Complexation-Induced Unfolding of Heterocyclic Ureas: A Hydrogen-Bonded, Sheetlike Heterodimer

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Considerable effort has focused recently on the development of abiotic oligomers that form β-sheet[1] and helical structures.[2] The prospect of a discrete alteration in the secondary structure of abiotic oligomers, for example, from a helix to a β-sheet, with changes in concentration or environment is appealing and may lead to artificial peptides or proteins with "switchable" functions[3] as well as to useful, responsive materials.[4] Our longstanding interest in multiply H-bonded complexes[5] has led us to consider the use of novel H-bonding switch elements in the design of such adaptive oligomers. Thus, we have studied ureas **1**−**3** and report herein a concentration-dependent unfolding process to form a robust, sheetlike heterodimer, **2·3**. The modules described are useful building blocks for self-assembly, and the study of ureas **1**−**3** is a first step toward the development of naphthyridinyl urea oligomers, which have the potential to exist as β-sheet (unfolded) and helical (folded) structures.

The synthesis of **1**−**3** was straightforward. In summary, bis-ureido naphthyridines **1** and **2** were prepared by heating 2,7-diamino-1,8-naphthyridine[5a] with butylisocyanate and 3,4,5-tridodecyloxyphenyl isocyanate, respectively.[6] To prepare the chloroform-soluble naphthyridinyl urea **3**, 2-amino-5,7-dipropyl-1,8-naphthyridine, which was available by a Knorr condensation of 2,6-diaminopyridine and 4,6-nonanedione,[7] was treated with triphosgene and DMAP.

The solid-state structure of **1** was investigated by X-ray crystallographic analysis. As shown in Figure 1A, **1** was folded with two intramolecular H bonds between the peripheral NH groups and the naphthyridine nitrogen atoms. These structures were further organized into H-bonded ribbons by $R_2^2(8)$ dimerization[8] of the unpaired, amide-like sites in **1′**. A similar folded

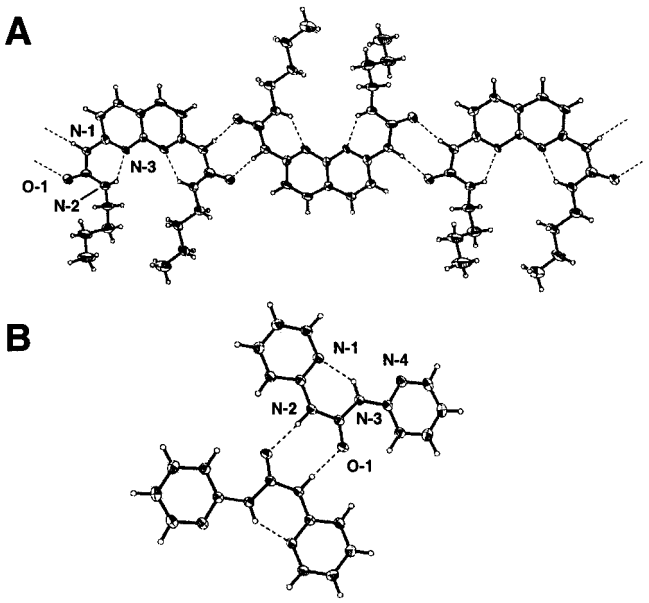

Figure 1. Solid-state structure of **1** (A) and *N*,*N*′-di-2-pyridyl urea (B) showing intramolecular folding and intermolecular $R_2^2(8)$ dimerization.

structure was inferred from IR and ^{1}H NMR studies of analogue **2** in chloroform. Thus, in IR solution spectra of **2** there were two NH bands, a concentration independent, H-bonded stretch at 3217 cm^{-1} and a concentration dependent, non-H-bonded stretch at 3428 cm^{-1}.[9] The intensity of the latter signal decreased at higher concentrations with concomitant increase of a new H-bonded NH stretch at 3150 cm^{-1}. In the IR spectrum (KBr) of urea **1**, there were two bands for H-bonded NH groups at 3220 and 3142 cm^{-1}.

In the ^{1}H NMR spectrum of **2** at 28 μM in chloroform-*d* ($CDCl_3$), a concentration at which **2** was monomeric, two NH resonances were observed at 12.4 and 7.15 ppm. Examination of non-hydrogen-bonded aryl ureas revealed NH signals in a region from ∼6.4 to 7.2 ppm in $CDCl_3$.[10] As the concentration of **2** was increased from 28 μM to 35 mM the chemical shift of the downfield NH resonance changed only slightly (∼ 0.3 ppm), while the other NH signal shifted downfield by ∼3 ppm (Figure 2A, at 6 mM). The chemical shift data for the latter signal fit reasonably well to a 1:1 binding isotherm and gave an association constant (K_{assoc}) of approximately 95 M^{-1}.[11] Combined with the observation of a strong NOE from H-2 to H-3 (Scheme 1), all NMR and IR data were consistent with folded structure **2′** at all concentrations, with noncooperative, oligomeric association as shown in $(\mathbf{2'})_n$, rather than dimerization as in **2·2**.

By analogy to solution studies of *N*-2-pyridyl ureas and thioureas,[9] it was anticipated that **3** would exist in a dynamic equilibrium between two degenerate, intramolecularly hydrogen-bonded forms (i.e., **3′**). Although a crystal structure of **3** was not obtained, the X-ray crystal structure of a closely related analogue, *N*,*N*′-di-2-pyridyl urea, confirmed the presence of an intramolecular H bond in the solid state (Figure 1B). As in **1**, the unpaired, amide-like sites dimerized.[12]

(1) See, e.g.: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (b) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287−296. (c) Kelly, J. W., Ed., *Bioorg. Med. Chem.* **1999**, 7, issue 1 (Symposium-in-Print). (d) Gong, B.; Yan, Y.; Zeng, H.; Skrzypczak-Jankunn, E.; Kim, Y. W.; Zhu, J.; Ickes, H. *J. Am. Chem. Soc.* **1999**, *121*, 5607−5608.

(2) See, e.g.: (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.

(3) To our knowledge, only peptides have been reported to be capable of controlled changes between two discrete secondary structures: (a) Schenck, H. L.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 12487−12494. (b) Mutter, M.; Gassmann, R.; Buttkus, U.; Altmann, K.-H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1514−1516.

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

(5) For robust, multiply H-bonded complexes see, e.g.: (a) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710−9711. (b) Sessler, J. L.; Wang, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1726−1729. (c) Lüning, U.; Kuhl, C. *Tetrahedron Lett.* **1998**, *39*, 5735−5738. (d) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601−1604. (e) Zimmerman, S. C.; Murray, T. J. In *Computational Approaches in Supramolecular Chemistry*; NATO ASI Series, Vol. 426; Wipff, G., Ed.; Kluwer: Amsterdam, 1994; pp 109−115.

(6) All compounds described herein gave correct elemental analyses and had spectral properties consistent with the assigned structures.

(7) Bernstein, J.; Stearns, B.; Shaw, E.; Lott, W. A. *J. Am. Chem. Soc.* **1947**, *69*, 1151−1158.

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

(9) For IR and NMR studies of: (a) *N*-methyl-*N*′-2-pyridyl urea: Sudha, L. V.; Sathyanarayana, D. N. *J. Mol. Struct.* **1984**, *125*, 89−96. (b) *N*,*N*′-di-2-pyridyl thiourea: Sudha, L. V.; Sathyanarayana, D. N.; Bharati, S. N. *Magn. Reson. Chem.* **1987**, *25*, 474−479. (c) *N*,*N*′-di-2-(6-methylpyridyl) urea: Vdovichemnko, A.; Chervinskii, A. Y.; Galat, V. F.; Kaplan, L. *Sov. Prog. Chem.* **1990**, *46*, 108−110.

(10) For example, *N*,*N*′-(2-methylphenyl)urea, δ (NH) ≈ 6.4 ppm; *N*-butyl-*N*′-2-(1,8-naphthyridinyl)urea, δ (NH) ≈ 7.2 ppm.

(11) Wilcox, C. S. *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Durr, H., Eds.; VCH: New York, 1991, 123−143.

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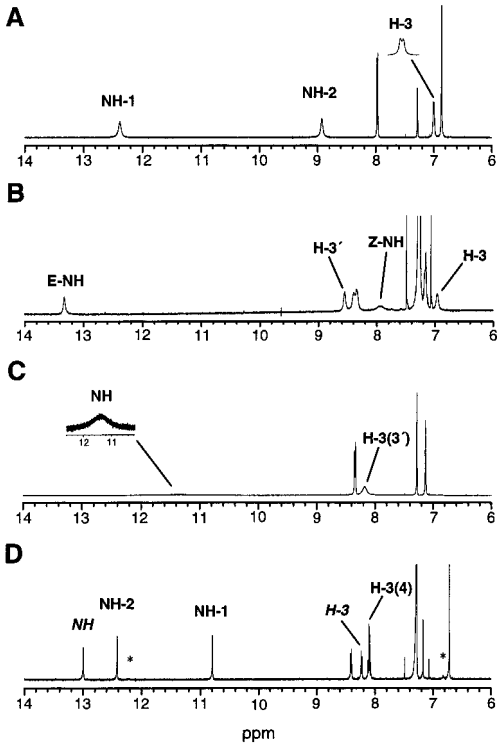


Figure 2. ^{1}H NMR spectra in $CDCl_3$ of (A) urea **2** at ~6 mM containing ~50% association, (B) bis-urea **3** at −45 °C, ~0.1 mM containing ~10% dimer, (C) bis-urea **3** at 25 °C, ~6 mM containing ~60% dimer (note: the NH peak was not seen at concentrations below 1.5 mM. A broad coalesced NH peak was observed in a 0.1 mM sample at 50 °C, where **3** was monomeric), and (D) complex **2·3**, with signals for **3** italicized and asterisks showing uncomplexed compound.

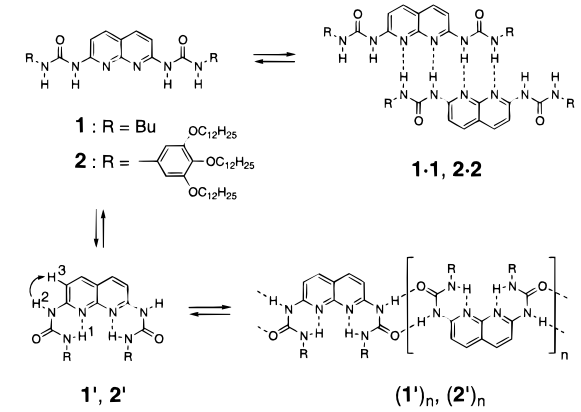
In dynamic ^{1}H NMR studies of **3** in $CDCl_3$, there were two NH resonances ($\Delta\delta \approx 5.4$ ppm) in slow exchange at −40 °C and a single broad NH resonance near 25 °C, the coalescence temperature (Figure 2B, C). Significantly different chemical shifts were also observed for the two H-3 signals ($\Delta\delta > 1$ ppm) at −40 °C, which also coalesced at higher temperatures. These observations can be best interpreted in terms of structure **3′** because in the folded state one of the H-3 protons lies within the anisotropic deshielding cone of the urea carbonyl group, and one of the NH groups is shifted downfield by an internal H bond.

A dilution study (13 mM to 41 μM) was carried out at room temperature, and a fit of the chemical shift data for H-3 to a 1:1 isotherm gave a $K_{dimer} = 259$ M^{-1}. In contrast, the dimerization constants for *N*-butyl-*N′*-4-methyl-2-pyridylurea, *N*-3,4,5-tridodecyloxyphenyl-*N′*-4-methyl-2-pyridylurea, and **2′**, which were shown to dimerize in their folded state, were much lower, ranging from ~15−95 M^{-1}. This suggested that **3** dimerized in its unfolded state, **3·3**. Two other strong indications were the large downfield shift observed for H-3 ($\Delta\delta \approx 0.7$ ppm) upon dimerization and an NOE observed between the urea NH signal and the Ar−CH_2 signal (Scheme 2).

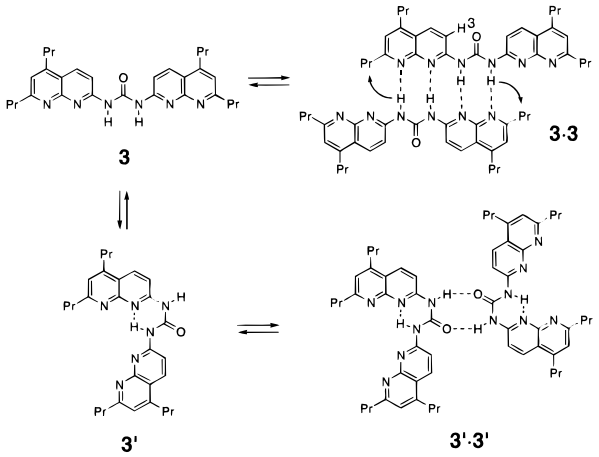
To investigate the potential for the mutual unfolding of **2′** and **3′** to form heterodimer **2·3**, ^{1}H NMR studies were carried out in $CDCl_3$ on 1:1 mixtures of the two components (see, e.g., Figure 2D) Definitive peak assignments were made by NOE and gradient COSY experiments and were, along with intermolecular NOEs (Scheme 3), fully consistent with the formation of complex **2·3**. The large downfield shift observed for the H-3 signal of **2** (compare with Figure 2A), indicated that the urea was unfolded and that H-3 was in the proximity of the carbonyl group. The chemical shift for the H-3 signal of **3** in the complex was also similar to its shift in the unfolded dimer **3·3**. In further studies,

(12) Dilution studies indicated that *N,N′*-di-2-pyridyl urea dimerized weakly in chloroform and in the same manner as observed in the solid-state.

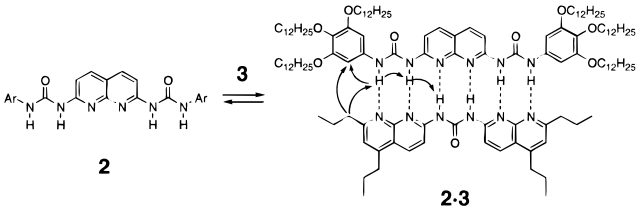
Scheme 1



Scheme 2



Scheme 3



separate peaks were observed for **2** or **3** and complex **2·3** when one of the components was in excess, indicative of a slow exchange of the complex and its constituents on the NMR time scale. The K_{assoc} was estimated to be approximately 5×10^5 M^{-1} from the integration of signals for monomer and complex in spectra obtained at concentrations where self-association of **2** and **3** was negligible.

In conclusion, ureas **2** and **3** have been prepared and shown to exist as intramolecularly H-bonded conformers **2′** and **3′** in solution. In the same manner, **2** and *N,N′*-di-2-pyridylurea were folded in the solid-state. At high concentrations, **3** unfolds and forms dimer **3·3**. Similarly, **2** and **3** mutually unfold in solution to form a robust, sextuply H-bonded complex. Such systems are likely to be useful as length-tunable modules for self-assembly and self-organization, and the results bode well for the development of larger adaptive oligomers built from naphthyridinyl urea building blocks.

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Supporting Information Available: Descriptions of the X-ray crystallographic analyses and binding studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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