44 mmol) and triethylamine (377 mg, 3.72 mmol) in THF (20 mL) at 0 °C under an inert atmosphere. A white precipitate of triethylammonium chloride was produced instantly. The reaction mixture was stirred first for 3 h more at 0 °C, then slowly allowed to rise at room temperature (2.5 h) and finally stirred at room temperature for 64 h. Removal of the solid and evaporation of the THF in vacuo gave a orange residue that was washed with water (5 × 10 mL). After drying, the solid was purified by column chromatography on silica gel (dichloromethane/methanol 98:2) to yield compound **9** (153 mg, 33.7%): mp 201.6 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 10.44 (br s, 1 H, 1-NH), 7.99 (d, 2 H, $^3J_{4'\text{-H}}$ = 8.1 Hz, 3′-H), 7.97 (s, 2 H, CO-NH), 7.53 (t, 2 H, 4′-H), 7.39 (m, 6 H, *m*-H, *p*-H), 7.31 (m, 4 H, *o*-H), 6.80 (d, 2 H, $^3J_{4'\text{-H}}$ = 7.5 Hz, 5′-H), 2.28 (s, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 158.2 (CO), 157.1 (C6′), 150.1 (C2′), 138.2 (C4′), 132.3 (C_{ipso}), 130.8 (C*o*), 129.1 (C*m*), 128.4 (C*p*), 127.3 (C3/C4), 124.6 (C2/C5), 119.1 (C5′), 110.9 (C3′), 24.0 (CH_3); ^{15}N NMR ($CDCl_3$) δ (ppm) −95.8 (N1′), −228.5 (N1), −240.6 ($^1J_{NH}$ = 88.8 Hz, HNCO); Anal. Calcd for $C_{30}H_{25}N_5O_2$ 1/2 H_2O: C, 72.56; H, 5.28; N, 14.10; Found: C, 72.34; H, 5.35; N, 14.08.

Synthesis of *N*,*N*′-Bis(7-methyl-1,8-naphthyridin-2-yl)-3,4-diphenyl-1*H*-pyrrole-2,5-dicarboxamide (10). A solution of 3,4-diphenyl-1*H*-pyrrole-2,5-dicarbonyl dichloride (300 mg, 0.87 mmol) in CH_2Cl_2 (13 mL) was slowly added (for 1,5 h) to a solution of the 2-amino-7-methyl-1,8-naphtyridine (1.11 g, 6.96 mmol) and triethylamine (352 mg, 3.48 mmol) in CH_2Cl_2 (70 mL) at 0 °C under an inert atmosphere. A white precipitate was produced. The reaction mixture was stirred first for 2 h more at 0 °C and then allowed to warm to room temperature and finally stirred at room temperature for 90 h. Removal of the solid and evaporation of the CH_2Cl_2 in vacuo gave a residue that was purified by column chromatography on silica gel (dichloromethane/methanol 98:2) to yield compound **10** (144 mg, 28.0%): mp 242.8 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 10.54 (br s, 1 H, 1-NH), 8.50 (d, 2 H, $^3J_{4'\text{-H}}$ = 9.0 Hz, 3′-H), 8.37 (br s, 2 H, CO-NH), 8.12 (d, 2 H, 4′-H), 7.98 (d, 2 H, $^3J_{6'\text{-H}}$ = 8.2 Hz, 5′-H), 7.39 (m, 6 H, *m*-H, *p*-H), 7.27 (m, 4 H, *o*-H), 7.24 (d, 2 H, 6′-H), 2.72 (s, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 163.2 (C7′), 159.1 (CO), 154.6 (C8a′), 153.0 (C2′), 138.7 (C4′), 136.4 (C5′), 131.6 (C_{ipso}), 130.6 (C*o*), 129.3 (C*m*), 129.0 (C*p*), 128.2 (C3/C4), 124.5 (C2/C5), 121.6 (C6′), 118.7 (C4a′), 115.1 (C3′), 25.6 (CH_3). ^{15}N NMR ($CDCl_3$) δ (ppm) −80.3 (N8′), −110.7 (N1′), −226.7 (N1), −239.1 ($^1J_{NH}$ = 92.4 Hz, HNCO); Anal. Calcd for $C_{36}H_{27}N_7O_2$ 0.8 H_2O: C, 71.58; H, 4.77; N, 16.23; Found: C, 71.66; H, 4.92; N, 16.09.

NMR Spectroscopy. NMR spectra were recorded at 300 K (9.4 T, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C, and 40.56 MHz for ^{15}N) with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil. Chemical shifts (δ in ppm) are given from internal solvent $CDCl_3$ 7.26 for ^{1}H and 77.0 for ^{13}C, and for ^{15}N NMR, nitromethane was used as external standard. gs-HMQC (^{1}H−^{13}C), gs-HMBC (^{1}H−^{13}C), gs-HMQC (^{1}H−^{15}N), and gs-HMBC (^{1}H−^{15}N), were carried out with the standard pulse sequences[35] to assign the ^{1}H, ^{13}C, and ^{15}N signals. 1D ^{15}N NMR spectra were obtained with an inverse gated ^{1}H decoupling technique using a 5-mm direct-detection QNP probe equipped with a z-gradient coil. Complete details for the ^{1}H NMR titrations are given in the Supporting Information.

Crystal Structure Determination. Suitable crystals for X-ray diffraction experiments were obtained by crystallization of $C_{25}H_{19}N_7O_2$ (**8**) in chloroform and $C_{36}H_{27}N_7O_2\cdot SOC_2H_6\cdot{}^1/_2H_2O$ (**10**) from dimethyl sulfoxide. Data collection for both compounds were carried out at room temperature on a CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) operating at 50 kV and 25 kV, respectively. In both cases, data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s for (**8**) and 10 s for (**10**) covered 0.3 in ω.

The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. A summary of the fundamental crystal and refinement data is given in Table 4.

The structures were solved by direct methods and refined by full-matrix least-squares procedures on F^2 (SHELXL-97).[36] All non-hydrogen atoms were refined anisotropically. In both cases, all hydrogen atoms bonded to carbon atoms were included in calculated positions and refined, riding on the respective carbon atoms. The hydrogens bonded to nitrogen atoms, H1 bonded to N1 atom for (**8**), and H1, H4, and H5 bonded to N1, N4, and N5 atoms for (**10**) were located in a difference Fourier synthesis, included and not refined.

Molecular Modeling. MacroModel v.8.1, with the GB/SA model for chloroform, was used to perform the molecular simulations of hosts, guests, and complexes.[37] All calculations were achieved with Monte Carlo (MC) conformational analyses.[38] Minimization is carried out using the Polak−Ribiere conjugate gradient (PRCG) optimizer[39] as implemented in the program version, and the energy gradient was chosen as the convergence criteria with a value of 0.05 and at least 2000 iterations. All MC calculations were performed with MCMM (Monte Carlo multiple minimum) method, and the variables were torsion angles, molecule coordinates, or both. The minimization method was PRCG with the same characteristics as described above. In a typical MC run a MCMM is never performed with less than 8000 steps. To carry out the search, both torsional rotations in host and guest and translation/rotation (10 Å/360°) of the guest are performed, and for all the MC,

dx.doi.org/10.1021/jo201191x |*J. Org. Chem.* 2011, 76, 6780–6788

a cutoff is applied to van der Waals, electrostatic, and H-bond interactions with 7, 12, and 4 Å, respectively. These calculations were carried out with the AMBER* force field[40] as implemented in the version of the program.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for hosts **8**−**10**, experimental details for molecular modeling NMR titrations, and selected data for the X-ray crystal structures of **8** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work is supported by Grants CTQ2007-62113 and CTQ2010-16122 (Ministerio de Ciencia e Innovación, MICINN, Spain).

■ DEDICATION

‖In Memoriam of our friend Professor Rafael Suau.

■ REFERENCES

(1) Atwood, J. L.; Steed, J. W. *Encyclopedia of Supramolecular Chemistry*; Marcel Dekker: New York, 2004.
(2) Verboom, W.; Rudkevich, D. M.; Reinhoudt, D. N. *Pure Appl. Chem.* **1994**, *66*, 679–686.
(3) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415–8426.
(4) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369–370.
(5) Claramunt, R. M.; Herranz, F.; Santa María, M. D.; Jaime, C.; de Federico, M.; Elguero, J. *Biosens. Bioelectron.* **2004**, *20*, 1242–1249.
(6) Claramunt, R. M.; Herranz, F.; Santa María, M. D.; Pinilla, E.; Torres, M. R.; Elguero, J. *Tetrahedron* **2005**, *61*, 5089–5100.
(7) Herranz, F.; Santa María, M. D.; Claramunt, R. M. *J. Org. Chem.* **2006**, *71*, 2944–2951.
(8) Herranz, F.; Santa María, M. D.; Claramunt, R. M. *Molecules* **2006**, *11*, 478–485.
(9) Herranz, F.; Santa María, M. D.; Claramunt, R. M. *Tetrahedron Lett.* **2006**, *47*, 9017–9020.
(10) Iglesias-Sánchez, J. C.; Santa María, D.; Claramunt, R. M. *Molecules* **2010**, *15*, 1213–1222.
(11) Hedge, V.; Hung, C.-Y.; Madhukar, P.; Cunningham, R.; Höpfner, T.; Thummel, R. P. *J. Am. Chem. Soc.* **1993**, *115*, 872–878.
(12) Goswami, S.; Mukherjee, R. *Tetrahedron Lett.* **1997**, *38*, 1619–1622.
(13) Goswami, S.; Ghosh, K.; Mukherjee, R. *Tetrahedron* **2001**, *57*, 4987–4993.
(14) Goswami, S.; Mukherjee, R.; Ray, J. *Org. Lett.* **2005**, *7*, 1283–1285.
(15) Goswami, S.; Dey, S. *J. Org. Chem.* **2006**, *71*, 7280–7287.
(16) Engel, Y.; Dahan, A.; Rozenshine-Kemelmakher, E.; Gozin, M. *J. Org. Chem.* **2007**, *72*, 2318–2328.
(17) García-Garrido, S. E.; Caltagirone, C.; Light, M. E.; Gale, P. A. *Chem. Commun.* **2007**, 1450–1452.
(18) Benchabane, Y.; Boyer, G.; Humbel, S.; Alkorta, I.; Elguero, J. *J. Mol. Struct.* **2009**, *928*, 132–137.
(19) Ghosh, K.; Ghosh, K.; Sen, T. *J. Incl. Phenom. Macrocycl. Chem.* **2010**, *67*, 271–280.
(20) Sen, T. *Tetrahedron Lett.* **2009**, *50*, 4096–4100.
(21) Mahapatra, A. K.; Sahoo, P.; Hazra, G.; Goswami, S.; Fun, H.-K. *J. Luminesc.* **2010**, *130*, 1475–1480.
(22) Dorazco-González, A.; Höpfl, H.; Medrano, F.; Yatsimirsky, A. K. *J. Org. Chem.* **2010**, *75*, 2259–2273.
(23) Dixit, N.; Shukla, P. K.; Mishra, P. C.; Mishra, L.; Roesky, H. W. *J. Phys. Chem. A* **2010**, *114*, 97–104.
(24) Ghosh, K.; Sen, T.; Fröhlich, R.; Petsalakis, I. D.; Theodorakopoulos, G. *J. Phys. Chem. B* **2010**, *114*, 321–329.
(25) Ghosh, K.; Sarkar, A. R.; Sen, T. *Supramol. Chem.* **2010**, *22*, 81–94.
(26) Frimannsson, D. O.; McCabe, T.; Schmitt, W.; Lawler, M.; Gunnlaugsson, T. *Supramol. Chem.* **2010**, *22*, 483–490.
(27) Redmore, S. M.; Rickard, C. E. F.; Webb, S. J.; Wright, L. J. *Inorg. Chem.* **1997**, *36*, 4743–4748.
(28) Camiolo, S.; Gale, P. A.; Hursthouse, M. B.; Light, M. E. *Org. Biomol. Chem.* **2003**, *1*, 741–744.
(29) Li, R.; Evans, L. S.; Larsen, D. S.; Gale, P. A.; Brooker, S. *New J. Chem.* **2004**, *28*, 1340–1343.
(30) Gale, P. A.; Light, M. E.; McNally, B.; Navakhun, K.; Sliwinski, K. E.; Smith, B. D. *Chem. Commun.* **2005**, 3773–3775.
(31) Boatman, R. J.; Whitlock, H. W. *J. Org. Chem.* **1976**, *41*, 3050–3051.
(32) Brown, E. V. *J. Org. Chem.* **1965**, *30*, 1607–1610.
(33) Terpin, A.; Polborn, K.; Steglich, W. *Tetrahedron* **1995**, *51* (No. 36), 9941–9946.
(34) Fukuda, T.; Koga, Y.; Iwao, M. *Heterocycles* **2008**, *76*, 1237–1248.
(35) Braun, S.; Kalinowski, H.-O.; Berger, S. *150 and More Basic NMR Experiments*; Wiley-VCH: New York, 1998.
(36) Sheldrick, G. M. *SHELX97, Program for Refinement of Crystal Structure*, University of Göttingen, Göttingen, Germany, 1997.
(37) MacroModel, Schrödinger LLC, 2004. http://www.schrodinger.com/Products/macromodel.html.
(38) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1999**, *111*, 4379–4385.
(39) Polak, E. *Computational Methods in Optimization*; Academic Press: New York, 1971. Brodlie, K. W. in *The State of the Art in Numerical Analysis*; Jacobs, D. A. H., Ed.; Academic Press: London, 1977; Chapter III.1.7.
(40) Weiner, P. K.; Kollmann, P. A. *J. Comput. Chem.* **1981**, *2*, 287–303.