J|A|C|S
COMMUNICATIONS

Published on Web 01/31/2002

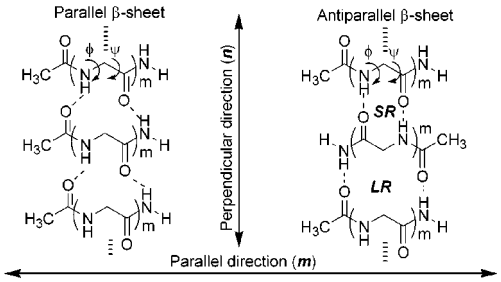
A Theoretical Study of β-Sheet Models: Is the Formation of Hydrogen-Bond Networks Cooperative?

Yi-Lei Zhao and Yun-Dong Wu*

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China

Received May 19, 2001; Revised Manuscript Received November 6, 2001

β-Sheets are ubiquitous in protein structures.[1] It has also been found that several diseases, such as Alzheimer's disease and mad-cow disease, are associated with the formation of β-amyloid fibrils by β-amyloid peptides.[2] Currently, there is an intense research effort to understand the stability and dynamic features of β-sheet formation.[3] One important question to answer is whether the formation of β-sheets is cooperative.[4] Several recent experiments using designed short peptides for the study of cooperativity in β-sheet formation all indicated a cooperativity in the perpendicular direction.[5]



β-Sheets are featured with the formation of regular hydrogen-bond (H-bond) networks (above). It is known that cooperative interactions are important for the stability of many H-bonded systems.[6,7] Recent experimental and theoretical studies of amide clusters indicate that there is strong cooperativity in the formation of one-dimensional H-bond chains.[8,9] It has been proposed that there is an important resonance interaction in a H-bond chain just like that in polyenes and that this resonance interaction is essential to the cooperativity of H-bonds in these systems.[8−10] Here, we report our preliminary results on a theoretical study of β-sheet models, which suggest that the formation of H-bond networks in β-sheets may not have significant cooperativity in terms of enthalpy contribution.

We utilized a simple repeating unit approach method, which has been successfully applied to the study of cooperativity of the α-helix.[11] We first optimized the dimer of a tripeptide model ($n = 2$, $m = 3$) to obtain repeating units for the parallel and antiparallel β-sheets. Figure 1 shows the optimized structures by the HF/6-31G* method along with important geometrical parameters.[12,13] These structures were constrained to be planar ($\phi = \psi = 180°$), with every glycine residue in the same geometry. Thus, each strand had three repeating glycine units. The parallel sheet had quite weak H-bonds with the adjacent O- - -H distances of 2.65 and 2.62 Å, respectively. The antiparallel sheet had a much shorter O- - -H distance of 2.15 Å, which was still longer than those in optimized amide clusters.[14] Similar geometries were obtained for the dimers of Ac−$(Gly)_2$−NH_2 with full geometric optimization (Figure S2 of SI), in support of the repeating unit approach.

* Author for correspondence. E-mail: chydwu@ust.hk.

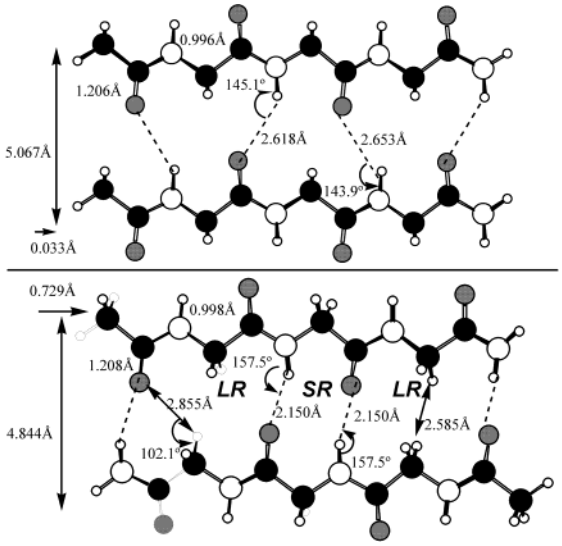


Figure 1. Calculated dimeric structures of the parallel (top) and antiparallel (bottom) β-sheet models with $n = 2$, $m = 3$.

The repeating units were then used to construct parallel and antiparallel β-sheets with ($n = 2$, $m = 0-7$), ($n = 3-6$, $m = 1$), and ($n = 3-6$, $m = 2$). The energies of these structures were calculated with the B3LYP/6-31G* method[15] in a vacuum without geometric optimization, which should give reasonably good relative binding energies of the repeating units.[14]

Figure 2a shows the calculated individual H-bond energies in the parallel direction ($n = 2$, $m = 0-7$). In the case of parallel β-sheets, the energy of each H-bond is nearly constant. For the antiparallel β-sheet, there are two situations. The second, fourth, sixth, and eighth H-bonds correspond to the formation of the large H-bonded rings (***LR***) and have higher stabilizations than the first H-bond. The third, fifth, and seventh H-bonds correspond to the formation of small H-bonded rings (***SR***) and cause small destabilizations. In the formation of ***LR***s, the extra stabilization is in accord with the C−H- - -O═C H-bonds proposed by Dixon et al.[16] The opposite feature in the formation of ***SR***s can be attributed to the secondary electrostatic repulsions between two H-bonds (short O/O and H/H distances) that have been discussed by Jorgensen et al.[17] Again, cooperativity is not found in the formation of both ***SR***s and ***LR***s. Therefore, it can be concluded that the repeating H-bonds in the parallel direction in both the parallel and antiparallel β-sheets are not cooperative in terms of enthalpy contribution. It should be pointed out that cooperativity could still be caused by the entropy effect and side-chain/side-chain interactions.[18]

The calculated binding energies for individual strands in the perpendicular direction are plotted in (b) and (c) of Figure 2 for parallel and antiparallel β-sheet models, respectively. When $m =$

10.1021/ja016230a CCC: $22.00

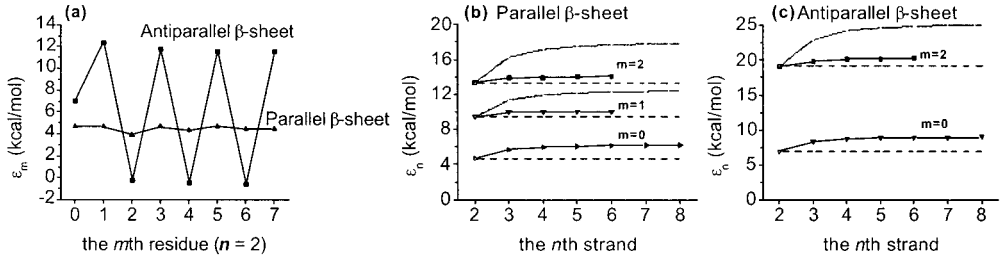


Figure 2. (a) Plot of calculated binding energy increment of the *m*th pair of residues in the parallel direction: $\epsilon_m = E_{B(m)} - E_{B(m-1)}$, where $E_{B(m)}$ is the total binding energy between two strands ($n = 2$) with *m* residues. In (b) and (c), the solid curves are plots of the calculated binding energy increment by the *n*th strand in the parallel and antiparallel β-sheet models, respectively: $\epsilon_n = E_{B(n)} - E_{B(n-1)}$, where $E_{B(n)}$ is the total binding energy with *n* β-strands. The dashed lines represent no cooperativity, and the dotted curves are calculated binding energies ϵ_1 and ϵ_2 based on the assumption that cooperativities for $m = 1$ and $m = 2$ double and triple that for the single H-bond chain ($m = 0$), respectively.

0, that is, in the acetamide H-bond chain, there is a large cooperative interaction as the binding energy increases when *n* becomes larger.

To test the effect of geometric optimization on the calculated binding energy and cooperativity, the dimer, trimer, tetramer, pentamer, and hexamer of formamide in the antiparallel sheet arrangement have been calculated in two different ways with the B3LYP/6-31G* method: (a) full geometric optimization and (b) repeating unit approach with the repeating unit derived from the optimization of the tetramer. These two sets of calculations give similar binding energies (see SI). This means that the repeating unit approach is valid.

We have also estimated the effect of methanol solvent on the binding energies of the dimer to hexamer of formamide using the self-consistent induced polarization continuum model (SCIPCM).[19] The calculated binding energies for the last formamide of the dimer to hexamer are −7.1, −9.2, −9.8, −10.0, and −10.1 kcal/mol, respectively, in the gas phase. They are reduced to −5.4, −5.6, −5.7, −5.7, −5.7 kcal/mol, respectively, in the methanol solution. The calculated cooperativity for binding is large in the gas phase, but it is significantly reduced in the methanol solution. The calculations clearly indicate that the cooperativity is largely due to long-range electrostatic interactions and not due to the resonance effect.

If the above cooperativity were due to the resonance effect, it would be additive. That is, the binding cooperativity for β-strands with $m = 1$ and $m = 2$ should double and triple that of the acetamide chain ($m = 0$), as represented by the dotted curves. This is obviously not the case. The cooperativity of the binding for $m = 1$ and $m = 2$ is much smaller (solid curves) for both the parallel and antiparallel β-sheets. Electrostatic interations best explain the above observations. When $m = 0$, the acetamide H-bond chain has all the amide dipoles aligned roughly head-to-tail. This allows strong electrostatic attractions among amide dipoles, resulting in large cooperativity. When $m \geq 1$, each H-bond chain still has large electrostatic attractions, but there are repulsive electrostatic interactions between adjacent H-bond chains. As a result, the cooperativity is significantly reduced.

Acknowledgment. This project is supported by the Research Grants Council of Hong Kong. W.Y.D. thanks the Croucher Foundation for a Senior Research Fellowship Award.

Supporting Information Available: Cartesian coordinates of the tripeptide dimer models, tables of binding energies of β-sheet models shown in Figure 2, structures and energies of formamide oligomers and dipeptide dimmer models (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Richardson, J. S. *Adv. Protein Chem.* **1981**, *34*, 167.
(2) (a) Sipe, J. D. *Annu. Rev. Biochem.* **1992**, *61*, 947. (b) Teplow, D. B. *Amyloid* **1998**, *5*, 121. (c) Prusiner, S. B. *Science* **1997**, *278*, 245
(3) (a) Gellman, S. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 717. (b) Sun, J. K.; Doig, A. J. *J. Phys. Chem. B.* **2000**, *104*, 1826 and references therein. (c) Dalal, S.; Balasubramanian, S.; Regan, L. *Nat. Struct. Biol.* **1997**, *4*, 548. (d) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287. (e) Das, C.; Raghothama, S.; Balaram, P. *Chem. Commun.* **1999**, *11*, 967. (f) Koide, S.; Huang, X. L.; Link, K.; Koide, A.; Bu, Z. M.; Engelman, D. M. *Nature* **2000**, 403, 456. (g) Lashuel, H. A.; LaBrenz, S. R.; Woo, L.; Serpell, L. C.; Kelly, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 5262.
(4) Yang, A. S.; Honig, B. *J. Mol. Biol.* **1995**, *252*, 366.
(5) (a) Kortemme, T.; Ramirez-Alvarado, M.; Serrano, L. *Science* **1998**, *281*, 253. (b) Schenck, H. L.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 4869. (c) Koepf, E. K.; Petrassi, H. M.; Sudol, M.; Kelly, J. W. *Protein Sci.* **1999**, *8*, 841. (d) Griffiths-Jones, S. R.; Searle, M. S. *J. Am. Chem. Soc.* **2000**, *122*, 8350.
(6) (a) Jeffrey, G. A.; Saenger, W. In *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, 1991. (b) Scheiner, S. *Hydrogen Bonding*; Oxford University Press: New York, 1997.
(7) Guo, H.; Sirois, S.; Proynov, E. I.; Salahub, D. R. In *Theoretical Treatment of Hydrogen Bonding*; Hadzi, D., Ed.; John Wiley & Sons Ltd: New York, 1997; Chapter 3.
(8) (a) Ludwig, R. *J. Mol. Liq.* **2000**, *84*, 65−75. (b) Ludwig, R.; Reis, O.; Winter, R.; Weinhold, F.; Farar, T. C. *J. Phys. Chem. B* **1998**, *102*, 9312. (c) Ludwig, R.; Weinhold, F.; Farrar, T. C. *J. Phys. Chem. A* **1997**, *101*, 8861.
(9) (a) Kobko, N.; Paraskevas, L.; delRio, E.; Dannenberg, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 4348. (b) Masunov, A.; Dannenberg, J. J. *J. Phys. Chem. B.* **2000**, *104*, 806. (c) Guo, H.; Gresh, N.; Roques, B. P. Salahub, D. R. *J. Phys. Chem. B.* **2000**, *104*, 9746. (d) Guo, H.; Salahub, D. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2985. (e) Guo, H.; Karplus, M. *J. Phys. Chem.* **1994**, *98*, 7104.
(10) (a) Gilli, P.; Bertolas, V.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **1994**, *116*, 909. (b) Sharman, G. J.; Searle, M. S. *J. Am. Chem. Soc.* **1998**, *120*, 5291.
(11) Wu, Y.-D.; Zhao, Y.-L. *J. Am. Chem. Soc.* **2001**, 123, 5313.
(12) All calculations were performed with: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A7M; Gaussian, Inc.: Pittsburgh, PA, 1998.
(13) The repeating unit for the antiparallel β-sheet was also obtained by the construction of the rings in SR−LR−SR fashion. The geometry is essentially the same as that obtained with the LR−SR−LR.
(14) (a) Gresh, N.; Guo, H.; Salahub, D. R.; Roques, B. P.; Kafafi, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 7885. (b) Shamovsky, I. L.; Ross, G. M.; Riopelle, R. J. *J. Phys. Chem. B.* **2000**, *104*, 11296. (c) Kang, Y. K. *J. Phys. Chem. B.* **2000**, *104*, 8321.
(15) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(16) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Am. Chem. Soc.* **2000**, *122*, 4750. Our preliminary calculations indicate that the stabilization might due to three-body electrostatic interactions (Figure S3 of SI).
(17) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008.
(18) Zeng, H. Q.; Miller, R. S.; Flowers, R. A.; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 2635.
(19) The SCIPCM calculations used Gaussian 94 program.

JA016230A