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Cooperative 4-Pyridone H-Bonds with Extraordinary Stability. A DFT Molecular Orbital Study

Yung-fou Chen and J. J. Dannenberg*

Department of Chemistry, City University of New York−Hunter College and the Graduate School,
695 Park Avenue, New York, New York 10021

Received January 21, 2006; E-mail: jdannenberg@gc.cuny.edu

In this communication, we report density functional molecular orbital calculations that illustrate how coupling of the NH and C═O of an amide through a polarizable π-system, together with cooperative H-bonding typical of amides, can combine to produce extraordinarily strong H-bonds between neutral molecules, with stabilization enthalpies as large as 23 kcal/mol.

Amidic (N−H···O═C) hydrogen bonds play an important role in both biochemical and synthetic self-assembling systems. Simple amide H-bonds contribute to the determination of the relative stabilities of peptide secondary structures. For example, the unusually large (up to 200%) cooperative interactions of chains of amidic H-bonds[1] contribute enormously to the stability of α-helices.[2] The more complex patterns of H-bonds in the nucleic acid base pairs generally occur as pairs or triads of cyclic H-bonds; however, amidic (HNC═O) subunits are always present in the cyclic systems. The self-assembly of nylons follows the pattern of peptides, while that of cyanuric acid/melamine[3] or those formed from structures containing 2-pyridone[4] units resemble that of the nucleic acid bases.

The $\Delta H_{\mathrm{inter}}$ of the cyclic 2-pyridone dimer[5] exceeds that of formamide by about 50% (−18 vs −12 kcal/mol), while that of a large ring diglycine dimer exceeds that of the isomeric small ring (see Figure 1) by about 9 kcal/mol.[6] Why do the stabilizations associated with amidic H-bonds differ so much? We have suggested that the enhanced stability of the large ring structure of Figure 1 is due to the coupling of the C═O and N−H involved in the H-bonds through a C_5 *intra*strand H-bonding interaction that affects the H-bonding groups at the termini of the strands. One could imagine 2-pyridone as a formamide whose NH and C═O are coupled via a −C═C−C═C− π-system in addition to the direct bond between them. As such π-systems can easily be polarized, one might reasonably expect the increased polarizability to enhance the H-bonding interactions.

All the calculations reported here used the B3LYP functional with the D95(d,p) basis set, which we have shown to be appropriate for H-bonding interactions.[1,2,7] Calculations of planar chains containing up to five monomers of 4-pyridone were completely optimized on the counterpoise (CP)-corrected energy surface[7] as were the vibrational frequencies needed to obtain the enthalpies at 298 K using the GAUSSIAN 03 suite of programs.[8] As in our previous study of H-bonding in formamides,[1] we found both the CP and vibrational corrections to be relatively constant upon addition of another monomer to the chain. We simply used these constants to correct the energies for chains containing more than five monomers. The geometric parameters plotted in the figures come from the normal (not CP-corrected) optimizations.

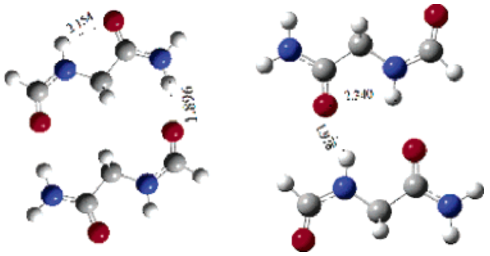

Figure 1. Large (left) and small (right) ring H-bonding dimers of a model diglycine. The enthalpies of interaction are −12.99 and −4.85 kcal/mol, respectively (ref 6).

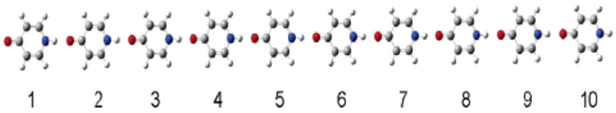

Figure 2. H-bonding chain of 4-pyridones.

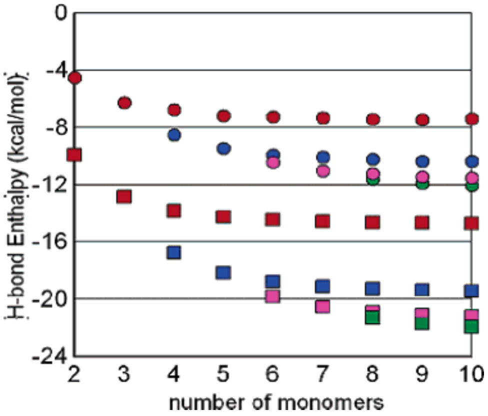

Figure 3. H-bond interaction energies by H-bond type. Circles denote formamide and squares 4-pyridone chains. Red symbols denote type 1 (terminal), blue denote type 2 (second from end), magenta type 3 (third from end), and green type 4 (fourth from end) H-bonds.

In the structure of 4-pyridone, the direct link between the NH and C═O of formamide is removed and replaced by two parallel −C═C− ethylenic π-systems. The molecule has C_{2v} symmetry, as do all planar H-bonding chains formed from this monomeric unit. Unlike its isomer, 2-pyridone, which is virtually isoenergetic with its tautomer, 2-hydroxypyridine, we calculated 4-pyridone to be 2.37 kcal/mol less stable than 4-hydroxypyridine. Nevertheless, the crystallographic evidence shows that the 4-pyridone molecule does exist.[9]

The $\Delta H_{\mathrm{inter}}$ values for each H-bond in chains of 4-pyridones (illustrated in Figure 2) containing from 2 to 10 monomeric units are compared with those previously reported[1] for chains of formamides and shown in Figure 3, while the H-bond distances for each H-bond are shown in Figure 4. We obtain each of the H-bonding enthalpies for a chain of N monomers from the simple expression $\Delta H_{\mathrm{inter}} = \Delta H_N - \Delta H_M - \Delta H_{N-M} - C_1 - C_2$, where M and $N - M$ are the number of monomers in each fragment after rupture of the H-bond, and C_1 and C_2 are the constants used to correct each H-bond for CP and vibrations.

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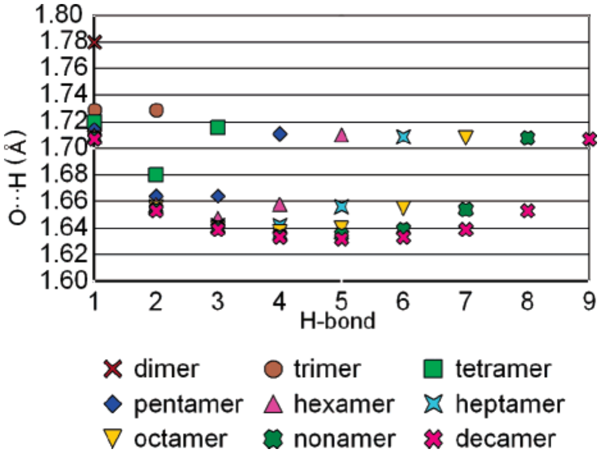

Figure 4. H-bond lengths (on surface uncorrected for CP) as a function of H-bond in 4-pyridone H-bonding chains.

The enthalpy of interaction for the H-bonding dimer of 4-pyridone is −9.90 kcal/mol, which is more than twice that of the analogous formamide dimer and more than half the H-bond enthalpy that we calculate for the 2-pyridone cyclic dimer (which has two, presumably cooperative, H-bonds) using the same methods. Inspection of Figure 3 and Table S1 shows that the strongest H-bond (that nearest the center of the decamer) has an enthalpy of interaction of −22.2 kcal/mol. Since the H-bonding enthalpies have clearly not yet reached their asymptotic limit, we expect even stronger H-bonds of approximately 23 kcal/mol near the middle of longer chains. This interaction for only one H-bond between neutral species is greater than that for the entire interaction in the cyclic 2-pyridone dimer (which has two H-bonds). Furthermore, the extent of the cooperativity in the chains of 4-pyridones is significantly greater in magnitude than that for formamide chains (∼13.3 vs ∼8.5 kcal/mol), although it is somewhat less in terms of percent of the dimeric interaction.

Putting these results in perspective, we see that the (deceptively) simple $N-H\cdots O=C$ H-bond can have interaction energies *in neutral systems* that vary from about −2 kcal/mol (one H-bond, or half the total interaction in the small ring dimer of a diglycine model[6]) to about −23 kcal/mol. Perhaps examples of even stronger $N-H\cdots O=C$ interactions can be found using more efficient coupling than that described here. Clearly controlling the extent of *intra*molecular coupling between the N−H and C═O of H-bonding molecules can become a key tool for modulating the energies of H-bonds for improved control of self-assembled systems. In retrospect, nature seems to have used similar tools to design different kinds of self-assembled biomaterials, such as proteins.

The large cooperative interactions between the 4-pyridones might be due to some combination of polarization, mutual polarization, and covalent interactions (charge transfer). As in the previously reported formamide chains, the cooperativity far exceeds that predicted by electrostatic interactions (which should be largely due to the sum over all dipole−dipole interactions). Figure 5 illustrates the change in dipole moment upon addition of a 4-pyridone molecule to the growing chain. This value should be constant for electrostatic interactions between the monomers. Instead, the asymptotic value exceeds 12 D, over 70% more than the dipole moment of monomeric 4-pyridone. Gilli has discussed the importance of resonance-assisted H-bonds (RAHBs), which have proved to be important to the stability of many crystal structures, including enaminones,[10,11] which are related to 4-pyridone. To evaluate the importance of covalent interactions (which we expected to be primarily between the π-orbitals) between the 4-pyridone units, we rotated the planes of adjacent molecules so that they became perpendicular to each other (thus eliminating π-overlap between them) both in the dimer and about the central H-bond of the decamer. Neither the change in the H-bond energy of the dimer (0.23 kcal/mol) nor the change in the central H-bond in the decamer (0.66 kcal/mol) is appreciable upon destroying the overlap in this manner. We must conclude that whatever covalent stabilization might exist between the monomers cannot be primarily within the π-system. We, therefore, conclude that the main contributions to the cooperativity in these systems must be some combination of polarization and mutual polarization. However, resonance *within the π-systems* certainly must contribute to the large polarizability of 4-pyridone.

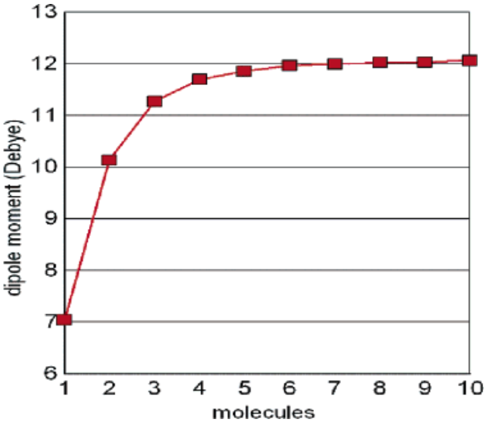

Figure 5. Change in dipole moment upon addition of a 4-pyridone molecule to the H-bonding chain.

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Supporting Information Available: The complete citation for GAUSSIAN 03 (ref 8) and Table S1 of interaction enthalpies. This material is available free of charge via the Internet at http://pubs.acs.org.

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