1888 J. Org. Chem. **1995**, *60*, 1888−1890

A Novel Hydrogen-Bonded Dimer Containing a 16-Membered Ring

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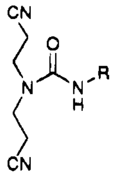
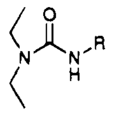
Received November 29, 1994

The creation of complex molecular architectures is critical to the development of new materials and supramolecular assemblies.[1] Hydrogen bonding[2] is particularly attractive for the creation of structured assemblies of molecules because arrays of hydrogen-bond donors and acceptors can be designed to induce self-assembly. Most hydrogen-bonded dimers (lactams, amides, carboxylic acids, nucleic acids, etc.) involve cyclic arrays of eight atoms. In this paper we report a hydrogen-bonded dimer involving an unprecedented 16-membered ring.

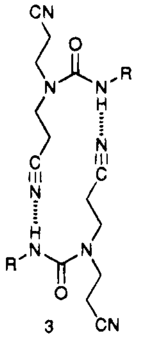
While studying various (2-cyanoethyl)urea derivatives,[3] we observed that *N,N*-bis(2-cyanoethyl)-*N′*-phenylurea[4] (**1a**) exhibits unusually low solubility (2 mM in $CHCl_3$ at 20 °C) and a relatively high melting point (158−159 °C). In contrast, *N,N*-diethyl-*N′*-phenylurea[3a] (**2a**) is highly soluble in chloroform (3 M) and melts at 86−87 °C. In chloroform solution, urea **1a** self-associates through intermolecular hydrogen bonding to a much greater degree than urea **2a**. In the ^{1}H NMR spectrum, the NH resonance of **1a** appears at 6.57 ppm at 1 mM in $CDCl_3$, but shifts to 6.72 ppm in a 20 mM supersaturated solution. At these concentrations, the NH resonance of urea **2a** is invariant (6.24 ppm). In the infrared spectrum, a 20 mM $CHCl_3$ solution of urea **1a** exhibits a free NH stretching band at 3442 cm^{-1} and a hydrogen-bonded NH stretching band at ca. 3390 cm^{-1}. The hydrogen-bonded band is similar in position to the NH stretch of **1a** in acetonitrile (a single band at 3392 cm^{-1}), suggesting that this band arises from intermolecular hydrogen bonding of the NH group to a nitrile group. Urea **2a** only exhibits a free NH stretching band (3464 cm^{-1}) in 20 mM $CHCl_3$ solution. At higher concentrations ($\geq$100 mM) **2a** also displays a hydrogen-bonded NH band at 3350 cm^{-1}, which results from intermolecular hydrogen bonding between urea groups. The relatively large shift in frequency that occurs when **2a** dimerizes (ca. 110 cm^{-1}) and small shift in frequency that occurs when **1a** dimerizes (ca. 50 cm^{-1}) indicate that different modes of hydrogen bonding are involved.



1a R = Ph
1b R = CH_3



2a R = Ph
2b R = CH_3



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Urea **1b**[5] was used for further solution-phase spectroscopic studies, because it is considerably more soluble in chloroform than **1a**. In the infrared spectrum, **1b** shows modest self-association at 10 mM and substantial self-association at 50 mM (Figure 1a,b). In contrast, urea **2b**[3b] shows no self-association at 10 mM, but exhibits a small hydrogen-bonded NH peak at 50 mM and a substantial hydrogen-bonded NH peak at 600 mM (Figure 1c,d). ^{1}H NMR studies provide additional evidence for the greater propensity of urea **1b** to self-associate. As the concentration of **1b** is increased from 0 to 100 mM, the NH resonance shifts downfield by 0.45 ppm (Figure 2). Over the same range of concentrations, the NH resonance of **2b** only shifts downfield by 0.09 ppm. From these data, we estimate ureas **1** to self-associate with an association constant of 3 M^{-1}.[6,7] This association constant is about 1 order of magnitude greater than that of ureas **2** and is comparable to that of simple lactams.[8]

X-ray crystallography offers an explanation for the unusual properties of ureas **1a** and **1b**.[15] Urea **1a** crystallizes as a hydrogen-bonded dimer (**3**), in which the nitrile groups and urea groups of two molecules hydrogen bond to form a 16-membered ring (Figure 3). The hydrogen bonds are slightly longer (N_2−N_{4a}, N_{2a}−N_4 = 3.26 Å) than typical hydrogen bonds between nitriles and amides (generally 3.0−3.1 Å, as indicated by a survey of the Cambridge Structural Database). The nitrile groups of the dimer are in close contact (C_{13}−N_{4a}, C_{13a}−N_4 = 3.388 Å), and electrostatic interactions between these groups may further stabilize the dimer. These hydrogen-

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[1] For examples, see: (a) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304. (b) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. (c) Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696. (d) Etter, M. C. *J. Phys. Chem.* **1991**, *95*, 4601. (e) Persico, F.; Wuest, J. D. *J. Org. Chem.* **1993**, *58*, 95. (f) Zimmerman, S. C.; Murray, T. J. *Phil. Trans. R. Soc. London A* **1993**, *345*, 49. (g) Hamilton, A. D.; Fan, E. K.; Van Arman, S.; Geib, S. J.; Yang, J. *Phil. Trans. R. Soc. London A* **1993**, *345*, 57. (h) Lehn, J.-M. *Makromol. Chem., Macromol. Symp.* **1993**, *69*, 1. (i) Chang, Y.-L.; West, M. A.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5991. (j) Wyler, R.; de Mendoza, J.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1699. (k) Fan, E. K; Yang, J; Geib, S. J.; Vicent, C; Garcia-Tellado, F.; Tecilla, P.; Hamilton, A. D. *Macromol. Symp.* **1994**, *77*, 209. (l) Branda, N.; Wyler, R.; Rebek, J., Jr. *Science* **1994**, *263*, 1267. (m) Zerkowski, J. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 4298. (n) Zerkowski, J. A.; Mathias, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 4305. (o) Mathias, J. P.; Simanek, E. E.; Zerkowski, J. A.; Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 4316. (p) Mathias, J. P.; Simanek, E. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 4326. (q) Hanessian, S.; Gomtsyan, A.; Simard, M.; Roelens, S. *J. Am. Chem. Soc.* **1994**, *116*, 4495. (r) Khazanovich, N.; Granja, J. R.; McRee, D. E.; Milligan, R. A; Ghadiri, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 6011.

[2] (a) Pauling, L. *The Nature of the Chemical Bond*; Cornell University Press: Ithaca, NY, 1939; Chapter 9. (b) Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*; W. H. Freeman and Company: San Francisco, 1960. (c) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, 1991.

[3] (a) Nowick, J. S.; Powell, N. A.; Martinez, E. J.; Smith, E. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 3763. (b) Nowick, J. S.; Abdi, M.; Bellamo, K. A.; Love, J. A.; Martinez, E. J.; Noronha, G.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 89.

[4] Urea **1a** was prepared by reaction of 3,3′-iminodipropionitrile with phenyl isocyanate in CH_2Cl_2, isolation of the resulting precipitate by filtration, and recrystallization from CH_2Cl_2: mp 158−159 °C; IR ($CHCl_3$) 3442, 2252, 1680, 1599 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5 H), 6.68 (s, 1 H); 3.73 (t, J = 6.4 Hz, 4 H), 2.76 (t, J = 6.4 Hz, 4 H).

[5] Urea **1b** was prepared by reaction of 3,3′-iminodipropionitrile with methyl isocyanate in CH_2Cl_2, followed by chromatographic purification of the resulting product: mp 62−63 °C; IR ($CHCl_3$) 3481, 2253, 1659, 1527 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (appar d, J = 3.8 Hz, 1 H), 3.63 (t, J = 6.5 Hz, 4 H), 2.82 (d, J = 4.5 Hz, 3 H), 2.70 (t, J = 6.5 Hz, 4 H).

[6] Connors, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley: New York, 1987; pp 202−205.

[7] The involvement of multiple equilibria (e.g., the formation of higher aggregates) limits the accuracy with which $K_{\mathrm{dimerization}}$ can be determined.

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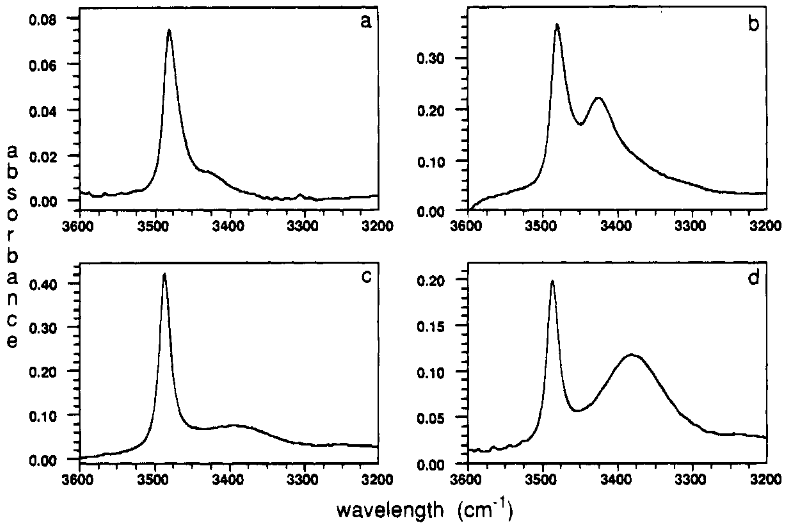

Figure 1. Infrared spectra (3200–3600 cm^{-1}) of ureas **1b** and **2b** in $CHCl_3$. (a) **1b** (10 mM, 1.0 mm pathlength): 3481, 3430 cm^{-1} (weak). (b) **1b** (50 mM, 1.0 mm pathlength): 3481, 3425 cm^{-1}. (c) **2b** (50 mM, 1.0 mm pathlength): 3487, 3394 cm^{-1} (weak). (d) **2b** (600 mM, 0.10 mm pathlength): 3487, 3380 cm^{-1}. Spectra were recorded at 295 K against a $CHCl_3$ reference and are not base line corrected.

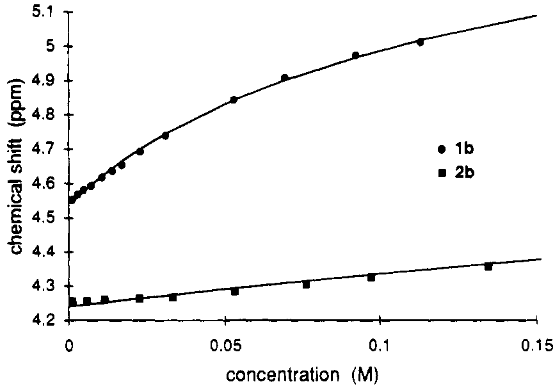

Figure 2. ^1H NMR chemical shifts of NH groups of ureas **1b** and **2b** in $CDCl_3$ solution as a function of concentration. The curves are dimerization isotherms (**1b**: $\delta_{monomer} = 4.535$ ppm, $\delta_{dimer} = 6.055$ ppm, $K_{dimerization} = 3$ M^{-1}; **2b**: $\delta_{monomer} = 4.240$ ppm, $\delta_{dimer} = 6.017$ ppm, $K_{dimerization} = 0.3$ M^{-1}). For details, see ref 6. Data was collected on a 500 MHz ^1H NMR instrument at 293 K.

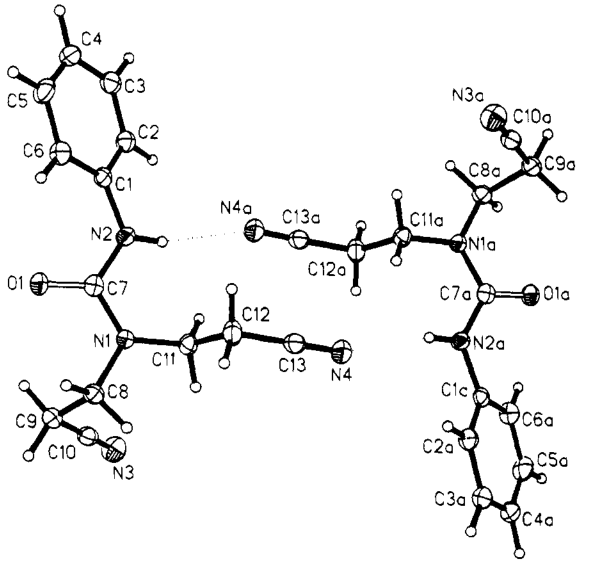

Figure 3. X-ray crystal structure of urea **1a** illustrating the hydrogen-bonded dimeric structure.[15]

bonding and electrostatic interactions are not available to trisubstituted ureas lacking cyanoalkyl groups, which form hydrogen-bonded chains in the crystal lattice.[9] That ureas **1** preferentially form dimers **3** is surprising, because nitriles are weaker hydrogen-bond acceptors than ureas,[10,11] yet in most crystals the strongest hydrogen bond donors and acceptors form intermolecular hydrogen bonds.[1b,d] Apparently, the two hydrogen bonds of the dimer are stronger than a single hydrogen bond between two urea groups. Even though a 16-membered ring is formed, rotational freedom is only lost for about four bonds (N_1–C_{11}, N_{1a}–C_{11a}, C_{11}–C_{12}, and C_{11a}–C_{12a}) upon dimerization. In contrast to hydrogen-bonded dimers involving eight-membered rings (e.g., lactams), no unfavorable Jorgensen secondary interactions occur between the hydrogen-bonding groups in dimer **3** because the hydrogen-bond donor and acceptor groups are separated.[12]

To our knowledge, this type of hydrogen-bonded dimer has not been noted previously. A survey of the Cambridge Structural Database reveals a related pattern of hydrogen bonding in 3-amino-3-chloro-2-cyanoacrylic acid anilide[13] and *N*-(2-furylmethyl)-α-cyanofuranacrylamide,[14]

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(9) For examples, see: Lewis, R. J.; Camilleri, P.; Kirby, A. J.; Marby, C. A.; Slawin, A. A.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1625, and corresponding X-ray crystallographic data in the Cambridge Structural Database.

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(13) Block, H. D.; Löckenhoff, H.-D.; Allmann, R. *Cryst. Struct. Commun.* **1975**, *4*, 77.

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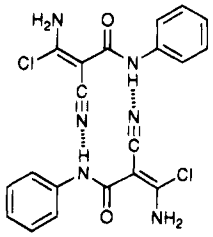
which form dimers **4** and **5** in the solid state. The dimers comprise 12-membered rings in which nitrile and amide groups are hydrogen bonded. The distance between the nitrile and amide nitrogens in these dimers is 3.140 and 3.108 Å, respectively. The dimeric structures of **3**–**5** suggest that the formation of macrocyclic hydrogen-bonded dimers involving nitriles and ureas or amides may be a general phenomenon. We anticipate that interactions of this sort may be useful for the creation of supramolecular architectures.



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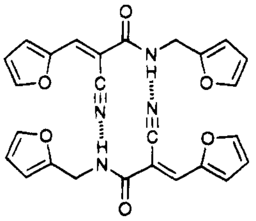

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Acknowledgment. We thank Professor Robert J. Doedens for help in using the Cambridge Structural Database. This work was supported by National Science Foundation Grant CHE-9118885, National Institutes of Health Grant GM-49076, the UCI Committee on Research, Zeneca Pharmaceuticals Group, the Upjohn Co., and Hoffman-La Roche Inc. J.S.N. thanks the following agencies for support in the form of awards: The Camille and Henry Dreyfus Foundation (New Faculty Award); The American Cancer Society (Junior Faculty Research Award); The National Science Foundation (Young Investigator Award); and the Arnold and Mabel Beckmann Foundation (Young Investigator Award).

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(15) The authors have deposited atomic coordinates for **1a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.