Energetic Superiority of Two-Center Hydrogen Bonding Relative To Three-Center Hydrogen Bonding in a Model System

Jihong Yang and Samuel H. Gellman*

Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

Received May 8, 1998

Hydrogen bonds involving three atoms (often termed "bifurcated") are frequently detected in the crystal structures of small molecules[1] and biopolymers.[2−7] Three-center H-bonding (or the absence thereof) has been proposed to play an important role in DNA,[3] RNA[4] and protein[5] conformation, small molecule-DNA[6] and protein-DNA[7] recognition, host−guest complexation,[8] and self-assembly.[9] Although extensive data are available regarding the strengths of two-center H-bonds,[10] the relative energetic merits of two-center vs three-center H-bonds have not been probed experimentally. There are two types of three-center H-bonds, (i) one H atom interacting with two acceptor atoms (which we refer to as an XHY interaction) and (ii) one acceptor atom interacting with two H atoms (which we designate HXH).

Here, we use the equilibrium among different H-bonding patterns in **1** to monitor the thermodynamic competition among
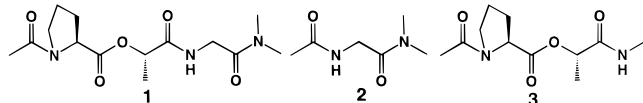
an XHY three-center interaction and alternative two-center H-bonds. The folding of **1** has been analyzed in dilute nonpolar solution, so that H-bonding sites either interact intramolecularly or forego amide−amide H-bonds. Our results show that the XHY three-center interaction is less energetically favorable than a two-center H-bond.

Depsipeptide **1** has one H-bond donor site and three potential acceptor sites for intramolecular H-bonds. The ester carbonyl is unlikely to form a 7-membered ring intramolecular H-bond.[11] Therefore, we expect three possible intramolecularly H-bonded states for **1** (Figure 1), **1a**, containing a two-center H-bond in a 5-membered ring ("C₅ interaction"[12]), **1b**, containing a two-center H-bond in a 10-membered ring, and **1c**, containing an XHY three-center interaction. The conformational equilibrium among **1a**−**c** was evaluated in dilute CH_2Cl_2 solution (1 mM). Under these

Figure 1. N−H stretch region FT-IR data for 1 mM samples of compounds **1**−**4** in CH_2Cl_2 at rm temp, after subtraction of the spectrum of pure CH_2Cl_2 (nominal resolution 2 cm⁻¹). Data acquired on a Nicolet 740 spectrometer as previously described.[14a,17] (**1**) Maxima at 3401 and 3331 cm⁻¹, (**2**) maximum at 3406 and shoulder at ca. 3447 cm⁻¹, (**3**) maxima at 3456 and 3334 cm⁻¹.

conditions, H-bonding is directly detectable via IR spectroscopic data from the N−H stretch region,[13,14] and there is no intermolecular H-bonding.[15]

IR data indicate that **1a** is the major form in CH_2Cl_2 solution at room temperature. The IR spectrum of **1** (Figure 1) displays two absorption maxima in the N−H stretch region, at 3401 and 3331 cm⁻¹. Assignment of these bands is aided by IR data for reference compounds **2**[16,17] and **3**.[18] Glycine derivative **2** is almost completely locked into the 5-membered ring H-bond under these conditions, displaying only one N−H stretch maximum, at 3406 cm⁻¹ (Figure 1). Amide **2** also displays a very small shoulder at ca. 3447 cm⁻¹, which corresponds to non-H-bonded N−H. Depsipeptide **3** folds largely to the 10-membered ring H-bonded form, as indicated by the dominant N−H stretch band at 3334 cm⁻¹; the minor band at 3456 cm⁻¹ indicates a small population of non-H-bonded N−H (Figure 1). For **1**, the larger band at 3401 cm⁻¹ is assigned to folding pattern **1a**. The smaller band at 3331 cm⁻¹ is consistent with folding pattern **1b**, containing only a 10-membered ring H-bond, because of the spectroscopic similarity to **3**. The XHY three-center interaction (**1c**) might also contribute

(1) (a) Baur, W. H. *Acta Crystallogr.* **1965**, *19*, 909. (b) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1982**, *104*, 244. (c) Jeffrey, G. A.; Mitra, J. *J. Am. Chem. Soc.* **1982**, *104*, 5546. (d) Reutzel, S. M.; Etter, M. C. *J. Phys. Org. Chem.* **1992**, *5*, 44.

(2) Baker, E. N.; Hubbard, R. E. *Prog. Biophys. Mol. Biol.* **1984**, *44*, 97.

(3) (a) Nelson, H. C. M.; Finch, J. T.; Luisi, B. F.; Klug, A. *Nature* **1987**, *330*, 221. (b) Coll, M.; Frederick, C. A.; Wang, A. H.-J.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8385. (c) For different conclusions about the role of three-center H-bonds in DNA conformation, see: Fritsch, V.; Westhof, E. *J. Am. Chem. Soc.* **1991**, *113*, 8271.

(4) Allain, F. H.-T.; Varani, G. *J. Mol. Biol.* **1995**, *250*, 333.

(5) (a) Sundaralingam, M.; Sekharudu, Y. C. *Science* **1989**, *244*, 1333. (b) Preissner, R.; Egner, U.; Saenger, W. *FEBS Lett.* **1991**, *288*, 192.

(6) (a) Kopka, M. L.; Yoon, C.; Goodsell, D.; Pjura, P.; Dickerson, R. E. *J. Mol. Biol.* **1985**, *183*, 553. (b) Jain, S.; Zon, G.; Sundaralingam, M. *Biochemistry* **1989**, *28*, 2360.
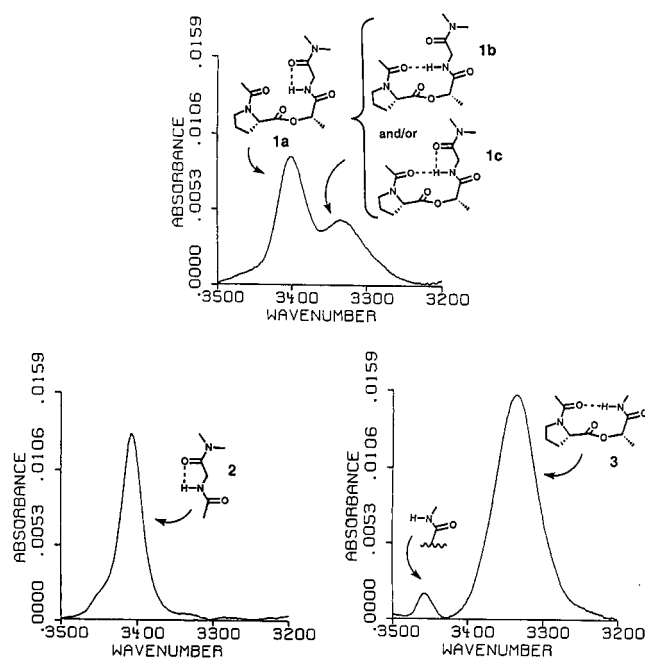
(7) Aggarwal, A. K.; Rodgers, D. W.; Drottar, M.; Ptashne, M.; Harrison, S. C. *Science* **1988**, *242*, 899.

(8) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J. *J. Am. Chem. Soc.* **1989**, *111*, 1082.

(9) Conn, M. M.; Rebek, J. *Chem. Rev.* **1997**, *97*, 1647 and references therein.

(10) (a) Joesten, M. D.; Schaad, L. J. *Hydrogen Bonding*; Marcel Dekker: New York, 1974. (b) Arnett, E. M.; Mitchell, E. J.; Murty, T. S. S. R. *J. Am. Chem. Soc.* **1974**, *96*, 3875.

(11) (a) Boussard, G.; Marraud, M. *Biopolymers* **1981**, *20*, 169. (b) Gallo, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 9774.

(12) (a) Avignon, M.; Huong, P. V.; Lascombe, J.; Marraud, M.; Néel, J. *Biopolymers* **1969**, *8*, 69. (b) Burgess, A. W.; Scheraga, H. A. *Biopolymers* **1973**, *12*, 2177. (c) Ashish; Kishore, R. *Tetrahedron Lett.* **1997** *38*, 2767.

(13) (a) Tsuboi, M.; Shimanouchi, T.; Mizushima, S. *J. Am. Chem. Soc.* **1959**, *81*, 1406. (b) Maxfield, F. R.; Leach, S. J.; Stimson, E. R.; Powers, S. P.; Scheraga, H. A. *Biopolymers* **1978**, *17*, 2507.

(14) (a) Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164. (b) For related work, see: Gung, B. W.; Zhu, Z. *J. Org. Chem.* **1996**, *61*, 6482.

(15) Relevant data may be found in the Supporting Information.

(16) Cung, M. T.; Marraud, M.; Néel, J. In *Proceedings of the 5th Jerusalem Symposium on Quantum Chemisty and Biochemistry*; Bergman, E.; Pullman, B., Eds.; Israel Academy of Sciences and Humanities, Jerusalem, 1973, pp 69ff.

(17) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228.

(18) (a) Boussard, G.; Marraud, M.; Néel, J.; Maigret, B.; Aubry, A. *Biopolymers* **1977**, *16*, 1033. (b) Aubry, A.; Protas, J.; Boussard, G.; Marraud, M. *Acta Crystallogr.* **1974** *B30*, 1992.

to this lower energy band, since it has been reported in one case that a two-center H-bond and a comparable XHY three-center interaction give rise to similar N−H stretch bands.[19] We assume that **1c** would not show an N−H stretch band above 3370 cm^{-1}, because the 10-membered ring H-bond alone (as in **3**) gives rise to a band at lower energy. This assumption is supported by the behavior of **1** in the solid state. The crystal structure of **1**[15] shows an intermolecular XHY three-center interaction; the NH is involved in a 5-membered ring H-bond (H···O = 2.34 Å, N−H···O angle = 101°) and in an intermolecular H-bond (H···O = 2.11 Å, N−H···O angle = 161°). Solid **1** has an N−H stretch IR band at 3236 cm^{-1}.[20]

The data discussed above indicate that the conformation containing the C_5 two-center H-bond (**1a**) is superior to the conformation containing the three-center XHY interaction (**1c**), and to the conformation containing the 10-membered ring H-bond (**1b**), in terms of Gibbs free energy at room temperature. To provide insight into enthalpic and entropic relationships, we carried out variable temperature IR studies. We have previously shown that N−H stretch region IR data can be used to quantify intramolecular H-bonding equilibria if one can identify reference compounds that provide integrated extinction coefficients for appropriate IR bands.[21]

The room-temperature N−H stretch data for **1** suggest that the folding of this molecule can be analyzed in terms of a two-state model (eq 1), in which one state has only the 5-membered ring
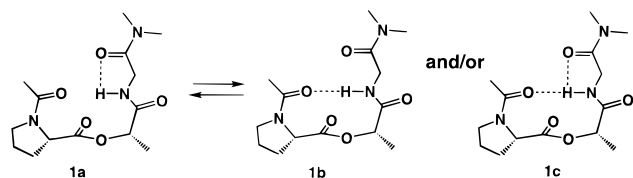
H-bond (**1a**; band at 3401 cm^{-1}) and the other state has the 10-membered ring H-bond and/or the XHY three-center interaction (**1b** and/or **1c**, band at 3331 cm^{-1}). As the temperature is lowered, the intensity of each band increases, but the proportions of the two bands remain similar.[15] We employed variable temperature data for reference compound **2** to estimate the integrated extinction coefficient for the band assigned to N−H involved in a 5-membered ring H-bond. Mathematical decomposition methods were used to "isolate" the band centered near 3406 cm^{-1} in the spectrum of **2** at various temperatures, and the integrated absorbance of this band was assumed to arise from the total concentration of **2**. (Since there is a tiny absorbance at higher wavenumber for **2**, this approach slightly overestimates the molar integrated extinction coefficient for the 5-membered ring H-bonded band; however, this small error should not influence our conclusions.) The population of folding pattern **1a** was then estimated by applying the temperature-dependent integrated extinction coefficient derived from **2** to the band centered near 3406 cm^{-1}, isolated by spectral decomposition, in the IR spectrum of **1** at several temperatures.[15] According to this analysis, the population of **1a** does not change between 220 and 300 K. In light of the van't Hoff relationship [ln $K_{eq} = (-\Delta H°/RT) + (\Delta S°/R)$], this temperature independence implies that the two states in eq 1 are isoenthalpic and that **1a** is heavily populated (ca. 80%) because of an entropic advantage. Thus, the conformation containing the three-center XHY interaction available to **1**, if it forms at all, is no more favorable

enthalpically than the alternative conformations containing two-center H-bonds. In other words, once the X···H interaction is formed, adding the H···Y interaction produces no significant enthalpic improvement.

Since the 10-membered ring H-bond is almost fully formed in reference compound **3** at all temperatures, the dominance of **1a** implies that formation of the 5-membered ring H-bond in **1** interferes with formation of the 10-membered ring H-bond. This interference is remarkable because the H-bond in the smaller ring is geometrically inferior and, therefore, presumably energetically inferior[2,21] to the H-bond in the larger ring. (The 5-membered ring interaction requires a pronounced nonlinearity of the N−H···O angle, while the 10-membered ring interaction allows an N−H···O angle near 180°.) The energetic preference manifested in **1** for a conformation containing a two-center H-bond over a conformation containing a three-center XHY interaction may represent a general trend because the dominant H-bond in **1** has a poor geometry (i.e., two-center H-bonds with better geometries than allowed by the 5-membered ring should also be superior to three-center XHY interactions).

It is important to note that the stability of a conformation containing an intramolecular H-bond is not necessarily related to the stability of the H-bond itself.[14a,22] Specifically, the extensive 5-membered ring H-bonding in **1** and reference compound **2** is probably *not* a result of the H-bond itself but rather a manifestation of other factors, including antiparallel alignment of adjacent dipoles, avoidance of allylic-type strain, and minimal entropic cost. None of these other factors in the 5-membered H-bonded ring should affect formation of the 10-membered ring H-bond available to **1**; therefore, the equilibrium among **1a**, **1b**, and **1c** should reflect the influence of one two-center interaction on the other. The dominance of **1a** indicates that the three-center XHY interaction is less favorable than a two-center H-bond.

Our data indicate that there is no enthalpic advantage to forming an XHY three-center interaction in **1**, relative to forming a two-center H-bond, even when failure to form the three-center H-bond means that a H-bond acceptor remains free of interaction with a good donor site. The behavior of **1** may be rationalized at least partially by the "secondary interaction" hypothesis of Jorgensen et al.[23] (i.e., for **1c**, competition between the electrostatic attraction of the amide proton for the two amide oxygen atoms and the electrostatic repulsion between the oxygen atoms). The Jorgensen hypothesis[23] and subsequent modifications[24] predict that XHY three-center interactions would become favorable if both acceptors occurred in the same molecule and were rigidly held in the proper arrangement.[25] Our results suggest that XHY three-center H-bonds observed in crystal structures of flexible molecules,[1−7] or inferred in hydration shells,[26] may result from the operation of other noncovalent forces rather constituting stabilizing forces in and of themselves.[27]

(19) Borah, B.; Wood, J. L. *Spectrochim. Acta* **1977**, *33A*, 381.

(20) Compound **3** displays an N−H stretch band at 3306 cm^{-1} in the solid state. The previously reported crystal structure of this compound shows the NH to be involved in a 10-membered ring H-bond (H···O = 1.82 Å, N−H···O angle = 168°), with no additional intermolecular H-bonding: Lecomte, P. C.; Aubry, A.; Protas, J.; Boussard, G.; Marraud, M. *Acta Crystallogr.* **1974**, *B30*, 1992.

(21) (a) Liang, G.-B.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 3994. (b) Liang, G.-B.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 925.

(22) (a) Peters, D.; Peters, J. *J. Mol. Struct.* **1980**, *68*, 255. (b) Mitchell, J. B. O.; Price, S. L. *Chem. Phys. Lett.* **1989**, *154*, 267.

(23) (a) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008. (b) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810. (c) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J. *J. Am. Chem. Soc.* **1991**, *113*, 201. (d) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 209.

(24) (a) Gardner, R. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 10411. (b) Gardner, R. R.; Gellman, S. H. *Tetrahedron* **1997**, *53*, 9881.

(25) (a) Zimmerman, S. C.; Murray, T. J. *Tetrahedron Lett.* **1994**, *35*, 4077. (b) Murray, T. J.; Zimmerman, S. C.; Kolotuchin, S. V. *Tetrahedron* **1995**, *51*, 635.

(26) Savage, H. J.; Elliot, C. J.; Freeman, C. M.; Finney, J. L. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 2609. For an opposing view, see: McDonald, I. K.; Thornton, J. M. *J. Mol. Biol.* **1994**, *238*, 777.

(27) We thank Dr. Douglas Powell for solving the crystal structure of **1**. This work was supported by the National Science Foundation (CHE-9622653).