Complexation-Induced Unfolding of Heterocyclic Ureas. Simple Foldamers Equilibrate with Multiply Hydrogen-Bonded Sheetlike Structures[1]

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Abstract: The synthesis and conformational studies of heterocyclic ureas (amides) **1**−**7** and their concentration-dependent unfolding to form multiply hydrogen-bonded complexes are described. Ureas **1** and **7** were prepared by reacting 2-aminopyridine and aminonaphthyridine **25**, respectively, with triphosgene and 4-(dimethylamino)-pyridine (DMAP). Amine **25**, in turn, was synthesized by a Knorr condensation of 2,6-diaminopyridine and 4,6-nonanedione. Heterocyclic ureas **3**, **4**, and **16** were prepared by treating their corresponding amino precursors with butylisocyanate, whereas bisureido naphthyridines **6** and **17** were prepared by heating 2,7-diamino-1,8-naphthyridine (**13**) with butylisocyanate and 3,4,5-tridodecyloxyphenyl isocyanate, respectively. The hydrogen-bonding modules **2** and **5** were synthesized by reacting **13** and 2-amino-1,8-naphthyridine with valeric anhydride. X-ray crystallographic analyses were performed on ureas **1**, **3**, **16**, and **17**, indicating that these ureas are intramolecularly hydrogen-bonded in the solid state. Moreover, detailed ^{1}H NMR solution studies of **1**, **3**, **4**, **6**, and **7** indicate that similar folded structures form in chloroform. In addition, naphthyridinylureas **3** and **7** unfold and dimerize by forming four hydrogen bonds at high concentrations, and ureas **1** and **4** unfold in the presence of their hydrogen-bonding complements, amides **2** and **5**, to form complexes with three and four hydrogen bonds, respectively. Likewise, the mixing of **6** and **7** results in a mutual unfolding and formation of a robust, sheetlike, sextuply hydrogen-bonded complex. The hydrogen-bonding modules described are useful building blocks for self-assembly, and the unfolding process represents a very primitive mimicry of the helix-to-sheet transition shown by peptides and potentially shown by the hypothetical naphthyridinylurea **8**.

Introduction

At an early age, children are fascinated with building blocks and LEGOs because elaborate structures may be created from far simpler objects. It is with much the same enthusiasm and fascination that chemists have approached the idea of using molecular building blocks to assemble noncovalent structures. This straightforward concept, self-assembly, is the basis of the ever-broadening domain of supramolecular chemistry[2] and is likely to play a key role in advancing the emerging field of nanotechnology.

Because of their strength and directionality, hydrogen bonds are an ideal "glue" for the noncovalent assembly of molecular building blocks. An assortment of elegant hydrogen-bonded supramolecules has been reported, including solution aggregates, engineered crystals, and liquid crystals.[3] However, the number of hydrogen-bonding modules available for use by the supramolecular chemist is, to an extent, limited. Thus, we have had a longstanding interest in extending this database by developing novel units capable of forming multiple (>2) hydrogen bonds.[4] Moreover, we are also interested in using such modules as "switching elements" in host−guest chemistry and to control the secondary structure of hydrogen-bonded polymers.[5] The prospect of a discrete alteration in the secondary structure of hydrogen-bonded, abiotic oligomers is especially intriguing and may lead to responsive materials with "switchable" functions.[6−8]

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(1) Taken in part from the Ph.D. Thesis of P. S. Corbin, University of Illinois at Urbana-Champaign, August, 1999.

(2) (a) Lehn, J.-M. *Supramolecular Chemistry Concepts and Perspectives*; VCH: Weinheim, 1995. (b) Vögtle, F. *Supramolecular Chemistry—An Introduction*; John Wiley & Sons: Chichester, U.K., 1991.

(3) For general reviews of hydrogen-bond-mediated self-assembly, see: (a) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229−2260. (b) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Sato, C. T.; Chin, D. N.; Mammen, M.; Gordon, M. *Acc. Chem. Res.* **1995**, *28*, 37−44. (c) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1688. (d) Raymo, F. M.; Stoddart, J. F. *Curr. Opin. Colloid Interface Sci.* **1996**, *1*, 116−126. (e) Rebek, J., Jr. *Heterocycles* **2000**, *52*, 493−504. (f) Sijbesma, R. P.; Meijer, E. W. *Curr. Opin. Colloid Interface Sci.* **1999**, *4*, 24−32. (g) Tsukruk, V. V. *Prog. Polym. Sci.* **1997**, *22*, 247−311. (h) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663−2704. (i) Paleos, C. M.; Tsiourvas, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1696−1711. (j) Zimmerman, S. C. *Science* **1997**, *276*, 543−544. (k) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311−2327. (l) Burrows, A. D.; Chan, C. W.; Chowdhry, M. M.; McGrady, J. E.; Mingos, D. M. P. *Chem. Soc. Rev.* **1995**, *24*, 329−339. (m) Subramanian, S.; Zaworotko, M. J. *Coord. Chem. Rev.* **1994**, *137*, 357−401. (n) Aakeroy, C. B.; Seddon, K. R. *Chem. Soc. Rev.* **1993**, *22*, 397−407. (o) Fan, E.; Vicent, C.; Geib, S. J.; Hamilton, A. D. *Chem. Mater.* **1994**, *6*, 1113−1117.

(4) For a recent review of hydrogen-bonding modules for self-assembly, see: Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63−94.

(5) For reviews of hydrogen-bonded polymers, see: (a) Lehn, J.-M. *Makromol. Chem., Macromol. Symp.* **1993**, *69*, 1−17. (b) Lehn, J.-M. *Pure Appl. Chem.* **1994**, *66*, 1961−1966. (c) Percec, V.; Heck, J.; Johannson, G.; Tomazos, D.; Kawasumi, M. *J. Mater. Sci.—Pure Appl. Chem., A* **1994**, *31*, 1031−1070. (d) Zimmerman, N.; Moore, J. S.; Zimmerman, S. C. *Chem. Ind.* **1998**, *15*, 604−610. (e) Corbin, P. S.; Zimmerman, S. C. Hydrogen-Bonded Supramolecular Polymers. In *Supramolecular Polymers*; Ciferri, A., Ed.; Marcel-Dekker: New York, 2000; pp 147−176.

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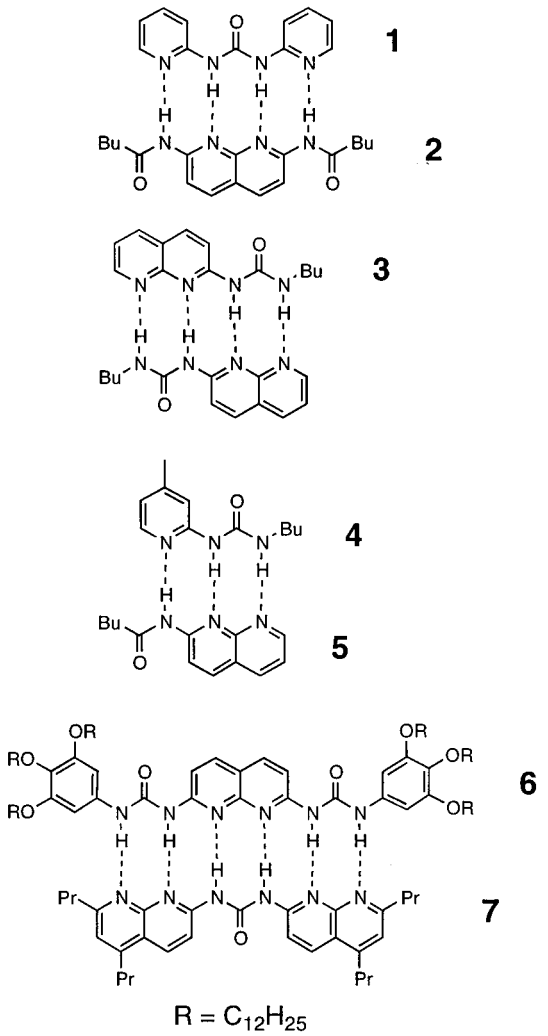
Chart 1



Herein, we describe conformational studies of heterocyclic ureas (amides) **1**−**7** (Chart 1) and their concentration-dependent unfolding to form either homo- or heterodimeric complexes.[9] Through the study of compounds **1**−**7**, we had hoped to answer several questions: (1) Are the heterocyclic ureas "folded" by an intramolecular hydrogen bond? (2) If they are, will the intramolecular hydrogen bond be broken and a complex form when the hydrogen-bonding complement is added or when there are high concentrations of self-complementary units? (3) What are the energetics of such processes; i.e., how strong is the complex that is formed? The modules described are useful building blocks for self-assembly. Most importantly, we viewed the studies described herein as a first step toward the development of naphthyridinylurea oligomers (**8**), which have the potential to exist as unfolded β-sheet (**8·8**) and folded helical (**8′**) structures (Scheme 1).

Results and Discussion

A Quadruply Hydrogen-Bonded ADDA·DAAD Complex (1·2). Two of the simplest substructural components of the hypothetical naphthyridinylurea oligomer **8** are the ADDA (A = hydrogen-bond acceptor; D = hydrogen-bond donor) module *N*,*N*′-di-2-pyridylurea (**1**) and diamidonaphthyridine (**2**). Previous ^{1}H NMR studies indicate that *N*,*N*′-di-2-pyridylthiourea exists in a dynamic equilibrium between two intramolecularly hydrogen-bonded forms in chloroform-*d* ($CDCl_3$).[10] Likewise, it has been proposed that a picolinic urea related to **1** is intramolecularly hydrogen-bonded in acetone.[11] Thus, experiments were designed to examine the conformation of **1** and the subsequent interaction of the pyridylurea with **2**.

The syntheses of **1** and **2** are outlined in Schemes 2 and 3, respectively. Initially, urea **1** was prepared by reacting 2-aminopyridine (**9**) with carbon disulfide and by treating the resulting thiourea with a basic solution of lead(II) acetate.[10,12] A relatively large quantity of **1** could be obtained using these reported procedures. However, because of the untidy nature of the purification in both steps and the relatively low overall yield, an alternative route to **1** and other symmetrical heterocylic ureas was sought.

Along these lines, **9** has been previously converted to **1** in a single step.[13] However, reaction conditions are somewhat harsh, requiring phosgene to be continuously bubbled through a solution of **9** in refluxing benzene for an extended time. Moreover, yields of the urea are low (32%) using this procedure. The difficulty in synthesizing symmetrical ureas from 2-aminopyridines and phosgene most likely arises because of the inferior nucleophilicity of an amine in the 2-position of a pyridine, as well as the propensity of the isocyanate of the pyridylamine, if formed, to irreversibly dimerize.[14] To counter these problems, attempts were made to prepare **1** by reacting **9** with triphosgene in the presence of a stoichiometric amount of 4-(dimethylamino)pyridine (DMAP). After several trials, urea **1** was produced in good yield by adding triphosgene dropwise to a solution of **9** and DMAP in methylene chloride, followed by reaction at room temperature (Scheme 2). This straightforward procedure is general and has been used to synthesize a variety of symmetrical, heterocyclic ureas.

With the ADDA unit in hand, its hydrogen-bonding complement, DAAD subunit **2**, was synthesized. The immediate precursor to **2**, 2,7-diamino-1,8-naphthyridine (**13**), was prepared from 2-acetamido-7-chloro-1,8-naphthyridine (**12**), which, in turn, was available by acetylation and chlorination of 2-amino-7-hydroxy-1,8-naphthyridine (**10**) (Scheme 3).[15] Concomitant

(6) For selected examples of abiotic oligomers that form β-sheet structures, see: (a) Bisson, A. P.; Hunter, C. A. *J. Chem. Soc., Chem. Commun.* **1996**, 1723−1724. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (c) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287−296. (d) Kelly, J. W., Ed. *Bioorg. Med. Chem.* **1999**, *7* (1) (symposium in print). (e) Gong, B.; Yan, Y.; Zeng, H.; Skrzypczak-Jankunn, E.; Kim, Y. W.; Zhu, J.; Ickes, H. *J. Am. Chem. Soc.* **1999**, *121*, 5607−5608. (f) Archer, E. A.; Goldberg, N. T.; Lynch, V.; Krische, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 5006−5007.

(7) For examples of abiotic oligomers that form helical structures, see: (a) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587−10593. (b) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793−1796. (c) Rowan, A. E.; Nolte, R. J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 63−68. (d) Ohkita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem.*−*Eur. J.* **1999**, *5*, 3471−3481.

(8) For a thermally irreversible change in a folded oligomer, see: Nguyen, J. Q.; Iverson, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 2639−2640.

(9) Complex **6·7** was described in a previous communication: Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2000**, *122*, 3779−3780.

(10) Sathyanarayana, D. N.; Sudha, L. V. *Magn. Reson. Chem.* **1987**, *25*, 474−479. See also: Singha, N. C.; Sathyanarayana, D. N. *J. Chem. Soc., Perkin Trans 2* **1997**, 157−162 and references therein. These authors have extensively studied the NMR spectra and conformations of dipyridylureas. Our results for **1** are in full agreement.

(11) (a) Vdovichemnko, A.; Chervinskii, A. Y.; Galat, V. F.; Kaplan, L. *Sov. Prog. Chem.* **1990**, *46*, 108−110. (b) Vdovichemnko, A. Y.; Galat, V. F.; Kaplan, L. M. *Ukr. Khim. Zh. (Russ. Ed.)* **1990**, *56*, 321−323.

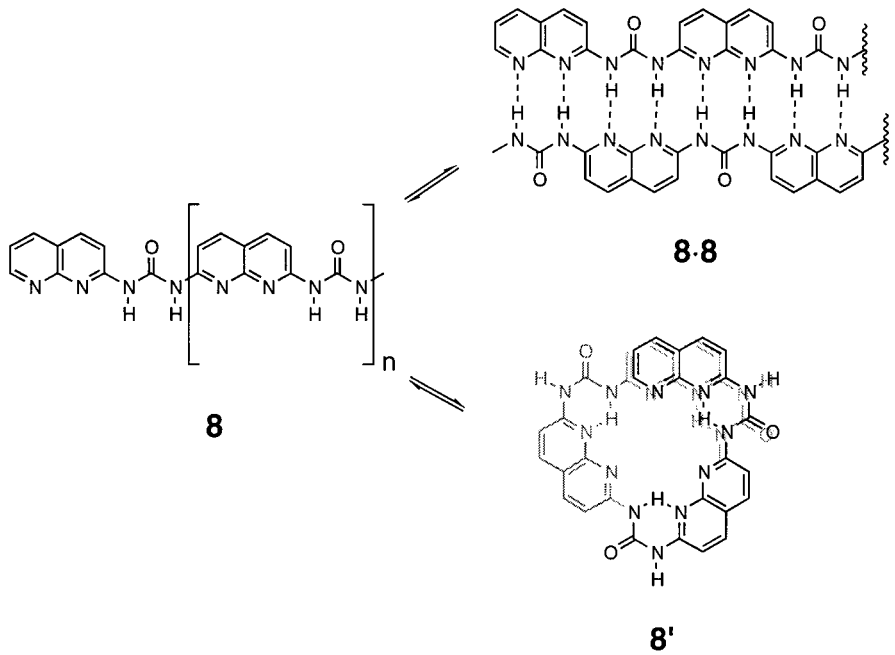
(12) Feist, K. *Arch. Pharm. (Weinheim, Ger.)* **1934**, *272*, 111.

(13) (a) Gerchuk, M. P.; Taits, S. Z. *Zh. Obshch. Khim.* **1950**, *20*, 910−916. (b) Gerchuk, M. P.; Taits, S. Z. *Chem. Abstr.* **1950**, 9443d.

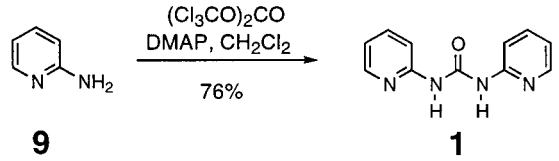
(14) L'abbé, G. *Synthesis* **1987**, *26*, 894−895.

(15) 2-Amino-7-hydroxy-1,8-naphthyridine and 2,7-dichloro-1,8-naphthyridine were prepared according to previously reported procedures: Newkome, G. R.; Garbis, S. J.; Majestic, V. K.; Fronczek, F. R.; Chiari, G. *J. Org. Chem.* **1981**, *46*, 833−839.

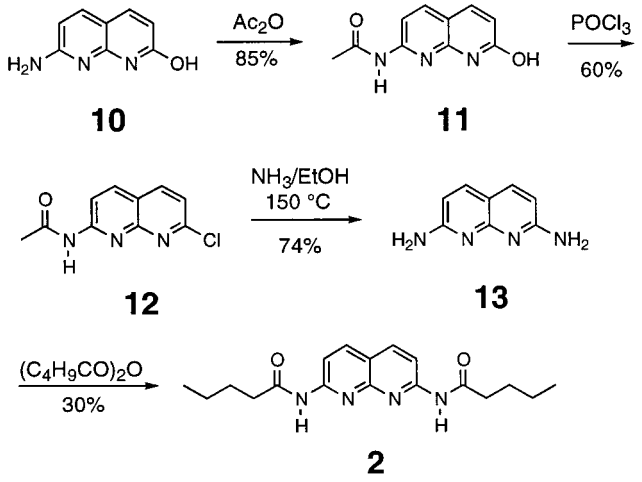
Scheme 1



Scheme 2



Scheme 3



cleavage of the acetamide group and nucleophilic displacement of the chloride atom gave diamine **13** in good yield. Alternatively, **13** was prepared by reacting 2,7-dichloro-1,8-naphthyridine[15] with aqueous ammonia. The former pathway was preferred because **12** was more soluble than the dichloronaphthyridine and, therefore, was more easily purified. The aminolysis of **12** could also be carried out in ethanolic ammonia, a solvent system in which the chloroacetamide was fully soluble. The chloroform-soluble DAAD unit **2** was readily prepared by reacting **13** with valeric anhydride.

A crystal of **1** suitable for X-ray analysis was grown from methanol by slow evaporation. In the solid state, **1** exists in an intramolecularly hydrogen-bonded *E,Z* conformation. Moreover, these folded units were further organized into dimers by $R_2^2(8)$ dimerization[16] of the unpaired amide-like sites (Figure 1).[17] The intramolecular hydrogen-bond length in the planar structure was 1.96 Å with an N−H−N angle of 140°, whereas the intermolecular hydrogen-bond length was 1.97 Å with an N−H−O angle of 176°. Further details of the crystal-structure data and analysis are available.[9]

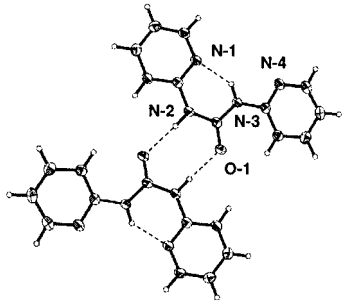


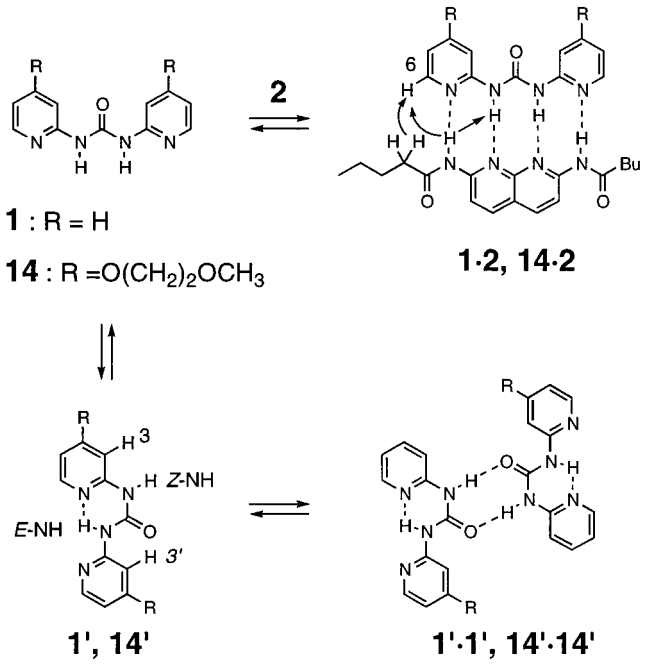
Figure 1. Solid-state structure of **1** showing intramolecular folding and intermolecular $R_2^2(8)$ dimerization.

By analogy to solution studies of *N,N′*-di-2-pyridylthiourea,[10] it was expected that **1** would exist in an equilibrium between the two degenerate, intramolecularly hydrogen-bonded conformers (i.e., **1′**, Scheme 4). Indeed, this was the case. The solution structure of **1** was studied by dynamic ^{1}H NMR spectroscopy. In summary, two sets of aromatic and NH signals were observed for **1** in $CDCl_3$ at −40 °C (Figure 2A), consistent with a slow equilibration of conformers on the time scale of the NMR experiment. In addition, the NH signal at 12.80 ppm was far downfield, and its chemical shift was concentration-independent. Both of these features were consistent with the NH being intramolecularly hydrogen-bonded. Thus, the signal was assigned to the *E*-NH group. Interestingly, the chemical shifts for the H-3 protons, H-3 and H-3′, differed by over 1 ppm. The downfield signal (ca. 8.40 ppm) was attributed to H-3′ because,

(16) For the application of graph notation to hydrogen-bonding motifs, see: Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120−126.

(17) A crystal structure of a Ni(II) complex was recently reported that uses pyridylureas as ligands: Kyriakidou, F.; Panagiotopoulos, A.; Perlepes, S. P.; Manessi-Zoupa, E.; Raptopoulou, C. P.; Terzis, A. *Polyhedron* **1996**, *15*, 1031−1034.

Scheme 4



in contrast to H-3, H-3′ sits within the anisotropic deshielding cone of the urea carbonyl group.[10]

At room temperature in $CDCl_3$, there was a single set of peaks for H-4(4′), H-5(5′), and H-6(6′) in the ^{1}H NMR spectrum (Figure 2B). However, the NH and H-3(3′) signals were not observed. When the solution was warmed to 50 °C, broad NH and H-3(3′) signals were detected, which indicated almost complete coalescence (Figure 2C). Observations at high temperature were again fully consistent with the equilibration of degenerate, intramolecularly hydrogen-bonded conformers. A chemical shift summary for experiments with **1** is given in Table 1, including data from spectra obtained in a competitive hydrogen-bonding solvent, dimethyl sulfoxide-d_6 (DMSO-d_6).

It should be noted that the chemical shifts for *Z*-NH and H-3 of **1** at −40 °C ($CDCl_3$), as well as the averaged NH and H-3(3′) signals at 50 °C ($CDCl_3$), were concentration-dependent, which implied that **1** self-associated. Self-association was also reflected in the observation that the chemical shifts of the *Z*- and *E*-NH, as well as H-3 and H-3′ signals, were not precisely averaged in coalesced spectra of **1** obtained at high concentrations. These signals were more closely averaged at lower concentrations at which **1** existed primarily as monomer at both low and high temperatures. Because the NH and H-3(3′) signals were not visible at room temperature, ^{1}H NMR dilution studies were carried out at 50 °C (300 MHz), and the resulting chemical shift data were fit to a 1:1 binding isotherm using standard, nonlinear curve-fitting procedures.[18] The dimerization constant (K_{dimer}) obtained was small, ca. 5 M^{-1}; thus, self-association was very weak. The most reasonable mode of association is amide-like $R_2^2(8)$ dimerization (i.e., **1′·1′**), as was observed in the crystal structure of urea **1** (Figure 1).

Infrared (IR) spectroscopic data was also consistent with folding and dimerization as in **1′·1′**. Specifically, there were two strong, hydrogen-bonded NH-stretches at 3142 and 3223 cm^{-1} in the solid-state (KBr) spectrum of **1**. Likewise, in chloroform solution spectra, there were two stretches at 3119 and 3224 cm^{-1}, in addition to a non-hydrogen-bonded NH-stretch at 3431 cm^{-1}. In line with the aforementioned folding and weak dimerization was the observation that the NH-stretch at 3224 cm^{-1} was concentration-independent (intramolecularly hydrogen-bonded), whereas the remaining NH stretches were concentration-dependent. In the case of the concentration-dependent stretches, the hydrogen-bonded stretch appeared to increase in intensity with increasing concentration, and the intensity of the non-hydrogen-bonded NH-stretch decreased. Similar observations have been made in studies of *N*,*N*′-di-2-pyridylthiourea.[19]

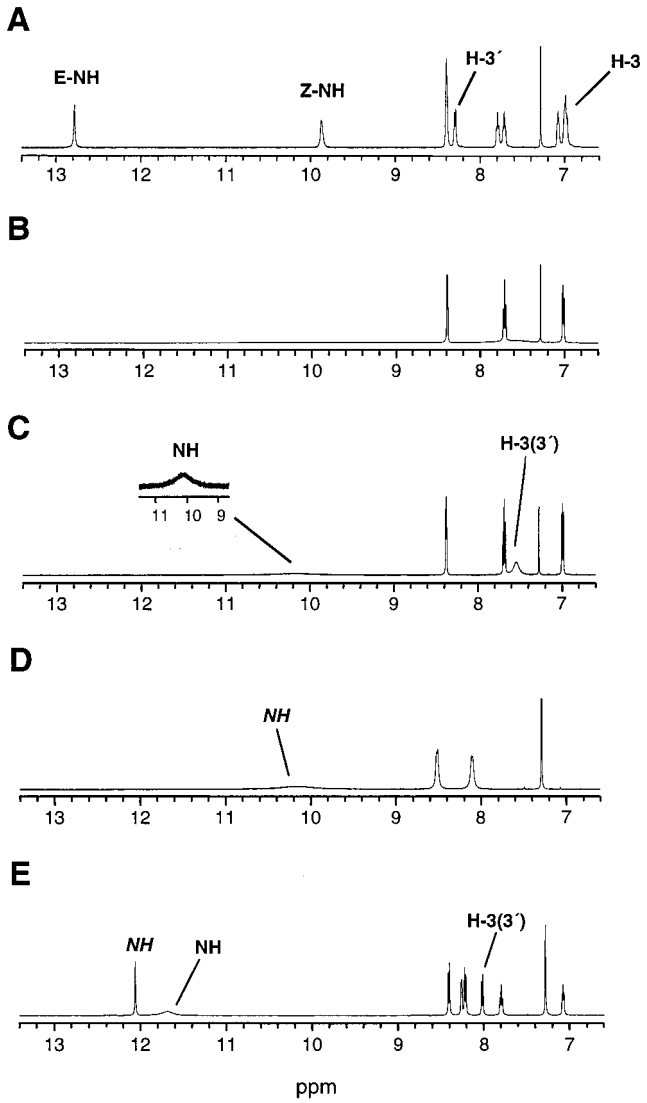


Figure 2. ^{1}H NMR spectra in $CDCl_3$ of (A) urea **1** at −40 °C, (B) urea **1** at 25 °C, (C) urea **1** at 50 °C, (D) naphthyridine **2** at −40 °C, and (E) complex **1·2** at −40 °C.

To determine whether the intramolecular hydrogen bond in **1′** would be broken and the quadruply hydrogen-bonded complex **1·2** formed in solution (Scheme 4), qualitative and quantitative ^{1}H NMR studies were carried out on mixtures of **1** and **2**.[20] That binding occurs can be best seen from a qualitative study of **1·2** carried out at −40 °C in $CDCl_3$. Interestingly, there was a single NH peak and a single set of aromatic peaks for **1** in mixtures of **1** and **2** (compare panel E of Figure 2 to panels

(18) (a) Wilcox, C. S. *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Durr, H., Eds.; VCH: New York, 1991; pp 123−143. (b) Connors, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley: New York, 1987; Chapter 5.

(19) Sudha, L. V.; Sathayanarayana, D. N. *Magn. Reson. Chem.* **1985**, *23*, 591−596.

(20) During the course of the work described herein, a complex related to **1·2** was reported: Lüning, U.; Kühl, C. *Tetrahedron Lett.* **1998**, *26*, 6604−6610.

Table 1. ^{1}H NMR Chemical Shift Data[a] for Urea **1**

sample	solvent	temp (°C)	H-3 (H-3′)	H-4 (H-4′)	H-5 (H-5′)	H-6 (H-6′)	*Z*-NH (*E*-NH)
1	DMSO-d_6	25	7.60−7.80	7.60−7.80	7.04	8.28	10.58
2[b]	$CDCl_3$	50	[7.49][c,d]	[7.71][c]	[7.01][c]	[8.38][c]	[10.14][c,d]
3[b]	$CDCl_3$	−40	6.99[d] (8.29)	7.71 (7.79)	6.99 (7.08)	8.40 (8.40)	9.85[d] (12.80)

[a] Chemical shifts are in ppm. Assignments were corroborated with the aid of gradient COSY and 1-D ^{1}H NMR exchange studies. [b] The concentration of samples two and three was ∼33 mM. [c] Numbers in brackets represent the proton peak "average". [d] Concentration dependent.

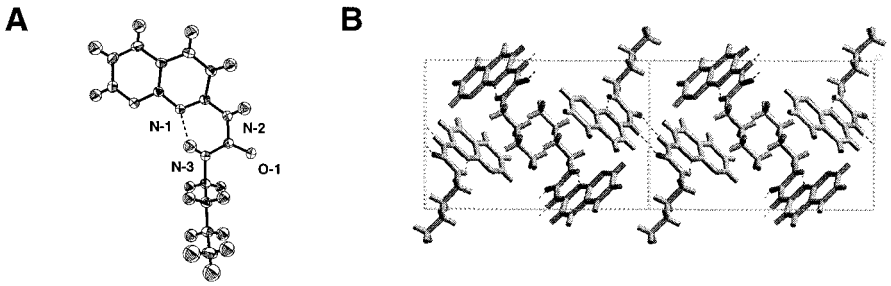


Figure 3. An ORTEP representation of the intramolecularly hydrogen-bonded urea, **3** (A) and a view of two unit cells viewed along the *b*-axis (B).

A and D), which implied that the corresponding protons on each pyridine ring were equivalent and that a symmetric complex was formed. Similar observations were made at room temperature. As was the case for the signal of H-3′ in spectra of **1** (Figure 2A), the H-3(3′) signal for **1** in the complex was downfield, which was consistent with the urea being unfolded and indicated that the H-3(3′) chemical shift was influenced by the carbonyl anisotropy. The downfield shift of the naphthyridine NH and the sharpening of peaks for **2** in mixtures of **1** and **2** were also indicative of hydrogen-bond complexation.

Although nuclear Overhauser effect (NOE) studies were not carried out with **1·2**, studies of an analogous complex, **14·2**, were consistent with formation of a quadruply hydrogen-bonded structure. Important contacts (Scheme 4) include the enhancement of H-6 (urea **14**) observed when irradiating both the amide NH and the α-methylene of **14**.

To determine the strength of the DAAD·ADDA complex, quantitative ^{1}H NMR dilution studies were carried out at room temperature with 1:1 mixtures of **1** and **2** (K_{dimer} of **2** was less than 5 M^{-1}) in $CDCl_3$ and gave an association constant (K_{assoc}) of approximately 1200 M^{-1} (23 °C). Likewise, a K_{assoc} of 3500 M^{-1} was obtained from studies at 0 °C. Although complex **1·2** was strong, the association was weakened because an intramolecular hydrogen bond had to be broken to form **1·2**. This effectively reduces the number of primary hydrogen bonds in the complex to three (see Summary and Conclusions). Despite numerous attempts, a crystal of **1·2** suitable for X-ray analysis could not be obtained.

Self-Complementary, Hydrogen-Bonding AADD Module 3 and Related AAD and DDA Units 4 and 5. Of the heterocyclic building blocks in Chart 1, *N*-butyl-*N*′-(2-naphthyridinyl)urea (**3**) is unique because the open (*E*,*E*) conformation of this urea is self-complementary (an AADD hydrogen-bond array); thus, there was potential for homodimerization. In addition, **3** is attractive because it is the repeat unit of the hypothetical naphthyridinylurea oligomer **8**. The synthesis of **3** was straightforward. In short, a multigram quantity of 2-amino-1,8-naphthyridine was prepared using a modified procedure of Van der Plas and co-workers.[21] Subsequent reaction of the aminonaphthyridine with butyl isocyanate gave the chloroform soluble derivative **3**.

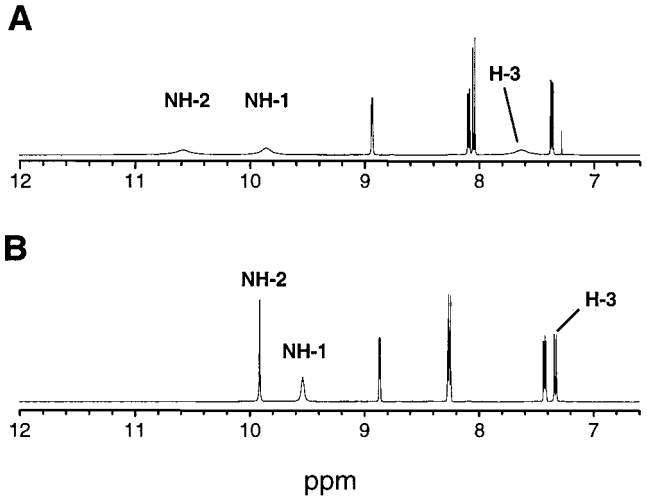


Figure 4. ^{1}H NMR spectra of **3** in (A) $CDCl_3$ (∼70 mM) and (B) the competitive hydrogen-bonding solvent DMSO-d_6. The H-3 and NH signals in part A were distinguished by gradient COSY and homonuclear decoupling experiments.

Prior to solution studies with **3**, an X-ray crystal structure was obtained. As illustrated in Figure 3, compound **3** existed in an intramolecularly hydrogen-bonded conformation that, again, formed amide-like $R_2^2(8)$ dimers in a manner similar to that observed for **1** (vide supra). The structure, with the exception of the butyl chain, was relatively planar, with intra- and intermolecular hydrogen-bond lengths of 1.96 (N−H−N angle = 136°) and 1.94 Å, respectively (see Supporting Information).

The self-association of **3** was investigated in solution by ^{1}H NMR spectroscopy. Along these lines, dilution studies (50 mM to 60 μM, $CDCl_3$) with **3** gave a K_{dimer} of 105 M^{-1}. Representative spectra are shown in Figure 4. A series of compounds containing non-hydrogen-bonded aryl and alkyl urea groups were examined, and their NH signals were found in a region from approximately 3.5 to 7.5 ppm.[22] Thus, the observation that the NH-1 signal of **3** was downfield (ca. 9.85 ppm) at low concentrations was consistent with the monomer being intramolecularly hydrogen-bonded. Moreover, the chemical shift for NH-2 was highly concentration-dependent, whereas no signifi-

(21) Van der Plas, H. C.; Wozniak, M.; van Veldhuizen, A. *Tetrahedron Lett.* **1977**, *24*, 2087−2089.

(22) For example, for *N*,*N*′-(2-methylphenyl)urea, δ(NH) ≈ 6.4 ppm, and for *N*,*N*′-dibutylurea, δ(NH) ≈ 3.5 ppm (chloroform-*d*).

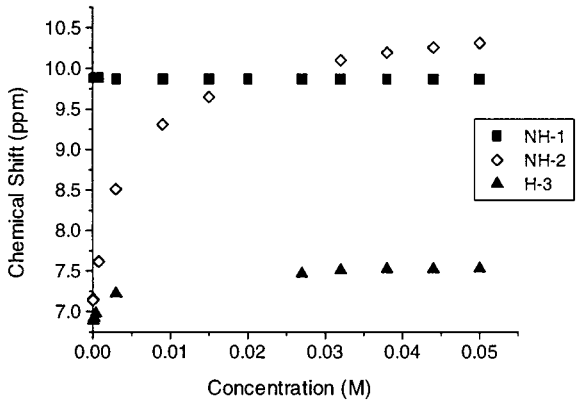
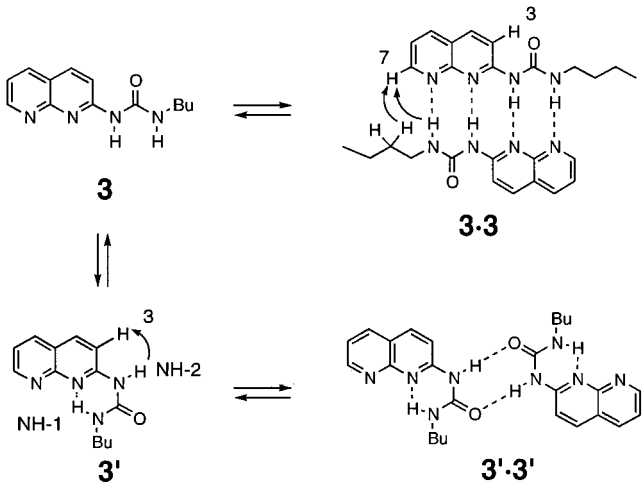


Figure 5. A chemical shift summary from a ^{1}H NMR dilution study of **3** in $CDCl_3$. The gap in data for H-3 represents points at which the signal overlapped with that of residual protio chloroform.

Scheme 5

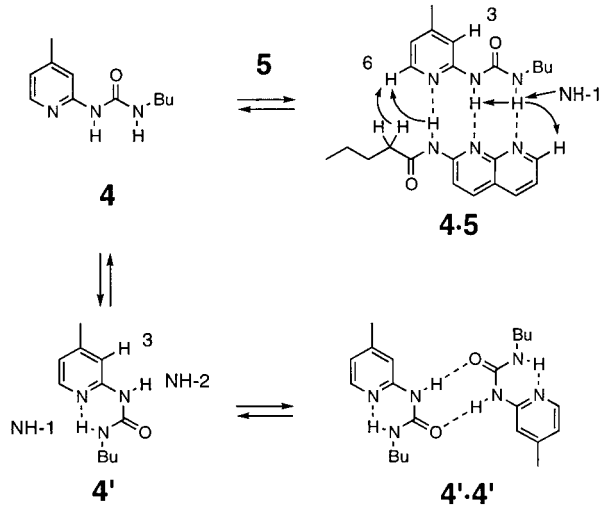


cant change in the NH-1 signal was observed (Figure 5). A downfield shift ($\Delta\delta \approx 0.8$ ppm) was also observed for the broad H-3 signal with increasing concentration. From a fit of the chemical shift data for H-3 to a 1:1 binding isotherm, the maximum change in chemical shift ($\Delta\delta_{max}$) was determined to be approximately 0.9 ppm, which, in turn, gave a maximum chemical shift (δ_{max}) of 7.8 ppm for H-3.

A qualitative assessment of these observations immediately raised the question of whether **3** dimerized as structure **3′·3′**, as in the solid state, or as the quadruply hydrogen-bonded dimer, **3·3**, (Scheme 5). The concentration-independent chemical shift of NH-1 appeared to support $R_2^2(8)$ dimerization because NH-1 remains intramolecularly hydrogen-bonded in **3′·3′**. However, NH-1 is also hydrogen-bonded to a naphthyridinyl nitrogen in **3·3**. Therefore, the NH-1 chemical shift in this dimer was expected to be similar to that observed in the folded monomer. Thus, no definite conclusions could be made concerning the dimerization state solely upon the basis of the NH-1 signal.

In further analysis, the large downfield shift observed for H-3 (Figure 5) was consistent with the formation of the quadruply hydrogen-bonded dimer because, as was the case with complex **1·2**, the unfolding of **3** forces H-3 into the anisotropic deshielding cone of the urea carbonyl group. Although H-3 and the carbonyl moiety are brought into proximity in **3′·3′**, they are still relatively far apart. Therefore, the H-3 signal for **3** in dimer **3·3** was expected to be further downfield than the same signal in **3′·3′**. Furthermore, only small changes in the H-3 chemical shift would have been expected in dilution studies if the amide-like homodimer was formed.

Scheme 6



To test this hypothesis, studies were carried out with pyridylurea **4**, which is believed to dimerize as in **4′·4′** (Scheme 6). IR studies of *N*-methyl-*N*′-2-pyridylureas have indicated an intramolecularly hydrogen-bonded conformation in chloroform solution.[23] However, a K_{dimer} was not reported. Therefore, urea **4** was prepared by reacting 2-amino-4-methylpyridine with butyl isocyanate, and self-association was investigated by ^{1}H NMR spectroscopy. A chemical shift summary from a dilution study (460 mM to 300 μM) is displayed in Figure 6A. A fit of the data for NH-2 and H-3 to a 1:1 binding isotherm gave a K_{dimer} of only 16 M^{-1}, which was almost 10 times less than that of **3**. As suspected, the downfield change in chemical shift for H-3 ($\Delta\delta_{max} \approx 0.45$ ppm) was considerably less than the change ($\Delta\delta_{max} \approx 0.9$ ppm) observed for the H-3 signal in dilution studies of **3**. Moreover, the chemical shift for H-3 in **4′·4′** was 6.88 ppm and, thus, was 1 ppm upfield from the corresponding signal in the dimer of **3** and the H-3 signal for **4** in the unfolded complex **4·5** (vide infra). Although the difference in dimerization constants for **3** and **4** may be partially accounted for by variances in primary hydrogen-bond strength, the notably disparate chemical shift changes and K_{dimer}'s for **3** and **4** suggested that the quadruply hydrogen-bonded dimer **3·3** likely forms in solution.

NOE studies in $CDCl_3$ were also consistent with the formation of quadruply hydrogen-bonded dimer **3·3**. Thus, NOE difference spectra were obtained for **3** at a concentration of 130 mM, a nearly saturated solution containing approximately 85−90% dimer. In these studies, intermolecular contacts (Scheme 5) were observed between the β-methylene protons and H-7, as well as between NH-1 and H-7. Both of these enhancements are expected in **3·3** but not in the amide-like dimer, **3′·3′**. An NOE was also observed between NH-2 and H-3. Although this enhancement is consistent with the doubly hydrogen-bonded dimer, it was attributed to the ca. 10−15% monomer in the folded state (Scheme 5).

This evidence, as a whole, was most consistent with formation of the quadruply hydrogen-bonded dimer **3·3** in solution. Although the four hydrogen bonds in **3·3** come at the price of two intramolecular hydrogen bonds, the urea·naphthyridine (DD·AA) contacts are stronger than those in the amide dimer (AD·DA).[24] Alternatively expressed, **3·3** contains two net attractive secondary hydrogen bonds, whereas **3′·3′** contains two

(23) Sudha, L. V.; Sathyanarayana, D. N. *J. Mol. Struct.* **1984**, *125*, 89−96.

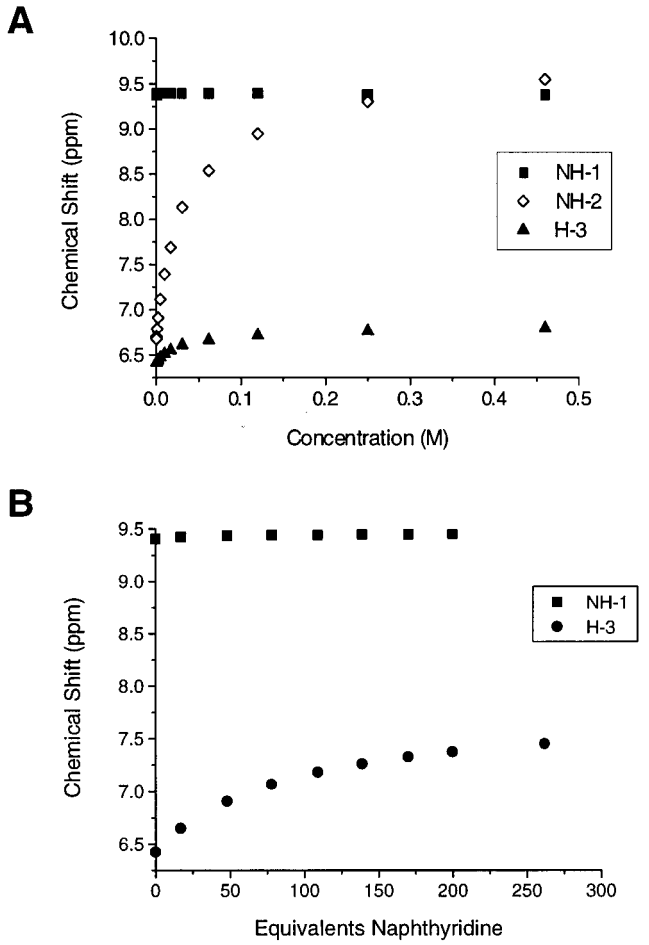


Figure 6. Chemical shift summaries from (A) a dilution study of **4** in $CDCl_3$ and (B) the titration of **4** (390 μM) with naphthyridine **5**.

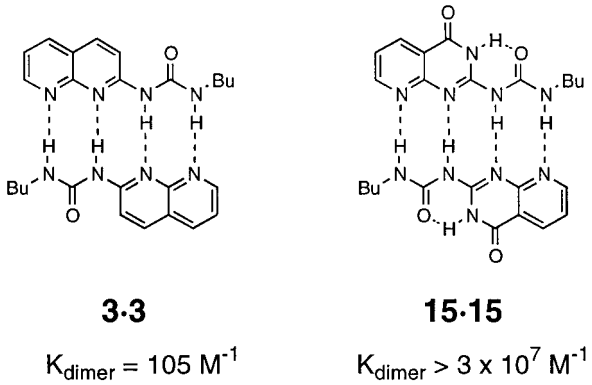


Figure 7. Comparison of K_{dimer} values for **3·3** and **15·15** in $CDCl_3$ at 296 K.

repulsive secondary hydrogen bonds. The cost of breaking the intramolecular hydrogen bond in **3** is dramatically illustrated by comparing the stability of **3·3** to that of **15·15** (Figure 7).[25] In **15·15**, a different intramolecular hydrogen bond can be maintained within each heterocyclic subunit of the dimer.

In addition to the dimerization studies of **3**, we were interested in investigating the possibility that the intramolecular hydrogen bond in **4′** would be broken and that AAD·DDA complex **4·5** (Scheme 6) would form in solutions containing both components. Thus in ensuing studies, a chloroform solution of **4** (390 μM) was titrated with **5**. Because the K_{dimer} for **5** was less than 5 M^{-1}, its self-association was negligible over the concentration range of the titration studies. A fit of the chemical shift data (Figure 6B) for H-3 to a 1:1 binding isotherm gave a K_{assoc} of 30 M^{-1}. As observed in the dimerization of **3**, there was only a small change in the chemical shift of NH-1 of **4** upon complex formation (Figure 6). However, a large downfield shift of the H-3 signal ($\Delta\delta_{max}$ = 1.38 ppm, $\delta_{complex}$ = 7.8 ppm) was observed. Both shifts are fully consistent with urea unfolding and formation of the triply hydrogen-bonded complex **4·5**. Likewise, the key intra- and intermolecular NOE contacts observed from difference NOE studies (Scheme 6) fully support formation of **4·5**.

Crystal Structure of Bisdibutylpyridylurea (16): A Module Containing a DDADD Array. As indicated by the crystal structures of **1** and **3**, there is an apparent propensity for pyridyl and naphthyridinylureas to crystallize in intramolecularly hydrogen-bonded (i.e., folded) forms. Bisurea **16** is interesting from the standpoint that only one of the butyl NH's can be intramolecularly hydrogen-bonded at a given time. Thus, an X-ray analysis was performed on **16** to examine whether it crystallized with an intramolecular hydrogen bond or in an analogous manner to the urea crystal structures reported by Etter and Pasternak, wherein both urea NH's are intermolecularly hydrogen-bonded to a urea carbonyl group.[26,27] Urea **16** was easily synthesized by reacting 2,6-diaminopyridine with butyl isocyanate, and a crystal suitable for X-ray crystallographic analysis was grown from methanol by slow evaporation.

As shown in Figure 8, **16** was indeed intramolecularly hydrogen-bonded. A depiction of the tetragonal unit cell, viewed along the *c*-axis, is shown in Figure 8B. The intermolecular hydrogen-bonding pattern in the lattice was intriguing, yet rather complicated, and, thus, was difficult to display. In summary, both NH-1′ and NH-2 were hydrogen-bonded to carbonyl-2, and NH-2′ was hydrogen-bonded to carbonyl-1. Details of crystal structure data and analysis are provided as Supporting Information.

Folding and Unfolding of Hydrogen-Bonding AADDAA and DDAADD Modules. The most elaborate modules examined in this study contained DDAADD (**6**, **17**) and AADDAA (**7**) hydrogen-bond arrays. These subunits with complementary six hydrogen-bond donor−acceptor sites contain one and one-half repeat units of the hypothetical polymer **8**.

Bis-2,7-(3-butyl)uryl-1,8-naphthyridine (**17**) was prepared by reacting diaminonaphthyridine **13** with butylisocyanate. Crystals of **17** obtained from methanol were suitable for X-ray crystallography. The solid-state structure of **17** (Figure 9) was similar to that of **3** (vide supra). In the case of **17**, both urea groups formed intramolecular hydrogen bonds and $R_2^2(8)$ dimerization of the amide-like sites was again observed, which with dual sites led to the formation of polymeric tapes, $(\mathbf{17}')_n$.

Because of the poor solubility of **17** in chloroform, a more soluble urea derivative, **6**, was prepared for solution studies (Scheme 7). In this synthesis, hydroxy-succinate ester **19** was produced from 3,4,5-tridodecyloxy benzoic acid (**18**)[28] and *N*-hydroxysuccinimide using standard dicyclohexylcarbodiimide

(24) (a) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1991**, *113*, 2810−2819. (b) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810−2819. (c) Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010−4011. (d) Zimmerman, S. C.; Murray, T. J. *Tetrahedron Lett.* **1994**, *35*, 4077−4080.

(25) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710−9711.

(26) Etter, M. C.; Urbañczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415−8426.

(27) Deshapande, S. V.; Meridith, C. C.; Pasternak, R. A. *Acta Crystallogr., Sect. B* **1968**, *24*, 1396−1397.

(28) Meier, H.; Prass, E.; Zerban, G.; Kosteyn, F. *Z. Naturforsch., B* **1988**, 889−896.

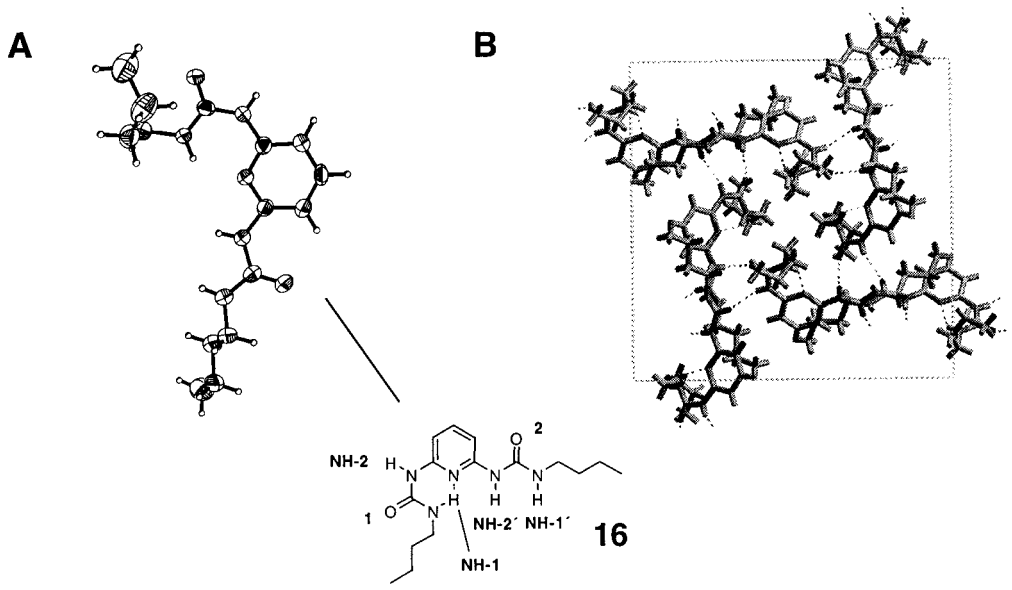
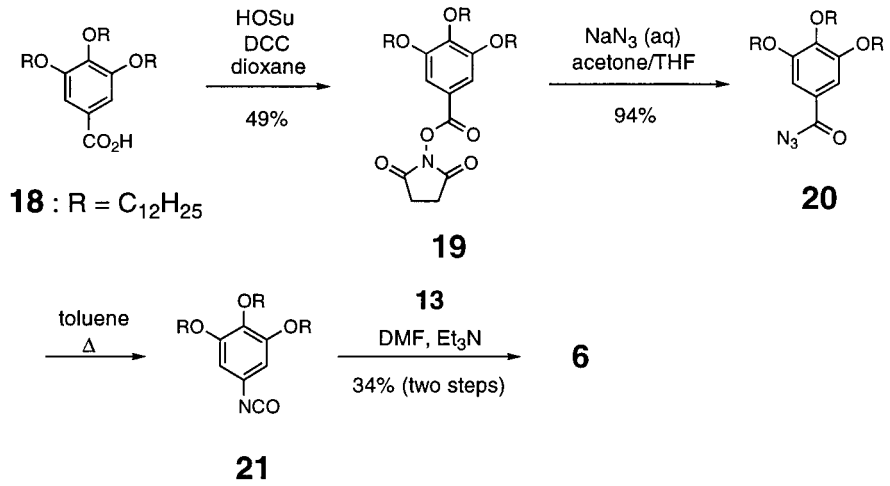


Figure 8. An ORTEP representation of urea **16** (A) and a view of the tetragonal unit cell (B).

Scheme 7



(DCC) coupling procedures. The activated ester was subsequently converted to acyl azide **20**, which rearranged to the corresponding isocyanate, **21**, upon heating. In the final step, **21** was reacted with **13** to give **6** in moderate overall yield. A simple analogue, urea **23**, was needed as a control compound for ^{1}H NMR studies and was prepared similarly (Scheme 8).

With urea **6** in hand, the chloroform soluble naphthyridinylurea **7** was synthesized (Scheme 9). In the first step, 2-amino-5,7-dipropyl-1,8-naphthyridine (**25**) was prepared by a Knorr cyclization of 4,6-nonanedione[29] and diaminopyridine **24**. Two units of **25** were then coupled with triphosgene and DMAP to give **7**. An unsubstituted variant of **7** was insoluble and, thus, was unsuitable for solution studies.

Prior to carrying out complexation studies with **6** and **7**, their solution conformation and potential for self-association were assessed. ^{1}H NMR dilution studies in $CDCl_3$ with the soluble bisurea derivative **6** suggested that the solution structure was analogous to that of **17** observed in the solid state (vide supra). In short, the NH-1 signal (ca. 12.4 ppm) was far downfield, and the chemical shift changed only slightly ($\Delta\delta \approx 0.3$ ppm) over a large concentration range (35 mM to 28 μM) (Figures 10 and 11A). The downfield shift observed at concentrations

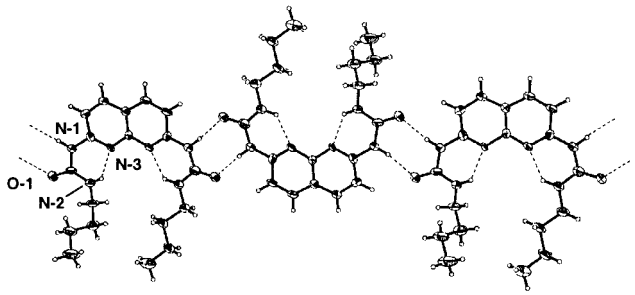


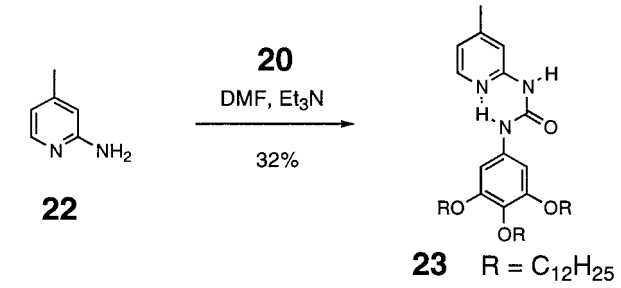
Figure 9. Solid-state structure of **17** showing intramolecular folding and intermolecular $R_2^2(8)$ dimerization.

at which there was no self-association was consistent with NH-1 being intramolecularly hydrogen-bonded in the monomer. In contrast, the chemical shift for NH-2 was highly concentration-dependent, varying approximately 3.5 ppm over the same concentration range, which indicated that NH-2 could form an intermolecular hydrogen bond at high concentrations.

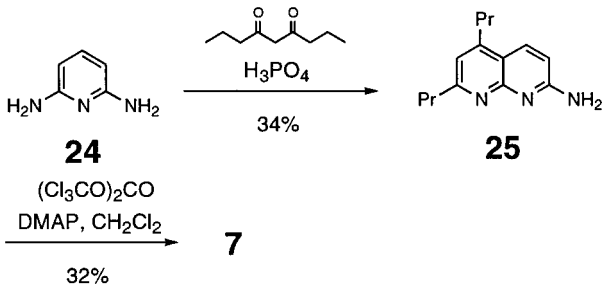
The observation that there were only small changes in the chemical shifts of the NH-1 and H-3 signals with increasing concentration was consistent with the preservation of the NH-1 intramolecular hydrogen bond and, thus, folding of **6** at high concentrations. For example, the δ_{max} of H-3 in the aggregate

(29) Ayer, W. A.; Villar, J. D. F. *Can. J. Chem.* **1985**, *63*, 1161−1165.

Scheme 8



Scheme 9



of **6** was 7.21 ppm, whereas the chemical shift of the H-3 signal of **6** in the unfolded complex **6·7** was approximately 8.11 ppm (vide infra). Moreover, the changes in chemical shifts observed for **6** upon self-association were similar to those for the NH-1, NH-2, and H-3 signals of pyridylurea **23** ($K_{dimer} \approx 30$ M^{-1}), which associated by $R_2^2(8)$ dimerization. Thus, ^{1}H NMR studies, including the observation of a strong NOE from H-2 to H-3 (Scheme 10), were consistent with self-association as in $(\mathbf{6}')_n$ as opposed to the formation of an unfolded, intermolecularly hydrogen-bonded complex **6·6**. It should be pointed out that if **6·6** were formed, an upfield shift of the NH-1 signal would have been likely with increasing concentration because the exterior NH's are non-hydrogen-bonded in this dimer. IR results were analogous to those reported for pyridylurea **1** and were also consistent with association by amide-like dimerization.

The chemical shift data from dilution studies of **6** fit reasonably well to a dimerization model and gave an apparent

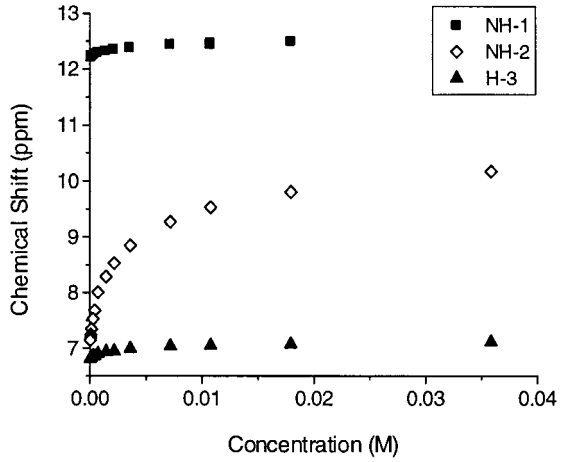
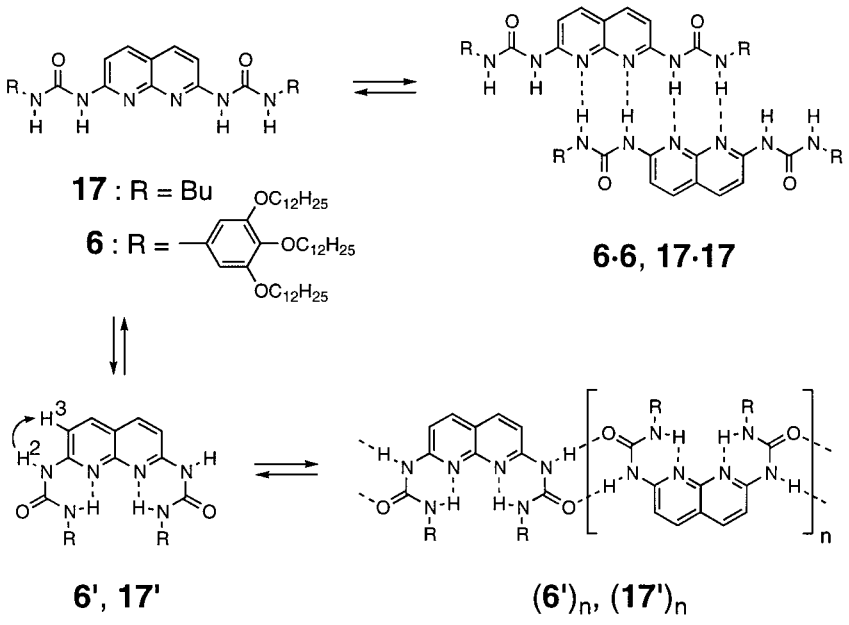


Figure 10. A chemical shift summary for a dilution study of **6** in $CDCl_3$.

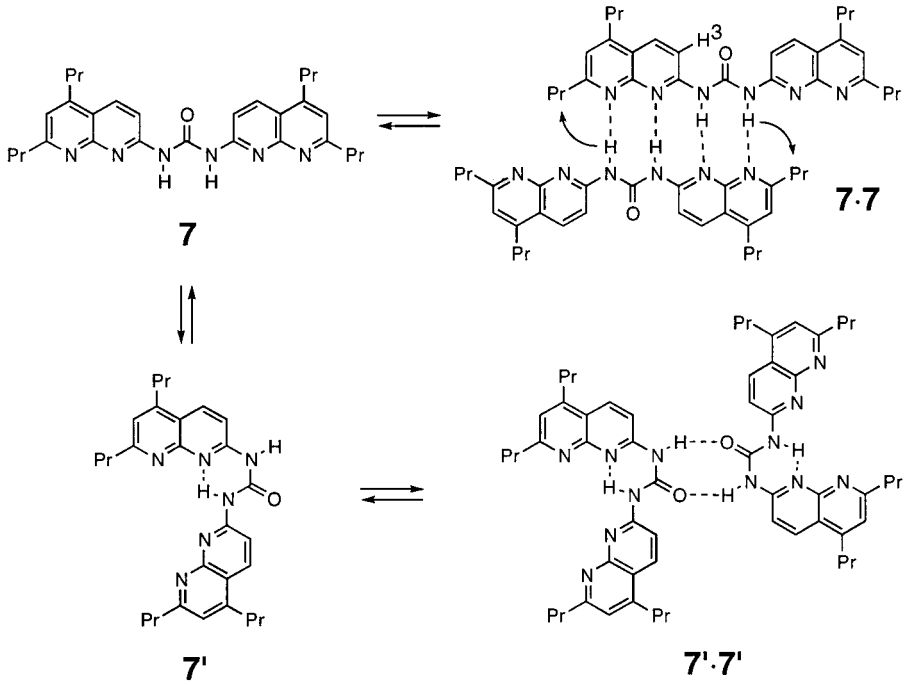
K_{dimer} of approximately 95 M^{-1} (based on the total concentration of binding sites). This K_{dimer} is comparable to that measured for **23** (vide supra). The fact that the chemical shift data could be fit to a dimerization model implied that the self-association was noncooperative. Interestingly, viscous solutions of **6** were obtained in cyclohexane at high concentrations, suggesting that hydrogen-bonded chains of substantial length were formed in this solvent. The molecular weight of the aggregate was not measured, and an association constant for **6** could not determined in cyclohexane-d_{12} because of peak broadening. However, a K_{dimer} of 10^4 M^{-1} was approximated for **23·23** in cyclohexane. Thus, assuming the stepwise association constants for $\mathbf{6}'\cdot(\mathbf{6}')_n$ are similar to the **23·23** K_{dimer}, then high number average molecular weights are theoretically possible for concentrated samples of **6** in cyclohexane.

It has been established that pyridylurea **1** exists in a dynamic equilibrium between two degenerate hydrogen-bonded conformers in $CDCl_3$ (vide supra). Thus by extension, it was anticipated that naphthyridinylurea **7** would be intramolecularly hydrogen-bonded as in **7′** (Scheme 11). Indeed, aspects of the ^{1}H NMR spectra of **7** were similar to those of **1**. The downfield shift (ca. 13.3 ppm) of the NH signal in the spectrum of **7** shown in Figure 11B (100 μM, ~90% monomer, −45 °C) was consistent with

Scheme 10



Scheme 11



the NH being intramolecularly hydrogen-bonded in the monomer; thus, the signal was tentatively assigned as *E*-NH. As was the case for **1**, the H-3 and H-3′ signals of **7** differed by over 1 ppm. The downfield signal (ca. 8.57 ppm) was again attributed to H-3′. As expected, both the NH and H-3 signals for this low concentration sample were averaged at 50 °C.

At ambient temperature and at relatively high concentrations, a single set of aromatic peaks and a broad NH peak were observed for **7** in $CDCl_3$ (Figure 11C). A dilution study (13 mM to 41 μM) was carried out at this temperature, and a fit of the chemical shift data for H-3(3′) to a dimerization model gave a K_{dimer} of 260 M^{-1}. Of the two likely dimers, **7·7** and **7′·7′** (Scheme 11), the K_{dimer} and observed chemical shift changes were most consistent with the formation of the quadruply hydrogen-bonded dimer **7·7**. More specifically, a smaller K_{dimer} would have been expected if the amide-like dimer **7′·7′** was formed (vide supra). Moreover, a relatively large downfield shift was observed for H-3 ($\Delta\delta$ = 0.7 ppm) with increasing concentration. This change in chemical shift was similar to that observed for the H-3 signals of ureas **1** and **3** upon forming the unfolded complex **1·2** and dimer **3·3**, respectively, and, therefore, was consistent with the formation of **7·7** at high concentrations. An NOE between the NH and the α-methylene of the propyl group in the 7-position (Scheme 11) was also consistent with **7·7**.

To investigate the potential for forming heterodimer **6·7** (Scheme 12), ^{1}H NMR spectroscopic studies were carried out on 1:1 mixtures of the two components in $CDCl_3$. A representative spectrum is shown in Figure 11D. Assignments of the peaks were corroborated by NOE and gradient correlation spectroscopy (COSY) experiments and were, along with intermolecular NOEs (Scheme 12), fully consistent with the unfolding of both **6′** and **7′** and formation of the desired sheetlike complex containing six hydrogen bonds. Especially notable was the large downfield shift observed for the H-3 signal of **6**. Furthermore, the chemical shift for the H-3 signal in **7** was similar to that observed for H-3′ in the folded form.

Complex formation was slow on the NMR time scale, as revealed by the observation of peaks for both monomer and complex in mixtures containing an excess of one of the components. The K_{assoc} of **6·7** was estimated to be approximately 5×10^5 M^{-1} from the integration of signals for monomer and complex in spectra obtained at concentrations at which self-association of the two components was negligible. The robust heterodimer described is one of the first examples of a nonnatural, hydrogen-bonded complex containing six contiguous hydrogen bonds.[30]

Summary and Conclusions

A series of folded, intramolecularly hydrogen-bonded ureas and their corresponding unfolded, multiply hydrogen-bonded complexes have been characterized. Dimerization and association constants for these complexes are summarized in Table 2 along with the number of primary and secondary[24] hydrogen-bonding interactions. Although the free energies of association reported in the last five entries do not appear to fit an incremental energy model proposed by Schneider and coworkers,[4,31] the energies do follow a general trend. As the effective number of primary hydrogen bonds increases (i.e., $n_{inter} - n_{intra}$), the association constant increases. Likewise, in cases in which the effective number of primary hydrogen bonds is identical, for example **1·2** and **6·7**, the relative stabilities appear to be influenced, in part, by the net number of secondary interactions in the complex.[24]

In addition to being simple, hydrogen-bonding switch elements, modules such as those described herein have the potential to be useful building blocks for self-assembly. Along these lines, the experiments described herein bode well for future studies of naphthyridinylurea oligomers and polymers. One can specu-

(30) During the course of this study, very elegant abiotic, hydrogen-bonded duplexes were reported with six interstrand hydrogen bonds: Zeng, H.; Miller, R. S.; Flowers, R. A., III; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 2635−2644. Bisson, A. P.; Carver, F. J.; Eggleston, D. S.; Haltiwanger, R. C.; Hunter, C. A.; Livingstone, D. L.; McCabe, J. F.; Rotger, C.; Rowan, A. E. *J. Am. Chem. Soc.* **2000**, *122*, 8856−8868. For synthetic duplexes containing six base-pairing-type hydrogen bonds, see: Sessler, J. L.; Wang, R. *J. Org. Chem.* **1998**, *63*, 4079−4091. Hamilton, A. D.; Little, D. *J. Chem. Soc., Chem. Commun.* **1990**, 297−299.

(31) Sartorius, J.; Schneider, H.-J. *Chem.−Eur. J.* **1996**, *2*, 1446−1452.

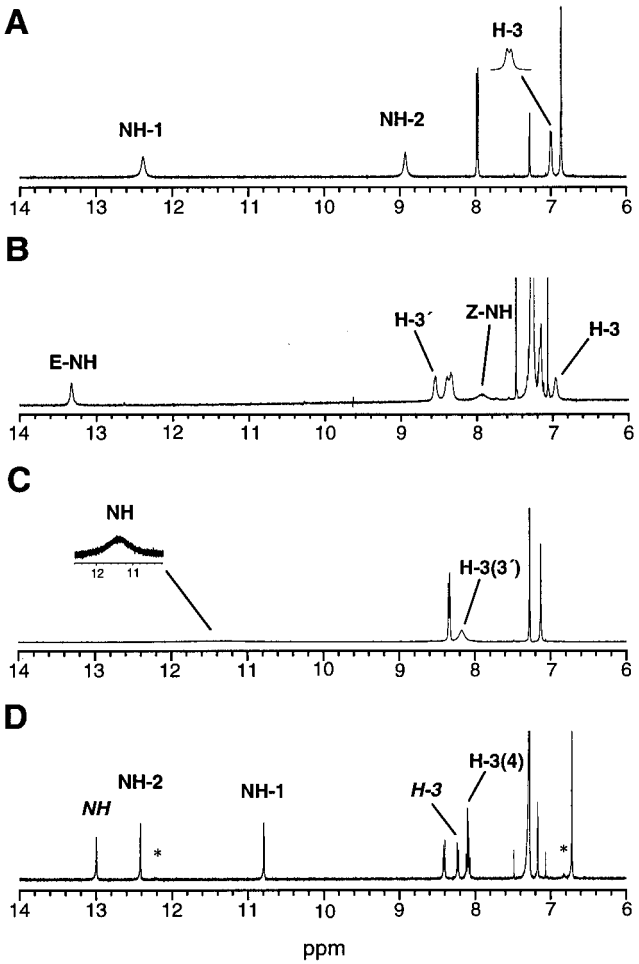
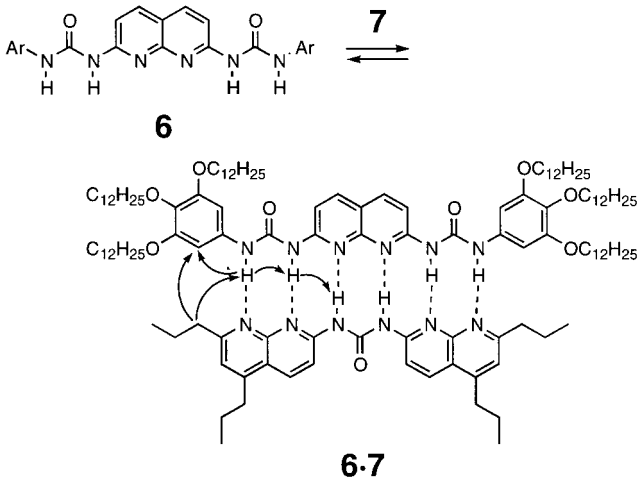


Figure 11. ^{1}H NMR spectra in $CDCl_3$ of (A) bisurea **6** at ~6 mM with ~50% association, (B) urea **7** at −45 °C at a concentration of ~0.1 mM containing ~10% dimer, (C) urea **7** at 25 °C at a concentration of 6 mM containing ~60% dimer (the NH peak was not observed at concentrations below 1.5 mM; a broad coalesced NH peak was observed in a 0.1 mM sample at 50 °C at which **7** was monomeric), and (D) complex **6·7** with signals for **7** italicized and asterisks showing uncomplexed compound.

Scheme 12



late that hydrogen-bonded, sheetlike structures ("molecular Velcro") of considerable stability might be produced from such units. Indeed, with the proviso that curvature in **8** may limit the length over which its hydrogen-bonded dimers might form and recognizing the uncertainty in such extrapolations, it can be calculated that when $n \geq 12$ the dimer, **8·8**, will have a stability comparable to that of a typical C—C bond. In addition, folded, intramolecularly hydrogen-bonded helices may arise under suitable conditions. Studies to test these possibilities will be reported in due course.

Table 2. A Summary of Dimerization and Association Constants

complex	K_{assoc} or K_{dimer} (M^{-1})[a]	$-\Delta G_{296}$ (kcal/mol)	n_{intra}[b]	n_{inter}[c]	n_{sec}[d]
1·1	5[e]	1.0	0	2	−2
4·4	16	1.6	0	2	−2
6·6	95	2.6	0	2	−2
4·5	30	2.0	1	3	0
3·3	105	2.8	2	4	2
7·7	260	3.3	2	4	2
1·2	1200	4.2	1	4	−2
6·7	5×10^5	7.7	3	6	2

[a] The association constants are typically averages of two experiments at 23 °C in which the values agreed within 10%. [b] Number of intramolecular hydrogen bonds broken. [c] Number of intermolecular hydrogen bonds formed in the complex. [d] Net number of secondary hydrogen-bonding interactions in the complex. [e] K_{dimer} was measured at 50 °C.

Experimental Section

General Methods. All reactions were carried out under a dry nitrogen atmosphere. Reaction temperatures reported are the temperatures of the heating medium, unless specified otherwise. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. Triethylamine, methylene chloride, and toluene were distilled from calcium hydride (CaH_2), and phosphorus oxychloride ($POCl_3$) was freshly distilled prior to use. 2,7-Dichloro-1,8-naphthyridine,[15] 2-amino-7-hydroxy-1,8-naphthyridine (**10**),[15] and 3,4,5-tridodecyloxy benzoic acid (**18**)[28] were synthesized according to published procedures. All other solvents and reagents were of reagent grade and were used without further purification, unless indicated otherwise.

Analytical thin-layer chromatography (TLC) was performed on 0.2 mm silica 60 coated on plastic plates (EM Science) with F_{254} indicator. Flash chromatography was carried out on Merck 40−63 μm silica gel following the procedure described by Still.[32] Ratios of solvents for flash chromatography are reported as volume percentages. Thin-layer, preparative radial chromatography was performed on silica gel coated plates (silica gel 60 F_{254} containing gypsum, EM Science) using a chromatotron (Harrison Research). Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected.

All NMR spectra were acquired in the Varian-Oxford Instrument Center for Excellence in NMR Spectroscopy (VOICE) laboratory at the University of Illinois at Urbana-Champaign. ^{1}H and ^{13}C NMR spectra of reaction products were recorded on a Varian Unity 500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz) in $CDCl_3$ unless otherwise noted. ^{1}H coupling constants are given in hertz. ^{1}H NMR chemical shifts were referenced to the residual protio solvent peak at 7.28 ppm in chlorform-*d* ($CDCl_3$) and to the solvent peak at 2.48 ppm in dimethyl sulfoxide-d_6 (DMSO-d_6). For ^{13}C spectra, chemical shifts were referenced to the solvent peak at 77.0 ppm in $CDCl_3$ and to the peak at 39.7 ppm in DMSO-d_6. ^{1}H NMR binding studies were carried out on a Varian INOVA 500NB (^{1}H, 500 MHz) or Varian INOVA 750 (^{1}H, 750 MHz) spectrometer at 23 ± 0.2 °C. Dynamic ^{1}H NMR studies were performed at 500 MHz, unless specified otherwise. IR spectra were obtained on a Mattson Galaxy series FTIR-5000 spectrometer, and UV spectra were recorded on a Shimadzu UV160U spectrophotometer. Mass spectra were obtained on Varian MAT CH-5 (EI), Varian MAT 731 (EI), Micromass 70-SE-4F (EI, FAB), and Micromass ZAB-SE (FAB) instruments in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, Urbana-Champaign. X-ray analysis data were collected on an Enraf-Nonius CAD4 or Bruker ACX diffractometer in the Materials Characterization Laboratory, University

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

of Illinois. Elemental analyses were also performed at the University of Illinois School of Chemical Sciences.

***N,N′*-Di-2-pyridylurea (1)**. A solution of triphosgene (940 mg, 3.20 mmol) in 10 mL of methylene chloride was added dropwise over 1 h to a solution of 2-aminopyridine (1.50 g, 15.9 mmol) and 4-(dimethylamino)pyridine (DMAP) (2.32 g, 19.0 mmol) in 15 mL of methylene chloride. The resulting solution was stirred at room temperature for 27 h or until no starting material remained by TLC. Nitrogen was bubbled through the reaction mixture to displace any unreacted phosgene, and solvent was removed in vacuo. The crude product was purified by column chromatography (R_f = 0.59, ethyl acetate) and recrystallized from ethyl acetate to provide 1.30 g (76%) of the product as white needles. Crystals suitable for X-ray crystallographic analysis were obtained from methanol by slow evaporation. Details of crystal structure data and analysis were reported previously.[9] mp 175−176 °C (lit.[12] mp 175−176 °C); ^{1}H NMR (DMSO-d_6) δ 10.58 (s, 2H, NH), 8.27 (d, J = 5.2, 2H, H-6), 7.68−7.78 (m, 4H, H-3, H-4), 7.03 (m, 2H, H-5); ^{1}H NMR ($CDCl_3$, 23 mM, 50 °C) δ 10.14 (br s, 2H, NH), 8.38 (d, J = 4.9, 2H, H-6), 7.68 (m, 2H, H-4), 7.55 (br s, 2H, H-3), 7.00 (m, 2H, H-5); ^{13}C NMR δ 153.63, 152.47, 147.15, 138.31, 118.18, 113.12; IR (KBr, cm^{-1}) 3223 (NH), 3142 (NH), 1698 (C═O); UV λ_{max} (chloroform, nm) 280, 250. Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.70; N, 26.15. Found: C, 61.61; H, 4.71; N, 26.18.

2,7-Dipentanoylamido-1,8-naphthyridine (2). A mixture of diaminonaphthyridine **13** (1.18 g, 7.38 mmol), valeric anhydride (15 mL), and triethylamine (1.80 mL, 12.9 mmol) was heated at 100 °C for 24 h or until no starting material remained by TLC. The resulting mixture was cooled to room temperature, and excess valeric anhydride was removed by kugelrohr distillation. The crude material was dissolved in 100 mL of methylene chloride and washed twice with 40 mL of water, twice with 40 mL of a saturated aqueous solution of sodium bicarbonate, and once with 30 mL of water. The organic solution was dried over sodium sulfate, filtered, and solvent was removed in vacuo. The crude product was purified by column chromatography (R_f = 0.80, 50% ethyl acetate, 50% methylene chloride) and recrystallized twice from ethyl acetate to give 640 mg (30%) of **2** as large white plates: mp 216−217 °C; ^{1}H NMR δ 9.25 (s, 2H, NH), 8.45 (d, J = 8.8, 2H, H-4, H-5), 8.06 (d, J = 8.8, 2H, H-3, H-6), 2.43 (t, J = 7.4, 4H, CH_2-$CH_2CH_2CH_3$), 1.65 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.32 (m, 4H, $CH_2CH_2CH_2CH_3$), 0.88 (t, J = 7.5, 6H, CH_3); ^{13}C NMR δ 172.64, 154.09, 153.40, 138.99, 118.17, 113.58, 37.54, 27.23, 22.20, 13.70; MS (EI, 70 eV) m/z 328 (M^+, 5.3), 299 (32.5), 160 (100); HRMS calcd for $C_{18}H_{24}N_4O_2$, 328.1899; found, 328.1900. Anal. Calcd for $C_{18}H_{24}N_4O_2$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.95; H, 7.22; N, 17.11.

***N*-Butyl-*N′*-(1,8-naphthyridin-2-yl)urea (3)**. A solution of 2-amino-1,8-naphthyridine (1.00 g, 6.90 mmol) and butylisocyanate (800 μL, 7.20 mmol) in 60 mL of THF was heated at reflux for 15 h or until no starting material remained by TLC. The suspension was cooled to room temperature, and the solid that formed was collected by vacuum filtration and recrystallized twice from methanol to give 1.05 g (68%) of the title compound as yellow prisms. Crystals suitable for X-ray crystallographic analysis were obtained from methanol by slow evaporation. Details of crystal structure data and analysis are provided as Supporting Information. mp 196−197 °C; ^{1}H NMR (DMSO-d_6) δ 9.91 (s, 1H, NH adjacent to heterocycle), 9.54 (s, 1H, butyl NH), 8.86 (dd, $J_{6,7}$ = 4.4, $J_{5,7}$ = 1.8, 1H, H-7), 8.24−8.27 (m, 2H, H-4, H-5), 7.42 (dd, $J_{5,6}$ = 8.0, $J_{6,7}$ = 4.4, 1H, H-6), 7.33 (d, $J_{3,4}$ = 8.8, 1H, H-3), 3.27 (t, J = 7.3, 2H, $CH_2CH_2CH_2CH_3$), 1.51 (m, 2H, $CH_2CH_2CH_2$-CH_3), 1.38 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.91 (t, J = 7.3, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 155.70, 155.00, 154.36, 153.48, 139.73, 137.43, 120.63, 118.92, 114.80, 32.12, 31.14, 20.10, 14.10; IR (Nujol, cm^{-1}) 3220 (NH), 3125 (NH), 1690 (C═O). Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.92; H, 6.60; N, 22.93. Found: C, 63.94; H, 6.80; N, 23.03.

***N*-Butyl-*N′*-(4-methylpyridin-2-yl)urea (4)**. A mixture of 2-amino-4-methylpyridine (5.00 g, 46.3 mmol) and butylisocyanate (6.80 mL, 60.4 mmol) in 125 mL of THF was heated at reflux for 24 h or until no starting material remained by TLC. The resulting mixture was cooled to room temperature, and solvent and excess isocyanate were removed in vacuo. The oily material obtained was triturated with low-boiling petroleum ether, which prompted precipitation of the product. The solid was collected by vacuum filtration, purified by column chromatography (R_f = 0.54, 10% hexane, 90% ethyl acetate) and recrystallized from petroleum ether to give 7.80 g (81%) of the title compound as white plates: mp 70−71 °C; ^{1}H NMR (DMSO-d_6) δ 9.07 (s, 1H, NH), 8.30 (s, 1H, butyl NH), 7.99 (d, J = 5.0, 1H, H-6), 7.08 (s, 1H, H-3), 6.72 (d, J = 5.0, 1H, H-5), 3.12 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.21 (s, 3H, Ar−CH_3), 1.43 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.29 (m, 2H, $CH_2CH_2CH_2$-CH_3), 0.87 (t, J = 7.3, 3H, CH_3); ^{13}C NMR (CD_3CN) δ 156.84, 154.86, 150.79, 146.79, 119.04, 112.53, 39.98, 32.91, 21.18, 20.85, 14.08. Anal. Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.63; H, 8.22; N, 20.47.

2-Pentanoylamido-1,8-naphthyridine (5). A mixture of 2-aminonaphthyridine (1.10 g, 7.90 mmol), valeric anhydride (25 mL), and triethylamine (1 mL) was heated at 100 °C for 74 h or until no starting material remained by TLC (R_f = 0.44, 5% methanol/methylene chloride). Excess valeric anhydride was removed by kugelrohr distillation, and the resulting residue was dissolved in 5% methanol/95% methylene chloride and passed through a short plug of silica. Solvent was removed in vacuo, and the crude product was recrystallized twice from ethyl acetate to give 680 mg (45%) of the title compound as a cotton-like solid: mp 148−150 °C; ^{1}H NMR (DMSO-d_6) δ 11.06 (s, 1H, NH), 8.96 (dd, $J_{6,7}$ = 4.3, $J_{5,7}$ = 1.9, 1H, H-7), 8.40 (m, 2H, H-3, H-4), 8.34 (dd, $J_{5,6}$ = 8.0, $J_{5,7}$ = 1.9, 1H, H-5), 7.48 (dd, $J_{5,6}$ = 8.0, $J_{6,7}$ = 4.3, H-6), 2.45 (t, J = 7.3, 2H, $CH_2CH_2CH_2CH_3$), 1.57 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.32 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.88 (t, J = 7.3, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 173.00, 154.82, 154.07, 153.65, 139.40, 136.55, 120.72, 120.53, 115.67, 37.47, 27.22, 22.17, 13.66. Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.12; H, 6.67; N, 18.55.

Bis-2,7-(3-(3,4,5-tridodecyloxyphenyl)uryl)-1,8-naphthyridine (6). A solution of azide **20** (754 mg, 1.08 mmol) in 10 mL of toluene was heated at 90−110 °C for 1 h. The resulting solution was cooled to room temperature, and solvent was removed in vacuo. The crude isocyanate **21** was used in the next step without further purification: ^{1}H NMR δ 6.29 (s, 2H, H-2, H-6), 3.92 (m, 6H, OCH_2), 2.77 (m, 2H, OCH_2CH_2-4), 1.81 (m, 4H, OCH_2CH_2-3,5), 1.47 (m, 6H, CH_2), 1.28 (m, 48H, CH_2), 0.90 (m, 9H, CH_3); IR (Nujol, cm^{-1}) 2263 (N═C═O). A mixture of isocyanate **21** (720 mg, 1.07 mmol) and naphthyridine **13** (67 mg, 0.51 mmol) in 250 μL of *N*,*N*-dimethylformamide (DMF) and triethylamine was heated at 80 °C overnight. The resulting solution was cooled to room temperature, and solvent was removed in vacuo. The crude product was purified by radial chromatography (0−10% gradient of methanol/methylene chloride) to give 275 mg (34% yield for the two steps) of **6** as a yellow powder: mp 223 °C (dec); TLC (R_f = 0.20, 10% methanol, 90% methylene chloride); ^{1}H NMR ($CDCl_3$, 15 mM) δ 12.50 (s, 2H, NH-1), 9.81 (s, 2H, NH-2), 7.95 (d, J = 7.9, 2H, H-4, H-5), 7.08 (d, J = 7.9, 2H, H-3, H-6), 6.89 (s, 4H, H-2′, H-6′), 3.92 (t, J = 6.3, 4H, OCH_2-4′), 3.66 (t, J = 5.5, 8H, OCH_2-3′,5′), 1.70 (m, 12H, OCH_2CH_2-3′,4′,5′), 1.49 (m, 4H, $OCH_2CH_2CH_2$-4′), 1.30 (m, 104H, CH_2), 0.82 (m, 18H, CH_3); ^{13}C NMR δ 155.06, 153.55, 153.32, 152.12, 138.54, 134.47, 133.28, 114.52, 119.92, 98.38, 73.44, 68.45, 31.97, 31.92, 30.58, 29.91, 19.88, 29.87, 29.86, 29.78, 29.72, 29.65, 29.50, 29.45, 29.40, 26.30, 26.19, 22.70, 22.68, 14.08; IR (KBr, cm^{-1}) 3220 (NH), 3142 (NH), 1690 (C═O). Anal. Calcd for $C_{99}H_{162}N_6O_8$: C, 75.07; H, 10.85; N, 5.59. Found: C, 75.07; H, 10.82; N, 5.77.

***N,N′*-Di-((5,7-dipropyl-(1,8-naphthyridin))-2-yl)urea (7)**. A solution of triphosgene (51 mg, 0.17 mmol) in 10 mL of methylene chloride was added dropwise over 1 h to a solution of aminonaphthyridine **25** (200 mg, 0.87 mmol) and DMAP (127 mg, 1.04 mmol) in 15 mL of methylene chloride. The resulting mixture was stirred at room temperature for 24 h or until no starting material remained by TLC. Nitrogen was bubbled through the reaction mixture to displace any unreacted phosgene, and solvent was removed in vacuo. The crude product was purified by column chromatography (R_f = 0.41, 5% methanol, 95% methylene chloride) and recrystallized from ethyl acetate to give 67 mg (32%) of the title compound as a white solid: mp 239−241 °C; ^{1}H NMR (DMSO-d_6) δ 11.32 (s, 2H, NH), 8.56 (d, J = 9.1, 2H, H-4), 7.92 (br s, 2H, H-3), 7.25 (s, 2H, H-6), 3.00 (t, J = 7.6, 4H, CH_2), 2.88 (t, J = 7.3, 4H, CH_2), 1.81 (m, 4H, CH_2), 1.67 (m, 4H, CH_2), 0.95 (m, 12H, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.63, 154.34, 153.68, 152.23, 149.70, 136.01, 120.39, 116.88, 113.32, 40.24, 32.68,

23.22, 22.34, 13.82, 13.78. Anal. Calcd for $C_{29}H_{26}N_6O$: C, 71.86; H, 7.49; N, 17.35. Found: C, 71.61; H, 7.36; N, 17.20.

2-Acetamido-7-hydroxy-1,8-naphthyridine (11). A suspension of 2-amino-7-hydroxy-1,8-naphthyridine (**10**)[15] (30.0 g, 93.2 mmol) in 300 mL of acetic anhydride was heated at reflux for 2.5 h. The resulting mixture was cooled to room temperature, and the precipitate was collected by vacuum filtration, washed with diethyl ether, and air-dried to give 32 g (85%) of the title compound as a yellow powder. The product was used in subsequent reactions without further purification: sublimes at ~300 °C; ^{1}H NMR (DMSO-d_6) δ 11.90 (s, 1H, naphthyridinone NH), 10.50 (s, 1H, NH), 8.02 (d, J = 8.4, 1H, H-4), 7.90 (d, J = 8.4, 1H, H-3), 7.82 (d, J = 9.2, 1H, H-5), 6.40 (d, J = 9.2, 1H, H-6), 2.12 (s, 3H, CH_3); ^{13}C NMR (sample was insufficiently soluble to obtain a ^{13}C NMR spectrum); MS (EI, 70 eV) m/z 203 (M^+, 42), 161 (100), 133 (31), 43 (25); HRMS calcd for $C_{10}H_9N_3O$, 203.0695; found, 203.0694.

2-Acetamido-7-chloro-1,8-naphthyridine (12). A mixture of naphthyridine **11** (20.00 g, 98.5 mmol) and $POCl_3$ (350 mL) was heated at 90−95 °C for 1.5 h. The resulting solution was cooled to room temperature, and excess $POCl_3$ was removed by kugelrohr distillation. The residue was dissolved in ice water, and the solution was made basic (pH = 8) with concentrated ammonium hydroxide, which prompted formation of a brownish green precipitate. The solid was collected by vacuum filtration, air-dried, and continuously extracted (Soxhlet extraction) with chloroform for 12 h. Solvent was removed in vacuo, and the crude product was purified by column chromatography (R_f = 0.59, 10% methanol, 90% methylene chloride) to give 13 g (60%) of the product as golden needles. A sample for elemental analysis was recrystallized from ethyl acetate: mp 250−252 °C; ^{1}H NMR (DMSO-d_6) 11.13 (s, 1H, NH), 8.40 (m, 3H, H-3, H-4, H-5), 7.54 (d, J = 8.5, 1H, H-6), 2.16 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 170.41, 155.13, 154.18, 152.76, 140.42, 139.66, 121.46, 118.99, 115.13, 24.25. Anal. Calcd for $C_{10}H_8N_3ClO$: C, 54.19; H, 3.46; N, 18.96. Found: C, 54.07; H, 3.64; N, 18.88.

2,7-Diamino-1,8-naphthyridine (13). Method A. A mixture of 2,7-dichloro-1,8-naphthyridine[15] (500 mg, 2.53 mmol) and concentrated ammonium hydroxide (50 mL) was heated at 180 °C in a sealed tube for 24 h. The mixture was cooled to room temperature, which prompted precipitation of the product. The resulting solid was collected by vacuum filtration and washed on the filter paper with cold methanol to give 283 mg (70%) of the title compound, which was used without further purification.

Method B. A suspension of **12** (1.50 g, 6.77 mmol) in approximately 150 mL of ethanolic ammonia (saturated) was heated in a steel bomb at 180 °C for 24 h. The resulting solution was concentrated to one-half of its original volume and cooled to prompt precipitation of the product (some solid formed prior to cooling). The crude product was collected by vacuum filtration and washed on the filter paper with cold ethanol. The solid was triturated with hot water, filtered again, and dried to give 800 mg of product (74%), which was determined to be >95% pure by ^{1}H NMR spectroscopy and was used in subsequent steps without further purification: mp 270−272 °C; ^{1}H NMR (DMSO-d_6) δ 7.79 (d, J = 8.7, 2H, H-4, H-5), 7.48 (s, 4H, NH_2), 6.54 (d, J = 8.7, 2H, H-3, H-6); ^{13}C NMR (DMSO-d_6) δ 159.38, 151.71, 138.91, 108.40, 107.23; MS (EI, 70 eV) 160 (M^+, 100); HRMS calcd for $C_8H_8N_4$, 160.0749; found, 160.0746.

(2-Methoxyethyl)-2-aminoisonicotinoate. A mixture of 2-aminoisonicotinic acid (4.00 g, 29.0 mmol) and concentrated sulfuric acid (5 mL) in 80 mL of 2-methoxyethanol was heated at 120−140 °C for 48 h. The resulting mixture was cooled to room temperature, and solvent was removed by kugelrohr distillation to give an oily, orange residue. The residue was dissolved in 15 mL of water, and the aqueous solution was made basic (pH = 8) with concentrated ammonium hydroxide. The aqueous solution was extracted four times with 35 mL of chloroform, and the combined organic layer was dried over sodium sulfate. Solvent was removed in vacuo to give an amber colored oil, which was triturated with 15 mL of diethyl ether and cooled to prompt precipitation. The solid that formed was collected by vacuum filtration and purified by column chromatography (R_f = 0.59, 10% methanol, 90% chloroform) to give 2.70 g (49%) of the product as light yellow plates: mp 75−77 °C; ^{1}H NMR δ 8.11 (d, J = 5.2, 1H, H-6), 7.11 (d, J = 5.2, 1H, H-5), 7.04 (s, 1H, H-3), 4.78 (s, 2H, NH_2), 4.41 (t, J = 4.5, 2H, CH_2), 3.66 (t, J = 4.5, 2H, CH_2), 3.36 (s, 3H, CH_3); ^{13}C NMR 165.48, 159.10, 148.90, 138.95, 112.88, 108.45, 76.66, 70.29, 64.47. Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.01; H, 6.08; N, 14.08.

***N,N′*-Di-4-(2-methoxyethoxycarbonyl)pyridin-2-ylurea (14)**. A solution of triphosgene (368 mg, 1.24 mmol) in 10 mL of methylene chloride was added dropwise over 1 h to a solution of (2-methoxyethyl)-2-aminoisonicotinoate (1.50 g, 6.25 mmol) and DMAP (91 mg, 7.45 mmol) in 15 mL of methylene chloride. The resulting solution was stirred at room temperature for 41 h or until no starting material remained by TLC. Nitrogen was bubbled through the reaction mixture to displace any unreacted phosgene, and solvent was removed in vacuo. The crude product was purified by column chromatography (R_f = 0.51, 10% methanol, 90% chloroform) and recrystallized from ethyl acetate to give 1.25 g (79%) of the title compound as a voluminous white solid: mp 132−133 °C; ^{1}H NMR (DMSO-d_6) δ 10.54 (s, 2H, NH), 8.49 (d, J = 5.1, 2H, H-6), 8.32 (s, 2H, H-3), 7.48 (dd, $J_{5,6}$ = 5.1, $J_{3,5}$ = 1.1, 2H, H-5), 4.36 (d, J = 4.8, 4H, CH_2), 3.66 (t, J = 4.8, 4H, CH_2), the CH_3 peak at 2.48 ppm was hidden by the DMSO peak; ^{13}C NMR δ 164.44, 153.14, 151.58, 148.67, 138.97, 116.99, 111.57, 69.61, 64.62, 58.17; IR (Nujol, cm^{-1}) 3383 (NH), 1725 (C=O), 1695 (C=O); UV λ_{max} (chloroform, nm) 313. Anal. Calcd for $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.30; N, 13.39. Found: C, 54.16; H, 5.27; N, 13.31.

Bis-(2,6-(3-(butyl))uryl)pyridine (16). A mixture of 2,6-diaminopyridine (**24**) (2.00 g, 18.4 mmol) and butylisocyanate (5.00 mL, 44.3 mmol) in 100 mL of THF was heated at reflux for 18 h or until no starting material remained by TLC. The resulting suspension was cooled to room temperature, and the white solid that formed was collected by vacuum filtration and washed with diethyl ether. The supernatant was concentrated and cooled to prompt precipitation of additional product, which was also collected by vacuum filtration. The combined precipitate was recrystallized from methanol to give 4.66 g (83%) of the title compound as clear prisms. The crystals obtained were suitable for X-ray crystallographic analysis. Details of crystal structure data and analysis are provided as Supporting Information. mp 201−203 °C; ^{1}H NMR (DMSO-d_6) δ 8.84 (s, 2H, NH), 7.50 (t, 2H, butyl-NH), 7.47 (t, J = 8.0, 1H, H-4), 6.92 (d, J = 8.0, 2H, H-3, H-5), 3.10 (m, 4H, CH_2CH$_2$CH$_2$CH$_3$), 1.42 (m, 4H, CH$_2$$CH_2CH_2CH_3$), 1.28 (m, 4H, CH$_2CH_2$$CH_2CH_3$), 0.87 (t, 6H, J = 7.4, CH_3); ^{13}C NMR (DMSO-d_6) δ 154.54, 151.31, 139.75, 103.41, 38.72, 31.87, 19.61, 13.69. Anal. Calcd for $C_{15}H_{25}N_5O_2$: C, 58.61; H, 8.20; N, 22.78. Found: C, 58.43; H, 8.23; N, 22.87.

Bis-(2,7-(3-(butyl))uryl)-1,8-naphthyridine (17). A solution of diaminonaphthyridine **13** (277 mg, 1.91 mmol) and butylisocyanate (450 μL, 4.0 mmol) in 30 mL of THF was heated at reflux for 12 h or until no starting material remained by TLC. The resulting solution was cooled to room temperature, which prompted precipitation of the product. The white solid that formed was collected by vacuum filtration and recrystallized from methanol to give 290 mg (51%) of **17** as a voluminous, white solid. Crystals suitable for X-ray crystallographic analysis were obtained from methanol by slow evaporation. Details of crystal structure data and analysis were reported previously.[9] mp >260 °C (dec); ^{1}H NMR (DMSO-d_6) δ 9.79 (s, 2H, NH), 9.38 (s, 2H, NH), 8.07 (d, 2H, J = 8.5, 2H, H-4, H-5), 7.13 (d, J = 8.5, 2H, H-3, H-6), 3.30 (alkyl peaks hidden by H_2O), 1.50 (m, 4H, CH$_2$$CH_2CH_2$-CH$_3$), 1.35 (m, 4H, CH$_2CH_2$$CH_2CH_3$), 0.90 (t, J = 7.5, 6H, CH_3); ^{13}C NMR (sample was insufficiently soluble to obtain a ^{13}C NMR spectrum); Anal.Calcd for $C_{18}H_{26}N_6O_2$: C, 60.32; H, 7.31; N, 23.45. Found: C, 59.94; H, 7.41; N, 23.05.

3,4,5-Trisdodecyloxybenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester (19). A mixture of 3,4,5-tridodecyloxybenzoic acid (**18**) (1.50 g, 2.23 mmol), *N*-hydroxysuccinimide (259 mg, 2.25 mmol), and dicyclohexylcarbodiimide (DCC) (515 mg, 2.50 mmol) in 20 mL of dioxane was stirred at room temperature for 24 h or until no starting material remained by TLC (R_f of product = 0.50, 100% methylene chloride). The suspension was filtered through a fine frit to remove dicyclohexylurea (DCU), and solvent was removed in vacuo. The resulting solid was redissolved in 150 mL of methylene chloride and filtered again to remove additional DCU. Solvent was removed in vacuo, and the crude product was recrystallized from 2-propanol to give 1.72 g (49%) of **19**

as a white powder: mp 56−58 °C; ^{1}H NMR δ 7.34 (s, 2H, H-2, H-6), 4.07 (t, J = 6.6, 2H, OCH_2-4), 4.02 (t, J = 6.3, 4H, OCH_2-3,5), 2.92 (s, 4H, succinate CH_2), 1.83 (m, 4H, OCH_2CH_2-3,5), 1.74 (m, 2H, OCH_2CH_2-4), 1.47 (m, 6H, $OCH_2CH_2CH_2$-3,4,5), 1.28 (m, 48H, CH_2), 0.90 (t, 9H, CH_3); ^{13}C NMR δ 169.33, 161.67, 153.05, 144.08, 119.02, 108.85, 73.63, 69.24, 31.91, 30.28, 29.73, 29.71, 29.68, 29.65, 29.61, 29.53, 29.38, 29.35, 29.19, 26.03, 25.99, 25.66, 22.68, 14.11; IR (KBr, cm^{-1}) 2920 (C−H), 2851 (C−H), 1764 (C═O), 1738 (C═O). Anal. Calcd for $C_{47}H_{81}NO_7$: C, 73.09; H, 10.58; N, 1.81. Found: C, 73.26; H, 10.66; N, 1.62.

3,4,5-Tridodecyloxybenzoyl Azide (20). A solution of sodium azide (261 mg, 2.48 mmol) in water (6 mL) was added to activated ester **19** (1.23 g, 1.60 mmol) in 40 mL of acetone and 8 mL of THF. The resulting solution was stirred for 12 h or until no starting material remained by TLC. The solvent was concentrated to approximately 15−20 mL (*no heating*), and cold water was added to the suspension. The solid that formed was collected by vacuum filtration, washed with cold water, and dried in vacuo to give 1.05 g (94%) of the title compound as a white powder: ^{1}H NMR δ 7.19 (s, 2H, H-2, H-6), 3.99 (t, J = 6.6, 2H, OCH_2-4), 3.96 (t, J = 6.4, 4H, OCH_2-3,5), 1.77 (m, 4H, OCH_2CH_2-3,5), 1.69 (m, 2H, OCH_2CH_2-4), 1.42 (m, 6H, CH_2), 1.22 (m, 50H, CH_2), 0.83 (m, 9H, CH_3); ^{13}C NMR δ 171.07, 152.95, 143.76, 125.06, 107.76, 73.59, 69.20, 31.91, 30.30, 29.72, 29.69, 29.67, 29.64, 29.61, 29.52, 29.36, 29.22, 26.03, 26.00, 22.67, 14.09; IR (KBr, cm^{-1}) 2152 cm^{-1} (N_3), 1694 (C═O); MS (EI, 70 eV) m/z 699.9 (M^+, 100), 676.6 ($M^+ - N_2$, 55).

2-(3-(3,4,5-Trisdodecyloxyphenyl)uryl-4-methylpyridine (23). 2-Amino-4-methylpyridine (32 mg, 0.30 mmol) was added to a solution of isocyanate **21** (205 mg, 0.30 mmol) in 15 mL of toluene. The resulting solution was heated at reflux for 12 h or until no starting material remained by TLC. The resulting mixture was cooled to room temperature, and solvent was removed in vacuo. The crude product was purified by column chromatography (R_f = 0.22, 5% methanol, 95% methylene chloride) to give 90 mg (32%) of the title compound as a white powder: mp 89−90 °C; ^{1}H NMR ($CDCl_3$, 15 mM) δ 11.74 (s, 1H, NH-1), 8.22 (s, 1H, NH-2), 8.13 (d, J = 5.2, 1H, H-6), 6.87 (s, 2H, H-2′, H-6′), 6.78 (d, J = 5.2, 1H, H-5), 6.67 (s, 1H, H-3), 4.02 (t, J = 6.4, 4H, OCH_2-3′,5′), 3.94 (t, J = 6.6, 2H, OCH_2-4′), 2.34 (s, 3H, Ar−CH_3), 1.82 (m, 4H, OCH_2CH_2-3′,5′), 1.78 (m, 2H, OCH_2CH_2-4′), 1.47 (m, 6H, CH_2), 1.28 (m, 48H, CH_2), 0.89 (m, 9H, CH_3); ^{13}C NMR δ 153.54, 153.18, 153.02, 149.95, 145.64, 134.42, 134.01, 118.63, 112.10, 99.66, 73.49, 69.10, 31.92, 31.91, 30.31, 29.75, 29.73, 29.69, 29.64, 29.43, 29.42, 29.38, 29.35, 26.16, 26.12, 22.67, 21.15, 14.10. Anal. Calcd for $C_{49}H_{85}N_3O_4$: C, 75.43; H, 10.98; N, 5.39. Found: C, 75.21; H, 10.86; N, 5.15.

2-Amino-5,7-dipropyl-1,8-naphthyridine (25). A mixture of 4,6-nonanedione (1.00 g, 6.41 mmol) and 2,6-diaminopyridine (**24**) (638 mg, 5.85 mmol) in approximately 8 mL of phosphoric acid was heated at reflux for 12 h. The resulting mixture was cooled to room temperature, poured over ice, and neutralized with concentrated ammonium hydroxide. The sticky solid that formed was collected by vacuum filtration and washed with cold water. The resulting solid was continuously extracted (Soxhlet extraction) with chloroform and dried over sodium sulfate. Solvent was removed in vacuo, and the crude product was purified by column chromatography (R_f = 0.14, 10% methanol, 90% methlene chloride) and recrystallized from ethyl acetate to give 450 mg (34%) of product as tan/brown needles: mp 144−146 °C; ^{1}H NMR (DMSO-d_6) δ 8.04 (d, J = 8.9, 1H, H-4), 6.86 (s, 1H, H-6), 6.73 (d, J = 8.9, 1H, H-3), 6.60 (s, 2H, NH_2), 2.81 (t, J = 7.5, 2H, CH_2), 2.68 (t, J = 7.5, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 0.88 (m, 6H, CH_3); ^{13}C NMR (DMSO-d_6) δ 163.39, 160.23, 156.65, 148.80, 133.69, 117.22, 113.62, 111.67, 40.16, 32.78, 23.43, 22.15, 13.83; MS (EI, 70 eV) m/z 228.1 (M^+, 10), 214.2 (25), 201.2 (100); HRMS calcd for $C_{14}H_{19}N_3$, 229.1579; Found, 229.1571.

^{1}H NMR Binding Studies. All ^{1}H NMR binding studies were carried out at 23 °C using variable temperature control, unless specified otherwise. $CDCl_3$ used in binding studies was passed through a short plug of dry (flame-dried or dried under vacuum), activated (Brockmann I), basic alumina prior to use. All other deuterated solvents were used as provided without purification or preparation. Volumetric flasks and syringes used in preparing solutions were typically washed with $CDCl_3$ and dried in vacuo prior to use. Samples were prepared from stock solutions, transferred to the NMR tube using a syringe, and diluted accordingly.

Association constants reported are the average of two or more replicate experiments and were obtained by fitting chemical shift data to 1:1 binding isotherms using standard, nonlinear curve-fitting procedures.[18] Binding data, thus obtained, were collected over a 20−80% saturation range for each binding curve. The nonlinear equations used in dilution studies (self-association), as well as titration and 1:1 dilution (complexation) studies, were derived from mass-balance equations and the relationship between the concentrations of free and complexed material and the "weighted" chemical shift under conditions of rapid exchange.[18]

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Supporting Information Available: X-ray crystallographic data for **3** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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