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Synthesis of a Soluble Ureido-Naphthyridine Oligomer that Self-Associates via Eight Contiguous Hydrogen Bonds

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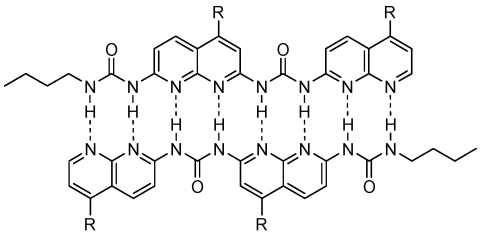
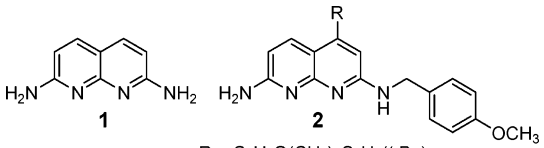
ABSTRACT



3 : R = $C_6H_4O(CH_2)_2C_6H_3(t\text{-}Bu)_2$

An iterative synthetic route to organic-soluble ureido-naphthyridine oligomers has been developed. Use of this protocol allowed synthesis of a short ureido-naphthyridine oligomer, which presents a self-complementary DDAADDAA hydrogen bonding array (D = hydrogen bond donor, A = hydrogen bond acceptor). Strong self-association via eight hydrogen bonds was observed in organic solution.

We recently suggested[1] that oligo- or polymeric ureas of 2,7-diamino-1,8-naphthyridine (**1**) might form either helical folded structures or hydrogen bonded sheets.[2] Model studies on simple substructures showed that intramolecular hydrogen bonds would break to form sheets with between three and six intermolecular hydrogen bonds.[1] Attempts to synthesize longer oligomers or polymers, however, were thwarted by the low solubility of **1** and longer oligoureas derived from it. Given our interest in these compounds as well as the recent use of amides of **1** for supramolecular chemistry,[3−5] there was a clear need for soluble analogues of **1**. Herein we report both the synthesis of **2**, a mono-protected and soluble analogue of **1**, and its conversion to **3**, which can form a linear duplex containing eight hydrogen bonds.



1 **2**

R = $C_6H_4O(CH_2)_2C_6H_3(t\text{-}Bu)_2$

The synthesis of **2** (Scheme 1) began with the amidation of 2,6-diaminopyridine with ethyl 3-(4-methoxyphenyl)-3-oxopropanoate and acid-mediated cyclization to **4**. A service-

(1) (a) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2000**, *122*, 3779. (b) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475.

(2) For selected, sheetlike oligomers not based on amino acids see: (a) Yang, X.; Martinovic, S.; Smith, R. D.; Gong, B. *J. Am. Chem. Soc.* **2003**, *125*, 9932. (b) Gong, H.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 1719. (c) 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. (d) Leung, M.; Mandal, A. B.; Wang, C.-C.; Lee, G.-H.; Peng, S.-M.; Cheng, H.-L.; Her, G.-R.; Chao, I. Lu, H.-F.; Sun, Y.-C.; Shiao, M.-Y.; Chou, P.-T. *J. Am. Chem. Soc.* **2002**, *124*, 4287.

(3) (a) Park, T.; Zimmerman, S. C.; Nakashima, S. *J. Am. Chem. Soc.* **2005**, *127*, 6520. (b) Corbin, P. S.; Lawless, L. J.; Li, Z.; Ma, Y.; Witmer, M. J.; Zimmerman, S. C. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 5099. (c) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710. (d) Park, T.; Mayer, M. F.; Nakashima, S.; Zimmerman, S. C. *Synlett* **2005**, 1435.

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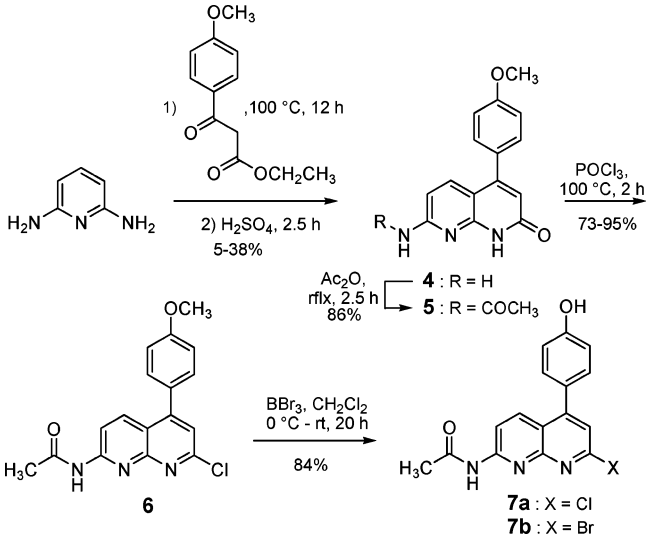
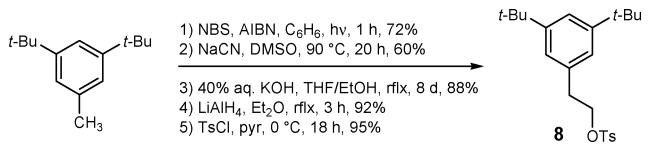
Scheme 1. Synthesis of a Trifunctionalized 1,8-Naphthyridine



able 38% yield of **4** could be obtained on a 68 g scale, but the reaction was somewhat unreliable, with one run giving only a 5% yield. Elaboration of naphthyridone **4** in a manner similar to that reported by Brown[6] provided **6** with three distinct sites for further functionalization. Demethylation of **6** provided phenol **7** in good yield. The product, however, was found to consist of a ca. 1:1 mixture of **7a** and **7b**. Rather than separating the mixture, we carried **7a** and **7b** forward together.

Although in principle any number of solubilizing groups could be readily attached to phenol **7**, including simple linear alkyl halides, we chose to use tosylate **8**. It combined a convenient and distinctive ^{1}H NMR signature with a balance of flexibility and a bulky aromatic substituent that was expected to resist packing. The synthesis of **8**, outlined in Scheme 2, involved a five-step homologation that began with

Scheme 2. Synthesis of a Solubilizing Group



NBS bromination and cyanide displacement. Hydrolysis, reduction, and tosylation afforded **8** in a 33% overall yield.

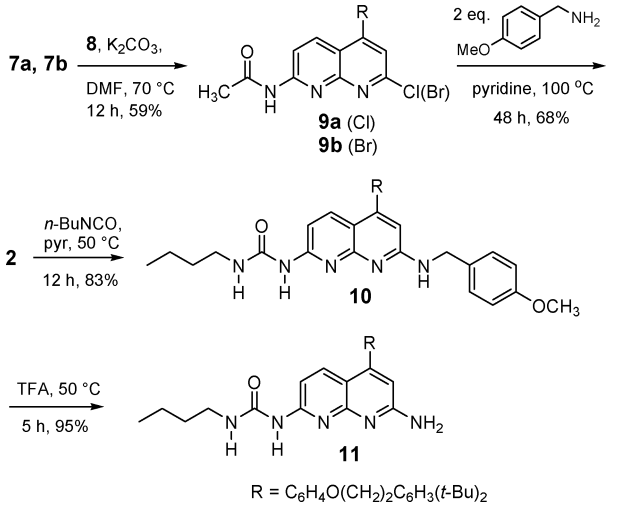
Tosylate **8** and the mixture of **7a** and **7b** were reacted under basic conditions to provide **9a** and **9b** (Scheme 3).

(4) (a) Li, X.-Q.; Feng, D.-J.; Jiang, X.-K.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 8275. (b) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128. (c) Wang, X.-Z.; Li, X.-Q.; Shao, X.-B.; Zhao, X.; Deng, P.; Jiang, X.-K.; Li, Z.-T.; Chen, Y.-Q. *Chem. Eur. J.* **2003**, *9*, 2904.

(5) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 810.

(6) Brown, E. V. *J. Org. Chem.* **1965**, *30*, 1607.

Scheme 3. Synthesis of the Ureido Terminus

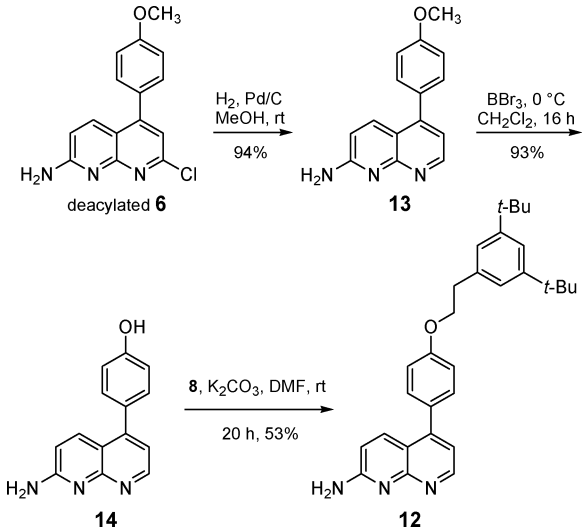


The preparation of monoprotected diaminonaphthyridine **2** was accomplished in a one-pot, two-step process by reaction of the halogenated mixture **9a**/**9b** with *p*-methoxybenzylamine. Thus, nucleophilic deacetylation was followed by nucleophilic aromatic substitution with a second equivalent of *p*-methoxybenzylamine. The bromide reacted more smoothly than the chloride, and as a result, from most preparations of **2** some N-deacetylated **9a** was also isolated.

To prepare **11**, the ureido terminus of target oligomer **3**, **2** was treated with *n*-butylisocyanate, affording the desired urea **10** in 83% yield. The remainder of the product consisted of the regioisomeric urea (8%) and the bis-urea (9%). The *p*-methoxybenzyl group in **10** was readily removed upon treatment with TFA, **11** being isolated in 95% yield.

The synthesis of naphthyridyl terminus **12**, outlined in Scheme 4, began with deacylated **6**, which was obtained as the main byproduct in the synthesis of **6** (vide supra). By

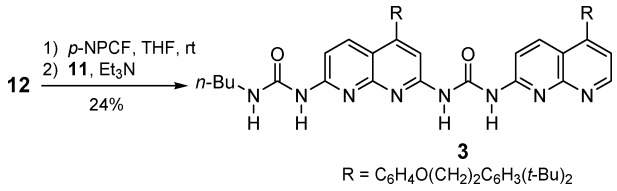
Scheme 4. Synthesis of the Naphthyridyl Terminus



carefully monitoring the reaction, hydrogenolysis of deacylated **6** was accomplished in high yield without reduction of the naphthyridine nucleus. Demethylation of **13** with BBr_3 produced **14**, which was reacted with **8** to provide 2-aminonaphthyridine **12**.

With the ureido (**11**) and the naphthyridyl (**12**) termini in hand, coupling of the two in a urea-forming reaction was investigated. Typically, the formation of an unsymmetrical bis-heteroaryl urea is not trivial.[7] It was found that treatment of **12** with *p*-nitrophenylchloroformate[8] (*p*-NPCF) followed by reaction with **11** did produce a sufficient quantity of compound **3** for study (Scheme 5).

Scheme 5. Coupling of the Ureido and Naphthyridyl Termini



^{1}H NMR was shown to be an excellent method for establishing pairing. Intramolecularly hydrogen bonded pyridyl and naphthyridinyl ureas often exhibit broad NH resonances due to slow conformational dynamics with the non-hydrogen bonded NH groups appearing upfield (typical aryl urea NH resonances δ ~6.4−7.2 ppm).[1] For example, the spectrum of **11** in chloroform-*d* exhibits broad NH resonances whereas the spectrum in DMSO-d_6 is sharp (see Supporting Information). In chloroform-*d*, the spectrum of **3** is very sharp with the aryl urea NH groups resonating downfield at δ 13.22, 13.02, and 11.72 ppm (Figure 1). The

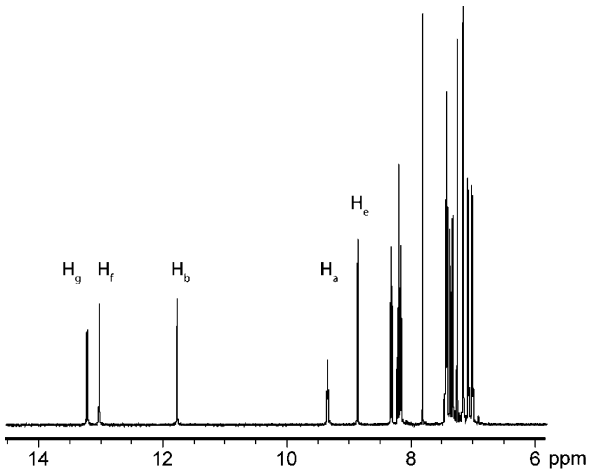


Figure 1. ^{1}H NMR of **3** in $CDCl_3$ showing aromatic region and urea NH protons. See Figure 2 for labeling.

aliphatic urea NH group appears at δ 9.35 ppm, suggesting that the terminal NH group is also paired. Importantly, at room temperature from 50 μM to 50 mM, **13** exhibited NMR spectral shifts that were independent of concentration.

Further evidence for a strong dimer with eight hydrogen bonds came from a difference NOE study, the results of which are summarized in Figure 2. Most notably, a key NOE

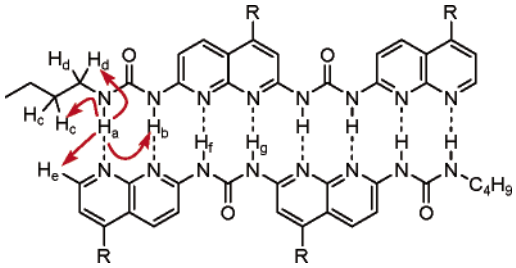
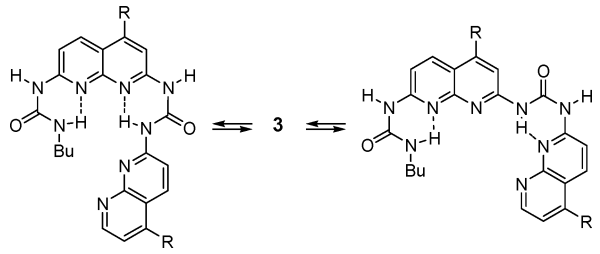


Figure 2. Observed contacts from NOE difference spectra.

was observed between H_a and H_e. None of the singly or doubly folded conformations for **3** place H_a proximal to H_e (Scheme 6). Taken together, the ^{1}H NMR data are consistent with the unfolded, antiparallel dimer $(\mathbf{3})_2$.

Scheme 6. Possible Folded Forms of **3**



To assess the stability of dimer $(\mathbf{3})_2$ NMR dilution experiments were performed in chloroform−DMSO mixtures. From 423 μM to 13.5 mM in 10% (v/v) DMSO-d_6−$CDCl_3$, the ^{1}H NMR spectra of $(\mathbf{3})_2$ were unchanged, allowing a lower limit to be placed on the dimerization constant, $K_{assoc} \geq 4.5 \times 10^5$ M^{-1}. Considering that DMSO is a strongly competitive solvent for hydrogen bonded complexes, this represents quite a stable dimer. However, in 20% (v/v) DMSO-d_6−$CDCl_3$, the self-association was dramatically reduced ($K_{dimer} = 40$ M^{-1}).

Attempts to crystallize **3** were unsuccessful, so its structure and that of dimer $(\mathbf{3})_2$ were examined computationally. As seen in Figure 3a, the monomer is planar but has a very distinctive crescent shape as a result of steric interactions between the urea carbonyl group and the ortho protons on the naphthyridine ring (C═O···H−C). There are three limiting ways in which **3** may dimerize. First, if the planarity

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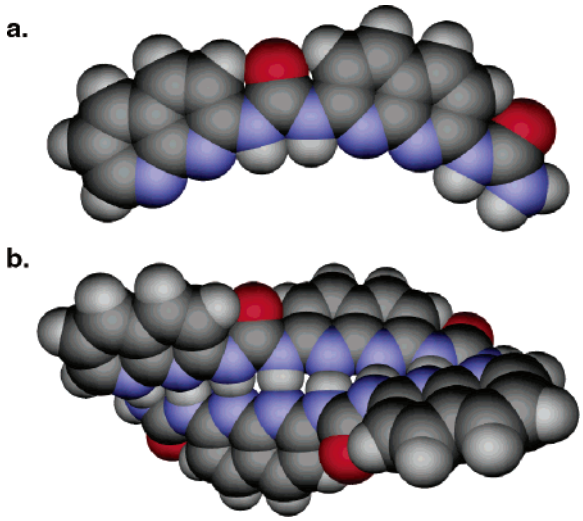

Figure 3. Structure of (a) **3** and (b) $(\mathbf{3})_2$. Minimization using the MMFF force field and equilibrium geometry determined using the HF-STO-3G method. Substituents left off for simiplicity.

is maintained with a shortening of the already close C═O···H−C contact, then the curvature seen in Figure 3a can be reduced or eliminated. Alternatively, four to six central hydrogen bonds may form, leaving the terminal urea and naphthyridine units to stack with little or no hydrogen bonding. Finally, as seen in Figure 3b, the docking of compound **3** with itself leads to an energy-minimized structure containing a substantial end-to-end twist, allowing eight good hydrogen bonds.

Of the numerous abiotic, oligomeric duplexes that form by interstrand hydrogen bonding,[1,2,9] **3** is the second wherein a linear array of donor and acceptor groups pairs with formation of eight hydrogen bonds. It is the first containing the DDAADDAA hydrogen bonding motif, the other, reported by Leung, having the DADADADAD motif (one overhanging donors).[2d] These strands are just two of the 136 possible unique sequences with eight contiguous hydrogen bond donor−acceptor sites. From these 136 possible sequences, 72 unique complexes can be formed, assuming full pairing without mismatches. Of the 72 complexes, eight are homodimers and 64 are heterodimers.

Which arrangements of donor and acceptor groups are best? The $(\mathbf{3})_2$ dimer is considerably stronger than the dimer reported by Leung ($K_{dimer} = 3.4 \times 10^2$ in $CDCl_3$).[2d] It is tempting to attribute some of this difference to the two net attractive secondary interactions present in the $(DDAADDAA)_2$ array as opposed to the $(ADADADAD)_2$ dimer possessing a total of 16 repulsive secondary electrostatic interactions.[10] However, the availability of stable folded structures and geometrical issues such as the curvature in the donor−acceptor array seen in Figure 3a complicate the picture. Indeed, we recently reported that extending a heterocomplex from three to four hydrogen bonds decreased its stability due to a similar curvature of the donor−acceptor array.[11]

In summary, the synthesis of a 2,7-diamino-1,8-naphthyridine subunit containing an organic solubilizing substituent has been developed. This enhanced solubility should increase further the utility of this important module in supramolecular science. As shown herein, it has allowed extension of our previously described ureidonaphthyridine oligomers to a very stable duplex containing eight hydrogen bonds. With **2**, **11**, and **12** in hand, a number of iterative syntheses can be envisioned providing access to custom lengths of DDAA hydrogen bonding arrays.

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Supporting Information Available: Detailed descriptions of all experimental procedures along with characterization data and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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