

Hydrogen Bonding Ability of the Amide Group

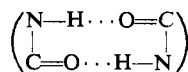
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Abstract: The hydrogen bonding of the amide linkage has been studied by *ab initio* molecular orbital methods using STO-3G and 431G basis sets. Amide-amide (C=O...H-N) hydrogen bonding is found to be stronger than amide-H₂O bonding at the STO-3G level but *not* at the 431G level. The possibility of forming "π" hydrogen bonds to the planar amide linkage is explored and it is found that only the carbonyl oxygen is a good "π" hydrogen bond donor. Amide-2H₂O complexes have been studied and the nonadditivity in hydrogen bonding found was qualitatively similar to that found in water polymers. The results found here are related to the experimental solution studies for amide association and further experiments are suggested to test the conclusions from our calculations.

The hydrogen bonding of the amide group is very important in determining the secondary and tertiary structure of proteins. In a biological environment the main competitors for the proton donor (N-H) site on the amide are nearby C=O linkages as well as side chains and the oxygens of nearby water molecules. The amide N-H and the water O-H compete for the carbonyl acceptor sites on the amide. Thus, we felt it important to examine amide-H₂O hydrogen bonding and compare it with amide-amide (C=O...H-N) hydrogen bonding.

Klotz and Franzen² examined the association of *N*-methylacetamide in aqueous solution using near-ir observation of the N-H overtone as a function of amide concentration and temperature and found very little association at concentrations less than 5 *M* amide. They interpreted their data in terms of $\Delta H_{\text{dimer}} = 0$ kcal/mol and $\Delta S_{\text{dimer}} = -10$ eu. Although these numbers are somewhat uncertain because of the small amount of association actually observed in water, the ΔH 's determined in chloroform and dioxane (-4.2 and -0.8 kcal/mol), where the association was more extensive, make them reasonable.

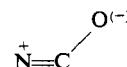
There have been a number of semiempirical molecular orbital studies of amide H bonding and these are reviewed by Murthy and Rao.³ There have been three *ab initio* studies of amide hydrogen bonding. Dreyfus, *et al.*,⁴ and Dreyfus and Pullman⁵ examined the association of formamide to form a cyclic



and linear⁵ (C=O...H-N) dimer. Their studies predicted a dimerization energy for linear (H₂NCHO)₂ of about 9 kcal/mol and a dimerization energy for cyclic (H₂NCHO)₂ of about twice this size (with the same basis set). A more extensive basis set predicted a

dimerization energy considerably smaller (14 kcal/mol) for the cyclic formamide dimer,⁴ in reasonable agreement with gas phase experiments.

A preliminary report of our STO-3G *ab initio* studies has appeared,⁶ in which we came to the following conclusions. (1) The relative stability of H bonds involving amide groups and H₂O is as follows: (a) amide-amide (C=O...H-N) = 9.4 kcal/mol, (b) amide-H₂O (N-H...OH₂) = 7.4 kcal/mol, (c) H₂O-H₂O \approx amide-H₂O (C=O...HOH) \approx 6.5 kcal/mol. (2) The resonance structure



plays a very important role in determining the hydrogen bonding of the amide group, with its proton acceptor ability far greater than that of an isolated C=O moiety ($\Delta E(\text{H}_2\text{CO} \cdots \text{HOH}) = 3.4$ kcal/mol; $E(\text{H}_2\text{NCHO} \cdots \text{HOH}) = 6.4$ kcal/mol) and its proton donor ability far greater than that of an amine N-H bond ($\Delta E(\text{H}_2\text{NH} \cdots \text{OH}_2) = 4.3$ kcal/mol, $\Delta E(\text{CHONH}_2 \cdots \text{OH}_2) = 7.4$ kcal/mol). In this present report we go into more detail on the nature of the amide-H₂O interaction, studying hydrogen bonding to the amide linkage as well as amide-2H₂O potential surfaces. We compare our *ab initio* results for planar formamide with nonplanar formamide and *N*-methylacetamide in an attempt to estimate the validity of formamide as a model for amide-H₂O hydrogen bonding and also examine the basis set dependence of our results. Finally, we attempt to relate our results to the experimental studies of Klotz and Franzen² and propose experiments which might shed further light on the strength and geometry of amide-H₂O hydrogen bonding.

Computational

These LCAO-MO-SCF calculations were carried out using STO-3G^{7a} and 431G basis^{7b} sets. A summary

(6) A. Johansson and P. A. Kollman, *J. Amer. Chem. Soc.*, **94**, 6196 (1972).

(7) (a) W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969); we have carried out these calculations using the MOLE quantum chemistry system (*Int. J. Quantum Chem., Symp.*, **3**, 715 (1970)); and Gaussian 70 (QCPE No. 236); (b) R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, **54**, 7241 (1971).

(1) (a) Åbo Akademi; (b) University of California, San Francisco; (c) Information Systems Design; (d) University of California, Berkeley.

(2) I. M. Klotz and J. S. Franzen, *J. Amer. Chem. Soc.*, **84**, 3461 (1962).

(3) A. S. N. Murthy and C. N. R. Rao, *J. Mol. Struct.*, **6**, 253 (1970).

(4) M. Dreyfus, B. Maigret, and A. Pullman, *Theor. Chim. Acta*, **17**, 109 (1970).

(5) M. Dreyfus and A. Pullman, *Theor. Chim. Acta*, **19**, 20 (1970).

of the monomer energies, Mulliken populations, and dipole moments for the STO-3G studies is presented in Table I.

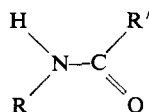
Table I. Monomer Results^a

| H ₂ NCHO ^b | | H ₂ O ^c | | H ₂ O ^e | |
|---|--------|-------------------------------|--------|-------------------------------|--------|
| $E_T = -166.67192$ au | | $E_T = -74.96178$ au | | $E_T = 74.96291$ au | |
| $\mu = 3.02$ (3.71) D | | $\mu = 1.68$ (1.82) D | | $\mu = 1.73$ (1.82) D | |
| Atomic Populations | | | | | |
| N | 7.4464 | O | 8.3654 | O | 8.3664 |
| C | 5.7513 | H | 0.8173 | H | 0.8168 |
| O | 8.2951 | | | | |
| H _{N_o} ^d | 0.7741 | | | | |
| H _{N_t} | 0.7890 | | | | |
| H _c | 0.9442 | | | | |

^a Experimental dipole moment in parentheses following calculated value. ^b Geometry from ref 4a. ^c Geometry from ref 9. ^d Cis to carbonyl. ^e Experimental geometry.

Dimer Potential Surfaces. The results of the formamide-dimer and formamide-water potential surfaces are presented in Table II (see Figure 1 for geometries). In these studies, the monomers were kept at a fixed geometry for formamide; the "monomer" geometry used was the planar geometry found for the formamide dimer.⁴ This is probably a better model of the planar peptide unit than the actual monomer geometry of formamide, which is considerably nonplanar.⁸ Most of the calculations employed the water monomer geometry calculated in ref 9 (results in Tables II-VI). In addition, the hydrogen bonds were assumed to be linear, $\theta(\text{X-H}\cdots\text{Y}) = 180^\circ$. This is a reasonably good assumption also; except in very strained systems, the optimum H-bond angle calculated for 1:1 complexes has always been very near linear, with the potential surface for bending off linearity very flat for X-H \cdots Y angles of more than 160° .¹⁰ The results for the σ hydrogen bonding (first three parts of the table) have been discussed previously,⁶ but we have carried out a few additional calculations along these lines.

We had previously examined the potential surface for water H bonding to the N-H which is trans to the carbonyl, since this is a model for the amide linkage



We now consider H bonding to the N-H cis to the carbonyl and find, at a geometry near the minimum energy of the trans form ($R(\text{O}\cdots\text{N}) = 2.8$ Å, $\theta(\text{NO-H}_{\text{bis}}) = 30^\circ$ ¹¹), an H bond of strength 7.6 kcal/mol, slightly stronger (0.3 kcal/mol) than the strength of the water-N-H_{trans} hydrogen bond. This can be simply rationalized on the basis of the hydrogen atomic populations of monomeric formamide; the cis hydrogen has 0.015 less electron than the trans. Previous studies¹² have also noted the good correlation of proton population in the monomer and that particular proton's ability to form a strong H bond; the smaller the population,

(8) C. C. Costain and J. M. Dowling, *J. Chem. Phys.*, **32**, 158 (1960).

(9) P. A. Kollman and L. C. Allen, *J. Chem. Phys.*, **51**, 3286 (1969).

(10) P. Kollman and L. C. Allen, *Chem. Rev.*, **72**, 283 (1972).

(11) H_{bis} is the bisector of the HOH angle in H₂O.

(12) P. Kollman, D. Giannini, W. Duax, S. Rothenberg, and M. Wolff, *J. Amer. Chem. Soc.*, **95**, 2869 (1973).

Table II. H-Bond Potential Surfaces

| R, Å | θ , deg | ΔE , kcal/mol |
|--|----------------|-----------------------|
| Amide-Amide ^a (Figure 1f) | | |
| 2.85 | 60 | -9.3 |
| 2.65 | 60 | -7.6 |
| 3.05 | 60 | -5.8 |
| 2.85 | 45 | -6.9 |
| 2.85 | 75 | -6.5 |
| 5.00 | 60 | -0.9 |
| Amide-H ₂ O ^b (H ₂ NHCO \cdots HOH) (Figure 1a) | | |
| 2.4 | 60 | -1.7 |
| 2.6 | 60 | -6.2 |
| 2.8 | 60 | -6.3 |
| 3.4 | 60 | -3.0 |
| 5.0 | 60 | -0.7 |
| 2.4 | 45 | -0.6 |
| 2.6 | 45 | -5.4 |
| 2.8 | 45 | -5.9 |
| 3.0 | 45 | -4.9 |
| 3.4 | 45 | -3.0 |
| 5.0 | 45 | -0.7 |
| 2.8 | 75 | -6.1 |
| 2.8 | 0 | -4.4 |
| 5.0 | 0 | -0.6 |
| Amide-H ₂ O ^c (CHONH ₂ \cdots OH ₂) (Figure 1b) | | |
| 2.6 | 30 | -7.1 |
| 2.8 | 30 | -7.3 |
| 3.0 | 30 | -5.9 |
| 2.8 | 15 | -7.3 |
| 2.8 | 45 | -7.2 |
| 2.4 | 0 | -1.0 |
| 2.8 | 0 | -6.9 |
| 3.5 | 0 | -2.9 |
| 4.0 | 0 | -1.6 |
| Amide-H ₂ O ^d (π Bond O-H \cdots N) (Figure 1c) | | |
| 2.7 | | 7.1 |
| 3.0 | | 1.6 |
| 3.3 | | 0.4 |
| 3.6 | | 0.2 |
| Amide-H ₂ O ^e (π Bond O-H \cdots Center of N-C Bond) | | |
| 3.3 | | 2.7 |
| 3.6 | | 0.4 |
| Amide-H ₂ O ^f (π Bond O-H \cdots O) (Figure 1d) | | |
| 2.6 | | 1.5 |
| 2.9 | | -2.0 |
| 3.2 | | -2.0 |
| 3.5 | | -1.4 |
| 3.8 | | -1.1 |
| Amide-H ₂ O ^g (π Bond O-H \cdots center of C=O) | | |
| 2.7 | | 7.4 |
| 3.0 | | 1.0 |
| 3.3 | | -0.6 |
| 3.9 | | -0.7 |
| 4.2 | | -0.5 |

^a The antiparallel configuration^{4b} of the linear formamide dimer was used; R is the O \cdots N distance, θ the C=O \cdots N angle; the N-H \cdots O angle was kept at 180° . ^b R is the O \cdots O distance, θ the C=O \cdots O angle; the O \cdots H-O angle was kept at 180° ; with $\theta \neq 0$ the water approaches the "lone pair" trans to the NH₂ group; the external O-H bond was trans to the formamide C-H bond. ^c R is the N \cdots O distance and θ the angle between the N-O line and the bisector of the HOH bond; the water was approaching the N-H trans to the carbonyl. ^d R is the O \cdots N distance, the O-H \cdots N angle was kept at 180° , and the projection of the external O-H bond vector on the plane of the formamide bisected the HNH angle. ^e R is the distance between the oxygen and the center of the C-N bond with the O-H bond normal to the formamide plane; the external hydrogen is pointed in the same direction as in the π O-H \cdots N bond. ^f R is the O \cdots O distance, the O-H \cdots O angle was 180° , and the projection of the external O-H bond vector on the formamide plane was along the C=O axis. ^g R is the distance between the O and the center of the C=O bond with the O-H bond normal to the formamide plane; the external hydrogen is pointed as in the π O-H \cdots O bond.

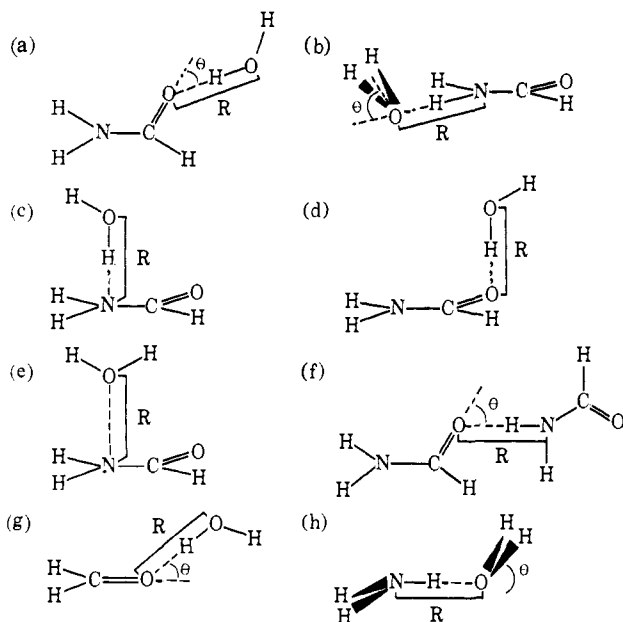


Figure 1. Amide-H₂O geometries.

the stronger the hydrogen bond formed. Note that this effect dominates the greater H₂O...O=C repulsion one expects in the cis hydrogen bond.

In Morokuma's¹³ study of formaldehyde hydrogen bonding, it was noted that the carbonyl could function quite well as a double proton acceptor, so we also calculated the hydrogen bond energy for a H₂O as a proton donor to the other lone pair (cis to the amide) of the carbonyl group; at $R(\text{O}\cdots\text{O}) = 2.8 \text{ \AA}$ and $\theta(\text{C}=\text{O}\cdots\text{O}) = 120^\circ$, the H-bond energy is 6.7 kcal/mol, slightly (0.4 kcal/mol) stronger than the H bond to the lone pair trans to the amide. This additional stabilization is very likely due to a weak H-bonding attraction between the N-H and the water oxygen, since the N-H trans to the carbonyl loses the same number of electrons (0.007) for approach to either C=O "lone pair," but the N-H cis to the carbonyl loses 0.005 electron when the H₂O is further from it and 0.012 electron when the water is nearer.

We have also examined a number of π hydrogen bonds to the amide group; the water molecule approached the N, the center of the C-N bond, the carbonyl oxygen, and the center of the C=O bond. The carbonyl oxygen forms the strongest " π " hydrogen bond. These results are quite consistent with electrostatic potential maps of formamide, from which it was inferred¹⁴ that the preferred site of protonation is the carbonyl group rather than the amide lone pair. The results here further demonstrate how different the amide linkage is from an amine in proton acceptor ability; the lone pair of the former is very little attracted to proton donors, the latter very strongly attracted.

Amide-2H₂O Interactions. Table III summarizes the results of the amide-H₂O and amide-2H₂O calculations. The results of the amide-single H₂O calculations have been discussed in the previous section and here we consider the nonadditivity effect; how much does the presence of the first water affect the ability

Table III. Amide-H₂O and Amide-2H₂O Interaction Energies

| Water at positions ^a | Total interaction energy ^b | H-bond energies ^c | Other two-body energies ^d | Nonadditivity ^e |
|---------------------------------|---------------------------------------|------------------------------|--------------------------------------|----------------------------|
| (1) | -6.3 | -6.3 | | |
| (2) | -6.7 | -6.7 | | |
| (3) | -7.3 | -7.3 | | |
| (4) | -7.6 | -7.6 | | |
| (5) | -2.0 | -2.0 | | |
| (6) | -0.7 | -0.7 | | |
| (7) | Repulsive | | | |
| (8) | Repulsive | | | |
| (1) + (2) | -12.2 | -13.0 | 0.7 | 0.1 |
| (1) + (3) | -14.5 | -13.6 | 0.1 | -0.1 |
| (1) + (4) | -14.7 | -13.9 | -0.1 | -0.7 |
| (1) + (5) | -8.0 | -8.3 | 0.3 | 0 |
| (1) + (9) | -14.8 | -12.8 | -0.3 | -1.7 |
| (1) + (10) | -10.2 | -12.8 | 1.0 | 1.6 |
| (3) + (4) | -13.5 | -14.9 | 0.5 | 0.9 |
| (3) + (11) | -15.8 | -13.8 | -0.4 | -1.6 |

^a Water placed at minimum energy position of Table II; for example, water (1) was at $R(\text{O}\cdots\text{O}) = 2.8 \text{ \AA}$; $\theta = 60^\circ$; $\pi(\text{O}-\text{H}\cdots\text{O})$ bond was at $R = 3.2 \text{ \AA}$, since this point had an energy ~ 0.05 kcal/mol lower than the $R = 2.9 \text{ \AA}$ point. ^b Energy of complex - sum of the monomer energies. ^c Sum of nearest neighbor H-bond energies, for example, for water at positions (1) + (3), this energy is the sum of the H-bond energy for water at (1) (-6.3 kcal/mol) and that at (3) (-7.3 kcal/mol). ^d Interaction energy of further apart molecules, for example, for water at (1) and (3), this is the energy for waters at positions (1) + (3) minus the sum of the monomer energies. ^e Nonadditivity - total energy for three-body complex minus the sum of monomer energies and two-body energies (the latter in the previous two columns). The total interaction energy of a trimer (2nd column) is the sum of the two-body energies (3rd and 4th column) and the three-body "nonadditivity" energy (5th column).

of the second water to form a hydrogen bond, either to the amide or to the water bonded to the amide?

In the cases where water is the central member of the trimer ((1) + (9), (1) + (10), and (3) + (11)), the nonadditivity follows the same trend as found by Hankins, *et al.*,¹⁵ in their studies of water dimers and trimers. When the central water is functioning as a proton donor and acceptor ((1) + (9) and (3) + (11)), the nonadditivity is negative (-1.7 and -1.6 kcal/mol) and the net hydrogen bonding is stronger than one would expect from just adding the H-bond energies of water (1)-amide, water (1)-water (9), and the small attraction of water (9)-amide. When the central water is functioning as a double proton donor, the nonadditivity is positive (1.6 kcal/mol) indicating that the amide-2H₂O complex is less tightly bound than one would expect by

(13) K. Morokuma, *J. Chem. Phys.*, **55**, 1236 (1971).

(14) R. Bonaccorsi, A. Pullman, E. Scrocco, and J. Tomasi, *Chem. Phys. Lett.*, **12**, 622 (1972).

(15) D. Hankins, J. Moskowitz, and F. Stillinger, *J. Chem. Phys.*, **53**, 4544 (1970).

Table IV. Charge Redistribution Effects on Formamide

| Complex | CT ^a | Atomic population changes ^b | | | | | | | | |
|--|-----------------|--|----------------|---------|----------------|---------|----------------|------------------|--------------------|----------------|
| | | C | C _π | N | N _π | O | O _π | H _{ois} | H _{trans} | H _o |
| (NH ₂ CHO) ₂ pd ^c | -0.036 | -0.0049 | 0.0032 | -0.0226 | 0.0114 | -0.0171 | -0.0146 | -0.0187 | 0.0310 | -0.0039 |
| (NH ₂ CHO) ₂ pa ^d | 0.036 | 0.0152 | 0.0233 | 0.0068 | 0.0134 | -0.0093 | -0.0368 | 0.0066 | 0.0077 | 0.0096 |
| (1) ^e | 0.037 | 0.0151 | 0.0244 | 0.0045 | 0.0122 | -0.0094 | -0.0367 | 0.0055 | 0.0075 | 0.0133 |
| (2) | 0.039 | 0.0158 | 0.0242 | 0.0028 | 0.0148 | -0.0097 | -0.0391 | 0.0129 | 0.0069 | 0.0101 |
| (1) + (2) | 0.073 | 0.0299 | 0.0469 | 0.0076 | 0.0272 | -0.0193 | -0.0742 | 0.0182 | 0.0142 | 0.0228 |
| (3) | -0.039 | -0.0041 | 0.0006 | -0.0261 | 0.0135 | -0.0160 | -0.0142 | -0.0162 | 0.0334 | -0.0098 |
| (1) + (3) | -0.002 | 0.0109 | 0.0248 | -0.0214 | 0.0270 | -0.0249 | -0.0518 | -0.0104 | 0.0403 | 0.0036 |
| (4) | -0.040 | -0.0033 | 0.0023 | -0.0256 | 0.0140 | -0.0159 | -0.0164 | 0.0326 | -0.0166 | -0.0111 |
| (3) + (4) | -0.076 | -0.0077 | 0.0024 | -0.0527 | 0.0282 | -0.0316 | -0.0307 | 0.0185 | 0.0190 | -0.0210 |
| (5) | 0.012 | 0.0032 | 0.0117 | 0.0032 | 0.0083 | -0.0083 | -0.0094 | 0.0044 | 0.0048 | 0.0045 |
| (1) + (5) | 0.048 | 0.0178 | 0.0206 | 0.0078 | 0.0351 | -0.0175 | -0.0454 | 0.0098 | 0.0122 | 0.0175 |
| (1) + (9) | 0.039 | 0.0173 | 0.0148 | 0.0056 | 0.0276 | -0.0138 | -0.0425 | 0.0069 | 0.0092 | 0.0138 |
| (1) + (10) | 0.033 | 0.0126 | 0.0086 | 0.0032 | 0.0200 | -0.0027 | -0.0286 | 0.0037 | 0.0041 | 0.0120 |

^a Charge transferred to or from amide; negative sign means increase of charge on amide. ^b Atomic population changes in amide; negative sign means increase in Mulliken population; positive sign means decrease in population. ^c The pd means proton donor in linear formamide dimer. ^d The pa means proton acceptor in linear formamide dimer. ^e Notation same as in Table III.

Table V. Charge Redistribution Effects on Central Water in Amide-2H₂O Complexes

| Complex | Atom ^a | | |
|---|-------------------|-----------------------------|----------------|
| | O | H ₁ ^d | H ₂ |
| (1) | -0.0424 | 0.0284 | -0.0225 |
| (H ₂ O) ₂ pa dimer with (9) ^b | 0.0002 | 0.0192 | 0.0192 |
| (H ₂ O) ₂ pd dimer with (10) ^c | -0.0431 | -0.0216 | 0.0262 |
| (1) + (9) | -0.0397 | 0.0473 | -0.0008 |
| (1) + (10) | -0.0882 | 0.0064 | 0.0089 |

^a Same convention as in Table IV; negative number indicates increased Mulliken population on atom. ^b (H₂O)₂ water molecules (1) + (9), populations are those of (1). ^c (H₂O)₂ water molecules (1) + (10), populations are those of (1). ^d H pointing at amide.

Table VI. Inner Shell Orbital Energies of Amide-H₂O Complexes

| Complex ^a | ε _C ^b | ε _N ^c | ε _O ^d |
|----------------------|-----------------------------|-----------------------------|-----------------------------|
| Isolated formamide | -11.145 | -15.365 | -20.198 |
| (1) | -11.169 | -15.384 | -20.223 |
| (2) | -11.169 | -15.381 | -20.222 |
| (3) | -11.122 | -15.324 | -20.171 |
| (4) | -11.123 | -15.325 | -20.171 |
| (1) + (2) | -11.193 | -15.399 | -20.245 |
| (1) + (3) | -11.147 | -15.343 | -20.195 |
| (3) + (4) | -11.100 | -15.284 | -20.144 |
| (1) + (5) | -11.183 | -15.393 | -20.233 |
| (1) + (9) | -11.176 | -15.389 | -20.227 |
| (1) + (10) | -11.159 | -15.375 | -20.214 |

^a Same notation as above. ^b Inner shell orbital energy of carbonyl carbon in au. ^c Inner shell orbital energy of amide nitrogen in au. ^d Inner shell orbital energy of carbonyl oxygen in au.

adding up the two-body energies. Extending our analysis to formamide as the central molecule in the trimer, we find similar trends; when formamide is functioning as a proton donor and acceptor ((1) + (3) and (1) + (4)), the trimer formed has a negative ("attractive") nonadditivity energy; when formamide is functioning as a double proton donor ((3) + (4)), the nonadditivity is repulsive. We also have considered trimers where formamide is a double proton acceptor ((1) + (2) and (1) + (5)), and the nonadditivity is very small (when one carries along one more significant figure, the nonadditivities are repulsive: 0.16 and 0.05 kcal/mol for (1) - (2) and (1) - (5), respectively).¹⁶

The difference in the nonadditivities for double proton donor and sequential water trimers can be rationalized quite simply on the basis of the Mulliken population on the hydrogen forming the additional H bond,¹⁷ but the sign of the nonadditivity found for double proton acceptor water trimers is somewhat more difficult to understand on this basis.¹⁸ However, it is clear from the above that the sign and magnitude of nonadditivity effects observed in these trimers are qualitatively similar to those found in the water trimer¹⁵ and thus these effects may be quite general phenomena. Del Bene and Pople have pointed out¹⁹ that the STO-4G basis exaggerates the nonadditivities compared to the most accurate trimer studies of Hankins, *et al.*,¹⁵ but that all the basis sets predict the extra stability from nonadditivity in the order sequential trimer > double acceptor > double donor.

Charge Redistribution Effects in Amide H Bonding. Table IV contains the Mulliken population results for a number of the H-bonded complexes discussed above. We have previously commented that in 1:1 H-bonded complexes A-X...H-Y-B, Y, B, and X gain charge on H-bond formation and H and A lose charge.^{6,20} In the 2:1 complexes with the amide the central molecule the charge redistribution effects for the 2:1 complex are nearly exactly equal to the sum of the charge redistribu-

(16) Hankins, *et al.*,¹⁵ find the water trimer where the central water is a double proton acceptor to have a positive (repulsive) nonadditivity, but this nonadditivity is smaller in magnitude than the nonadditivities of double proton donor or sequential trimers.

(17) J. Del Bene and J. A. Pople, *J. Chem. Phys.*, **52**, 4858 (1970).

(18) The central oxygen appears to gain a slight amount of charge when functioning as a proton acceptor in weak H bonds. Thus, one might expect the second proton donor water molecule to form a stronger O-H...^δ-O H bond. However, this "gain" in Mulliken population on the central oxygen is a compromise between charge transfer to the first water molecule and charge pulled from its two hydrogens. Examination of charge density maps (P. A. Kollman and L. C. Allen, *J. Chem. Phys.*, **52**, 5085 (1970)) shows that in the oxygen "lone pair" region of the H₂O...HF complex charge is lost, whereas there is charge build-up very close to the oxygen. This would provide a tentative rationalization for the slight repulsive nonadditivity in double proton acceptor trimers.

(19) J. Del Bene and J. A. Pople, *J. Chem. Phys.*, **58**, 3605 (1973).

(20) In weak H bonds X gains electrons, but as noted in the previous reference, this is due to a compromise between charge transfer and induction. In strong H bonds where charge transfer plays a larger role, the population on X will often decrease (P. A. Kollman, unpublished results on dimers involving HCl as a proton donor). There were two errors in Table I of ref 6; first in (formamide), the N in the proton acceptor was listed as having 7.7396 electrons instead of 7.4396; second, in the proton donor molecule populations, the H-bonded hydrogen is in row 3 rather than 2 (as inferred from the subscripts).

Table VII. H Bonding of Nonplanar Peptide Units

| Formamide ^a | $\phi = 0^\circ$ | | $\phi = 10^\circ$ | | $\phi = 20^\circ$ | | | |
|-----------------------------|-------------------------------|-----------------------|--|-----------------------|------------------------------|-----------------------|-----------------------------|-----------------------|
| O | 8.295 | | 8.294 | | 8.293 | | | |
| N | 7.446 | | 7.445 | | 7.444 | | | |
| H ₃ ^b | 0.789 | | 0.790 | | 0.790 | | | |
| | $\text{N}\cdots\text{O}\pi^c$ | | π bond (O-H \cdots N) ^d | | $\text{N-H}\cdots\text{O}^e$ | | $\text{C=O}\cdots\text{H}'$ | |
| | R, Å | ΔE , kcal/mol | R, Å | ΔE , kcal/mol | R, Å | ΔE , kcal/mol | R, Å | ΔE , kcal/mol |
| $\phi = 0^\circ$ | 2.7 | 1.5 | 2.7 | 6.1 | 2.6 | -6.8 | 2.6 | -6.1 |
| | 3.0 | 0.2 | 3.0 | 0.7 | 2.8 | -7.1 | 2.8 | -6.3 |
| | 3.3 | -0.1 | 3.3 | -0.5 | 3.0 | -5.9 | 3.0 | -5.2 |
| | 3.6 | -0.2 | 3.6 | -0.5 | | | | |
| $\phi = 10^\circ$ | 2.7 | 4.2 | 2.7 | 4.2 | 2.6 | -6.6 | 2.6 | -6.1 |
| | 3.0 | -0.3 | 3.0 | -0.3 | 2.8 | -7.0 | 2.8 | -6.3 |
| | 3.3 | -1.0 | 3.3 | -1.0 | 3.0 | -5.8 | 3.0 | -5.2 |
| | 3.6 | -0.8 | 3.6 | -0.8 | | | | |
| $\phi = 20^\circ$ | 2.7 | 2.6 | 2.7 | 2.6 | 2.6 | -6.1 | 2.6 | -6.0 |
| | 3.0 | -1.1 | 3.0 | -1.1 | 2.8 | -6.7 | 2.8 | -6.2 |
| | 3.3 | -1.4 | 3.3 | -1.4 | 3.0 | -5.5 | 3.0 | -5.1 |

^a Mulliken populations of atoms in formamide monomer as a function of ϕ . ^b Mulliken population of hydrogen trans to C=O. ^c Water approaching nitrogen from above amide plane; N \cdots OH₂ with water molecule and N-C bond all in one plane; HOH bisector along N \cdots O axis (Figure 1e). ^d Same approach as π bond (O-H \cdots N) in Table II for $\phi = 0$; for $\phi \neq 0$ the O-H bond approached along the bisector of the CNH_{bis} angle. (H_{bis} is the line bisecting the HNH angle.) ^e Same approach as in CHONH₂ \cdots OH₂ bond in Table II. θ fixed at 30° (Figure 1b). ^f Same approach as H₂NHCO \cdots HOH bond in Table II. θ fixed at 60° (Figure 1a).

tion effects for the two 1:1 complexes. For example, the charge redistribution (Mulliken population change) at each atom in the (1) + (3) 2:1 complex is almost equal to the Mulliken population change in the (1) complex and the (3) complex. The carbonyl carbon loses 0.0151 electron in complex (1), gains 0.0041 electron in complex (3), and loses 0.0109 electron in complex (1) + (3). This same additivity holds at the other atoms as well and is nearly exact (to round off error) in most cases. In these cases, one might speculate that the energy of nonadditivities observed are due mainly to electrostatic effects, since the charge redistribution effects are not hampered by the presence of a second H bond.

However, in the 2:1 complexes where water is the central molecule, one observes a small but not insignificant difference in charge redistribution at the amide depending on whether the central water is a double proton donor (1) + (10) or a proton donor and acceptor (1) + (9). When the central molecule is a double proton donor, the charge redistribution effects in the amide are *less* than that found in the 1:1 complex (1); when the central water is both a proton donor and acceptor, the charge redistribution in the amide is more than that found for complex (1). Comparing populations on the central water molecule in complex (1), (1) + (9), (1) + (10), and the water dimer (where water can function as either a proton donor or acceptor), one finds that the charge redistribution effects on the central water in (1) + (9) and (1) + (10) are close to the sum of those expected from summing the changes in the two 1:1 complexes (Table V). Although Mulliken populations are only approximate representations of the charge distribution, a comparison of density differences plots with Mulliken populations indicates that the atomic populations appear to be qualitatively correct in predicting charge redistribution on H-bond formation.⁹

In Table VI, the orbital energies of the amide inner shell orbitals are tabulated. As has been previously noted for 1:1 complexes, the orbital energies on the proton acceptor are generally lowered; those on the

proton donor are raised. As one can see from the table, the orbital energy changes for 2:1 complexes are also close to the change expected by summing the changes found in the appropriate 1:1 complexes.

Nonplanar Amide H Bonds

Although the planar formamide linkage is a first approximation to the bonding in peptides, there are situations where the peptide bond deviates from planarity and one would like to see how this affects the H-bonding strengths computed for the planar formamide-H₂O interaction. Thus, we have examined water forming H bonds to the formamide N-H, C=O, and N π lone pair as a function of the planarity of the formamide group. ϕ , the angle of deviation, represents the angle that the bisector of the two N-H bonds makes with the N-C-O plane, and we have made a limited search of the potential surface for H bonding at $\phi = 0, 10, \text{ and } 20^\circ$ (see Table VII).

The results at $\phi = 0$ are not the same as in Table II because of our use of the experimental water geometry in these calculations (Tables VII-IX). As one can

Table VIII. Comparison of Formamide and N-Methylacetamide H Bonding

| | Formamide | N-Methylacetamide |
|------------------------------------|-----------|-------------------|
| N-H \cdots O | | |
| Mulliken population on N-H | 0.789 | 0.797 |
| ΔE , ^a kcal/mol | -7.3 | -6.6 |
| C=O \cdots H | | |
| Mulliken population on C=O | 8.296 | 8.317 |
| ΔE , ^b kcal/mol | -6.3 | -6.7 |

^a $R = 2.8 \text{ \AA}$, $\theta = 30^\circ$. ^b $R = 2.8 \text{ \AA}$, $\theta = 60^\circ$.

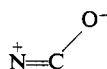
see, this makes relatively little difference in the intermolecular energies for the C=O \cdots HOH and N-H \cdots OH₂ H bonding but somewhat larger of a difference for the N π H bonding. In any case, N π H bonding is very weak, since the lone pair from the nitrogen is

Table IX. 431G Studies of H Bonding^a

| <i>R</i> , Å | <i>θ</i> , deg | ΔE , kcal/mol | <i>R</i> , Å | <i>θ</i> , deg | ΔE , kcal/mol |
|--|----------------|-----------------------|---|----------------|-----------------------|
| $\text{H}_2\text{NH}\cdots\text{OH}_2^b$ | | | $\text{H}_2\text{CO}\cdots\text{HOH}^c$ | | |
| 2.8 | 0 | -1.5 | 2.85 | 60 | -5.7 |
| 3.1 | 0 | -3.4 | 3.05 | 60 | -6.3 |
| 3.4 | 0 | -3.3 | 3.25 | 60 | -6.2 |
| 3.1 | 30 | -3.8 | | | |
| 3.1 | 60 | -4.0 | | | |
| $\text{HCOHNH}\cdots\text{OH}_2$ | | | $\text{H}_2\text{NHCO}\cdots\text{HOH}$ | | |
| 2.8 | 30 | -6.8 | 2.8 | 60 | -9.2 |
| $(\text{H}_2\text{NHCO})_2$ | | | $(\text{H}_2\text{O})_2^d$ | | |
| 2.85 | 60 | -8.2 | 2.83 | 147 | -8.2 |

^a Monomers at experimental geometries; $E_T(\text{H}_2\text{O}) = -75.90739$ au, $E_T(\text{H}_2\text{CO}) = -113.69031$ au; $E_T(\text{NH}_3) = -56.10259$ au; $E_T(\text{H}_2\text{NCHO}) = -168.67646$ au. ^b *R* is the N-O distance; *θ* is the angle the H_2O bisector makes with the N-O axis (Figure 1). ^c *θ* is $180 - \text{C}=\text{O}\cdots\text{H}$ angle; *R* is the O \cdots distance; the external H of water is trans to the C=O bond (Figure 1g). ^d Reference 19; see Figure 1 in this reference for the meaning of *R* and *θ*.

partially donated to the carbonyl group as represented by the resonance structure

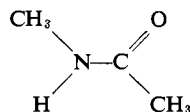


As one tilts the NH_2 group out of the plane, one sees that the N π bond becomes more favorable and the $\text{C}=\text{O}\cdots\text{HOH}$ and $\text{NH}\cdots\text{OH}_2$ H bonds become weaker. This is as expected since we are decreasing the contribution of the ionic resonance structure as we make the molecule nonplanar. From Table VII we can see that the changes in H bond energies as ϕ increases cannot be rationalized on the basis of simple electrostatic arguments based on Mulliken populations.

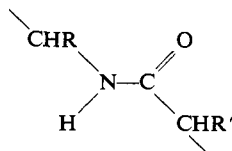
Small deviations from planarity of the peptide unit such as observed in X-ray structure studies²¹ cause significant changes in the H-bonding ability of the N lone pair. At $R = 3.0$ Å, the interaction goes from 0.7 kcal/mol (repulsive) for $\phi = 0$ to -1.1 kcal/mol (attractive) at $\phi = 20^\circ$.

N-Me Acetamide H Bonds

Formamide itself is a relatively simple model for peptide H bonding, *N*-methylacetamide



being a more realistic model for the peptide unit in proteins



How does the *N*-methylacetamide- H_2O H bonding compare with that of formamide- H_2O ? Only one point on the potential surface²² near the minimum was examined for $\text{N}-\text{H}\cdots\text{O}$ and $\text{C}=\text{O}\cdots\text{H}$ bonding

(21) L. L. Reed and P. R. Johnson, *J. Amer. Chem. Soc.*, **95**, 7523 (1973).

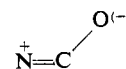
(22) A. Pullman and J. Post have informed us they are carrying out a more complete study of the *N*-methylacetamide-water surface.

in *N*-methylacetamide and the results are compared with formamide in Table VIII. The methyl group appears to donate electrons to the N-H and the C=O and thus make the carbonyl group a better electron donor than in formamide and the N-H group a poorer proton donor. These changes are reflected in the *N*-methylacetamide- H_2O H-bond strengths, where $\text{C}=\text{O}\cdots\text{H}$ and $\text{N}-\text{H}\cdots\text{OH}_2$ bonds are of approximately equal strength.

Basis Set Dependence of These Results. Table IX presents some points on the potential surface for $\text{H}_2\text{NH}\cdots\text{OH}_2$, $\text{H}_2\text{CO}\cdots\text{HOH}$, $\text{H}_2\text{NCHO}\cdots\text{HOH}$, $\text{H}_2\text{NCHO}\cdots\text{HNHCHO}$, $\text{CHOHNH}\cdots\text{OH}_2$, and $\text{HOH}\cdots\text{OH}_2$ interactions, studied with the 431G basis set. We did not do complete geometry searches, but comparative studies with STO-3G and 431G¹⁹ show them to have similar minimum energy geometries for $(\text{H}_2\text{O})_2$. In most cases, we used the STO-3G minimum energy geometry for the 431G calculation.

There are some important differences between the STO-3G and 431G results. First, amide-amide bonding ($\Delta E = -8.2$ kcal/mol) is predicted to be weaker than amide- H_2O $\text{C}=\text{O}\cdots\text{HOH}$ hydrogen bonding ($\Delta E = -9.2$ kcal/mol) but stronger than amide-water $\text{N}-\text{H}\cdots\text{OH}_2$ H bonding ($\Delta E = -6.8$ kcal/mol). Second, the 431G basis predicts the C=O group to be a far better H-bonding site than the N-H by 2.4 kcal/mol. Finally, unlike our previous calculations with the STO-3G basis, the 431G basis does "preserve" the concepts of intrinsic proton donor and proton acceptor strengths. From the H-bond energies of $\text{CHOHNH}\cdots\text{OCHNH}_2$ and $\text{HOH}\cdots\text{OCHNH}_2$ we conclude that the water OH is a better proton donor than the amide N-H by 1.0 kcal/mol; comparing $\text{H}_2\text{NH}\cdots\text{OH}_2$ and $\text{HCOHNH}\cdots\text{OH}_2$, we conclude that the amide N-H is a better proton donor than the amine N-H by 2.8 kcal/mol. Thus, we would predict that the water O-H is a better proton donor than the amine N-H by 3.8 kcal/mol and a comparison of $\text{H}_2\text{NH}\cdots\text{OH}_2$ and $\text{HOH}\cdots\text{OH}_2$ shows that this calculated difference in proton donor strength is 4.2 kcal/mol. A similar comparison can be made for the amide C=O, the aldehyde C=O, and the water oxygen from the following data: $\Delta E(\text{HCONHN}\cdots\text{OCHNH}_2) = -8.2$ kcal/mol; $\Delta E(\text{HCOHNH}\cdots\text{OH}_2) = -6.8$ kcal/mol; $\Delta E(\text{HOH}\cdots\text{OCH}_2) = -6.3$ kcal/mol; and $\Delta E(\text{HOH}\cdots\text{OCHNH}_2) = -9.2$ kcal/mol; one predicts that the water O is a better proton acceptor than the aldehyde C=O by 1.5 kcal/mol and $\Delta E(\text{H}_2\text{O}\cdots\text{HOH}) = 7.8$ bears this out exactly.

The amide resonance effect



predicts the amide C=O to be a 2.9 kcal/mol better proton acceptor than the aldehyde C=O and the amide N-H a 2.8 kcal/mol better proton donor than the amine N-H. These results are almost quantitatively the same as found with the STO-3G basis.

Neither the STO-3G nor 431G by bases are adequate for quantitative accuracy, the 431G greatly exaggerating H-bond energies because of its poor representation of monomer charge distributions (e.g., for H_2O , $\mu(431\text{G}) = 2.6$ D; for H_2NCHO , $\mu(431\text{G}) = 4.7$ D). The STO-3G basis predicts more reasonable monomer

dipole moments but exaggerates intermolecular effects because it represents the inner shell orbitals so poorly. One clearly needs to carry out calculations including polarization functions on the monomers¹⁵ to hope for more quantitatively correct dimerization energies. However, one expects the relative energies predicted by the 431G basis to be more reliable than those predicted by STO-3G²³ and thus amide-H₂O H bonding (the average of C=O...H-O and N-H...OH₂) to be *ca.* equo-energetic to amide-amide H bonding.

Recent *ab initio* calculations by Alagona, *et al.*,²⁴ who used a basis set somewhat lower in total energy than STO-3G, but higher than 431G, find qualitatively similar results for the formamide-H₂O surface, with C=O...H hydrogen bonding stronger than N-H...O.

Relation to Experimental Studies

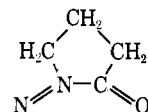
The results presented here are of most direct relevance to gas phase and inert matrix studies and a number of important experimental studies suggest themselves. Precise structural studies of 1:1 amide-water complexes might be carried out by the supersonic nozzle beam method for studying weakly bound complexes.²⁵ Low-temperature matrix ir studies or amide-H₂O ir studies in an inert solvent should provide definitive evidence whether in the most stable formamide-H₂O complex the amide is a proton donor or acceptor. Similar studies would give some insight into the relative H-

(23) L. Radom, W. A. Lathan, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, **94**, 2371 (1972).

(24) G. Alagona, A. Pullman, E. Scrocco, and J. Tomasi, *Int. J. Peptide Res.*, **5**, 251 (1973).

(25) T. R. Dyke, B. J. Howard, and W. Klemperer, *J. Chem. Phys.*, **56**, 2442 (1972).

bonding ability of different amides, such as *N*-methylacetamide and *N*-methylformamide. As noted above, one is not certain about the difference between formamide H bonding (studied in this paper) and *N*-methylacetamide H bonding (ref 1), so one would like to have more precise theoretical estimates for the effects of added methyl groups on the amide-amide and amide-H₂O H-bond strengths. One would also like to determine experimental ΔH dimerization for formamide, *N*-methylformamide, *N*-methylacetamide, and



by a number of different spectroscopic techniques.

Finally, one should note that the studies of Kuntz²⁶ are consistent with an average hydration of only one water per peptide linkage in polypeptides, most of the hydration being due to cationic or anionic side chains. From the above, it appears that it is the C=O rather than the N-H that is being hydrated. These are clearly a number of avenues for further experimental and theoretical studies of amide-amide and amide-H₂O hydrogen bonding.

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(26) I. D. Kuntz, *J. Amer. Chem. Soc.*, **93**, 514 (1971).

Calorimetric Investigation of the Reaction of Pyridine with Compounds of the Type Di- μ -chloro-dichlorobis(olefin)dipalladium(II)

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Abstract: The following reactions have been characterized *via* nmr, uv, and microcalorimetry: $[\text{PdCl}_2(\text{olefin})]_2 + 2\text{py} \rightarrow 2[\text{PdCl}_2(\text{olefin})(\text{py})]$ and $[\text{PdCl}_2(\text{olefin})(\text{py})] + \text{py} \rightarrow [\text{PdCl}_2(\text{py})_2] + \text{olefin}$, where olefin = ethylene, *cis*-butene, cyclopentene, cyclohexene, cycloheptene, *cis*-cyclooctene, and styrene. The enthalpy changes for these reactions are reported and the relative displacement energies of the ligands from the metal are 14.3 (py), 2.7 (C₃H₄), 1.6 (C₇H₁₂), 0.5 (C₂H₄), 0.4 (C₆H₁₀), 0.3 (styrene), and 0.0 (C₅H₈) kcal/mol. The equilibrium constants were too high to measure under the experimental conditions used. This and previously published data suggest that the σ contribution to the metal-olefin bond is more important than the π contribution for Ag(I) and Pd(II) and that the metal has increasing π character Ag(I) < Pd(II) < Rh(I) \sim Pt(II). The enthalpic data are related to catalytic phenomena, ionization potentials of the olefins, qualitative stability of metal-olefin compounds, and the decrease in the double bond stretching frequency upon coordination to the metal.

We have recently reported a series of studies involving the characterization of reactions involving metal-olefin compounds in weakly polar solvents *via* nmr and calorimetric techniques.¹⁻³ A re-

(1) W. Partenheimer, *Inorg. Chem.*, **11**, 743 (1972).
 (2) W. Partenheimer and E. F. Hoy, *J. Amer. Chem. Soc.*, **95**, 2840 (1973).

cent review has summarized the available thermodynamic data pertaining to metal-olefin compounds.⁴ We have previously pointed out the problems in interpreting the available thermodynamic data due to the

(3) W. Partenheimer and E. H. Johnson, *Inorg. Chem.*, **12**, 1274 (1973).
 (4) F. R. Hartley, *Chem. Rev.*, **73**, 163 (1973).