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Cooperativity in Amide Hydrogen Bonding Chains: Implications for Protein-Folding Models

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Protein folding is an important, yet still relatively poorly understood, field with many implications for a number of important biochemical processes. There have been several reviews[1,2] that are relevant to the chemical processes of protein folding. An entire issue of *Accounts of Chemical Research* was recently dedicated to this topic.[3] The dynamics of the folding process is typically studied using Monte Carlo techniques on a potential surface defined using the individual nearest neighbor contacts. While use of pairwise contact potentials has been criticized as inadequate,[4] success in using effective two-body potentials to simulate a many-body problem has also been reported.[5]

In this communication we present data that reveals an unusually high degree of cooperativity for hydrogen-bonding chains of formamide molecules. Similar chains form in proteins. To the extent that the H-bonding chains discussed here resemble those in proteins, the pairwise potentials that have been used to model the analogous hydrogen bonds in polypeptides might lead to misleading results. Cooperativity within complexes of *N*-methylformamides with formate has been recently reported in a DFT and molecular mechanics study.[6]

It is becoming increasingly apparent that cooperative interactions involving many molecules is an important component of intermolecular interactions, particularly those involving hydrogen bonds. These cooperative interactions are particularly important in the solid-state. In the gas phase, molecules are too separated to interact cooperatively. In the liquid phase, dynamic changes in the nearest neighbor molecules limit the importance of cooperativity. Many molecular crystals involve hydrogen-bonding interactions. A particular example is that of the enol of 1,3-cyclohexanedione. The crystal structure of this molecule involves infinite hydrogen bonding chains. The O...O distance across the hydrogen bond is quite short (2.58 Å),[7] implying a strong, possibly covalent, interaction. The C−C and C═C bonds shorten and lengthen respectively in the crystal, as do the C−O and C═O bonds. Interactions of this type have been referred to as resonance assisted hydrogen bonds (RAHB).[8] As one might expect, molecular orbital calculations indicate a strong cooperative component plays an important role in the intermolecular interactions. These H-bonds are poorly described as electrostatic interactions.[9] They are highly cooperative.[10]

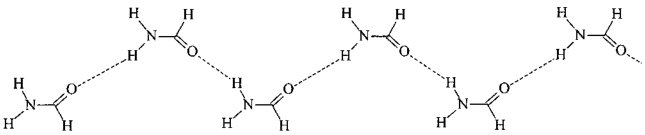

Figure 1. Schematic structure for planar formamide chains.

Hartree−Fock (HF) and density functional theory (DFT) calculations at the HF/D95** and B3LYP/D95** levels were performed on H-bonding chains of from two to ten formamide molecules using the GAUSSIAN 98 suite of computer programs.[11] The B3LYP method combines Becke's 3-parameter functional,[12] with the nonlocal correlation provided by the correlation functional of Lee, Yang and Parr.[13] The H-bonding chains were completely optimized with the restraint that each formamide molecule be geometrically equivalent and coplanar with the others. The intermolecular geometrical parameters were completely unrestrained. Molecules were arranged as in Figure 1. Vibrational frequencies were calculated to obtain the enthalpy and counterpoise (CP) corrections for basis set superposition error (BSSE) were calculated for the dimers. These values were used as corrections for the larger chains using the assumption that both the vibrational and CP corrections would be treated as additive. In this manner, nine times the vibrational and CP corrections for the dimer (one H-bond) are used for the decamer (nine H-bonds). The validity of this assumption was tested on fully optimized small aggregates containing from two to five formamides. The enthalpy correction per H-bond remained within 0.02 kcal/mol and the CP correction per H-bond within 0.1 kcal/mol of their respective average values. The H-bonding energies of each H-bond in each formamide chain was calculated by simple subtraction. Thus, the energy of the third H-bond in a chain of 10 (decamer) is simply the energy of the decamer less the combined energies of the heptamer and trimer.

Calculated H-bonding energy values for the dimer at the B3LYP/D95** and HF/D95** levels (−7.31 and −6.36 kcal/mol) are very close to the recently reported B3LYP/6-31G** and HF/6-31G** results (−7.27 and −6.34 kcal/mol).[14]

The calculated terminal and central H-bonding enthalpies are plotted in Figure 2 as a function of the number of molecules in the H-bonding chain. Selected energetic values for the dimer, hexamer and decamer are presented in Table 1. The energies of the two terminal H-bonds are equivalent as they form the same two species upon breaking. Similarly, the two central H-bonds are equivalent in energy for chains containing and odd number of formamides (and an even number of H-bonds). Figure 2 and Table 1 clearly illustrate the strong cooperative nature of the amide H-bond interactions. For example, the strongest H-bond (the central interaction in the decamer) is predicted to stabilize by 12.87 kcal/mol, approximately 2.5 times as much as that in the

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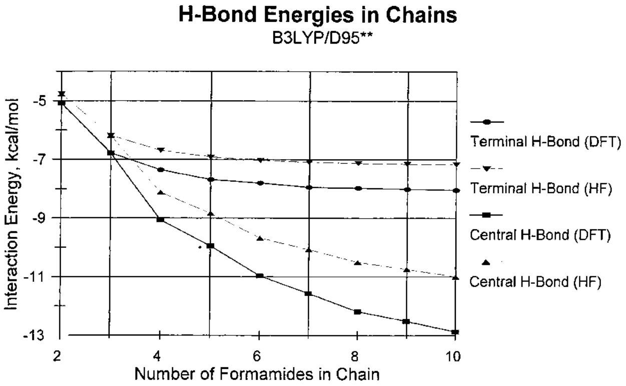

Figure 2. Energies of terminal and most central H-bonds in H-bonding chains containing from two to 10 formamide molecules. Note that chains containing odd numbers of formamides have two energetically equivalent central H-bonds.

Table 1. Bonding Energetics of Selected H-bonds in kcal/mol from B3LYP/D95** Calculations

H-bond	ΔE	ΔH (CP-corrected)
dimer	−7.31	−5.07
hexamer terminal	−10.04	−7.80
hexamer central	−13.20	−10.96
decamer terminal	−10.27	−8.03
decamer central	−15.11	−12.87

formamide dimer, 5.07 kcal/mol by the DFT method. The DFT calculations predict slightly stronger H-bonds throughout the series.

Interestingly, the cooperativity of the H-bonds in formamide resemble that of the cycloheanedione (enol form) much more than the less cooperative interactions of the H-bonds of (the structurally more similar) urea.[15]

The large variation of the H-bonding energy within formamide chains strongly suggests that pairwise interactions between individual hydrogen-bond donors and acceptors that are modeled solely upon interactions of one donor and one acceptor will be inadequate to evaluate the H-bonding contributions to the energies of variously folded conformations of polypeptides. Clearly the energies of the individual H-bonds within a (H-bonding) chain will depend on both the length of the (H-bonding) chain and the position of the individual H-bond in that chain.

We are currently in the process of extending these calculations using the more accurate CP-optimization method.[16] These calculations optimize the geometry of the H-bonding structure on a potential surface that is corrected for basis set superposition error (BSSE). We have shown that calculations of this type can remove many of the problems inherent in small basis set ab initio calculations.[17] However, the computer time required for complete optimization of the larger H-bonding complexes prevents us from reporting these results at this time. Optimizations currently can take weeks or months. Nevertheless, the implications of this work upon the many protein-folding modeling efforts currently underway prompts us to publish this preliminary report.

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