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Molecular Orbital Theory of the Hydrogen Bond. 18. Methyl Substituent Effects on Amide Hydrogen Bonding

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Abstract: Ab initio SCF calculations have been performed to investigate the effect of methyl substitution on amide hydrogen bonding. Equilibrium structures and stabilization energies of amide-water dimers which contain methylformamide, acetamide, and methylacetamide have been determined, and compared with the structures and stabilization energies of corresponding formamide-water dimers. When the amide molecule is the proton donor, or when it is the proton acceptor and hydrogen bond formation occurs on that side of the carbonyl group "trans" to nitrogen, the presence of a methyl group has little effect on the equilibrium structure. However, when the amide is the proton acceptor molecule and hydrogen bonding occurs "cis" to nitrogen, a methyl group bonded to the nitrogen "s-cis" to CO prevents cyclization. Methyl substitution decreases the stabilities of dimers with the amide molecules as proton donors, and increases to a lesser extent the stabilities of dimers with amides as proton acceptors. Hydrogen bond formation at the carbonyl oxygen "trans" to nitrogen is more favorable than "cis" hydrogen bond formation except when the "cis" structure is cyclic. Methyl substitution has little effect on the stabilities of 2:1 water-amide trimers relative to the corresponding dimers, and on the nonadditivity of hydrogen bond energies in open trimers. Greater nonadditivities of hydrogen bond energies are found in trimers in which the amide molecule is either a proton donor or a proton acceptor, and which therefore contain uninterrupted N-H...O-H...O or O-H...O-H...O chains of hydrogen bonds.

Introduction

Hydrogen bonding involving the amide group is an important factor in determining the structures of proteins and polypeptides. In view of the important role which proteins and polypeptides play in biochemistry, it is not surprising that a number of theoretical studies of hydrogen bonding have focused on the amide group. The first such investigations using ab initio SCF techniques were reported by Dreyfus, Maigret, and Pullman,¹ and by Dreyfus and Pullman,² who examined hydrogen bonding in formamide dimers. Hydrogen bonding in formamide-water systems has been studied by Johansson and Kollman,³ by Johansson, Kollman, Rothenberg, and McKelvey,⁴ by Ottersen,⁵ and by Ottersen and Jensen.⁶ Earlier papers in this present series reported the results of studies of formamide as a proton donor and a proton acceptor molecule in dimers and trimers containing formamide and water.^{7,8} A very detailed study of the solvation of formamide by water molecules has been published by Alagona, Pullman, Scrocco, and Tomasi.⁹ This work was followed by a note on the solvation of methylacetamide.¹⁰

While formamide, the simplest amide, may serve as a model for studies of hydrogen bonding in proteins and polypeptides, alkyl-substituted formamides are more representative of these hydrogen bonded systems. How suitable a model formamide is, and the effect of methyl substitution on amide hydrogen bonding, are points addressed in this paper. To this end, a systematic investigation has been undertaken of the structures and hydrogen bond energies of 1:1 and 2:1 water-amide

complexes containing the methyl-substituted formamide molecules methylformamide, acetamide, and methylacetamide as proton donor and as proton acceptor molecules. It is the purpose of this paper to report the results of this investigation.

Method of Calculation

Basis Set. Wave functions for the closed-shell ground states of the monomers and hydrogen bonded complexes have been expressed as single Slater determinants consisting of doubly occupied molecular orbitals. These orbitals have been obtained variationally through the Roothaan SCF procedure as linear combinations of atomic basis functions.¹¹ The atomic basis set used for the molecular orbital expansions is the minimal STO-3G basis set with standard scale factors.¹²

Geometry Optimization of Monomers. It has been noted previously that spurious dimer stabilization may occur when nonoptimized geometries are used for the monomers which form hydrogen-bonded complexes.^{8,13} Since this may be a serious error when substituent effects in dimers with similar stabilization energies are being compared, the first step in this study was to optimize the structures of methylformamide, acetamide, and methylacetamide. For these molecules, intramolecular coordinates were optimized cyclicly and independently to ± 0.01 Å in bond distances and $\pm 1^\circ$ in bond angles, subject to C_s symmetry and the constraints noted in Table I. Parabolic interpolation was then used to estimate bond distances to 0.001 Å and bond angles to 0.1°, yielding the struc-

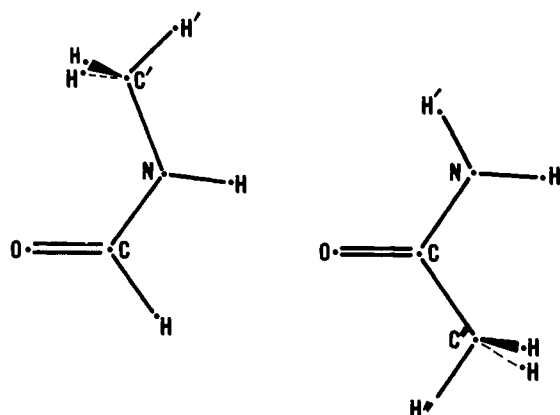


Figure 1. Methylformamide and acetamide.

Table I. Equilibrium Structures of the Amide Molecules^{a,b}

	Bond distances, Å		Bond angles, deg	
Formamide ^c	CO	1.218 (1.243)	OCN	124.3 (123.6)
	CH	1.105 (1.094)	OCH	124.3 (132.5)
	CN	1.403 (1.343)	CNH	121.6 (120.5)
	NH	1.013 (0.995)	CNH'	120.1 (120.5)
	NH'	1.014 (0.995)		
Methylformamide	CO	1.219	OCN	124.0
	CH	1.105	OCH	124.3
	CN	1.405	CNH	119.0
	NH	1.016	CNC'	122.0
	NC'	1.462	HC'H	108.4
	C'H'	1.091	NC'H'	109.4
Acetamide	CO	1.220 (1.21)	OCN	122.3 (125)
	CC''	1.544 (1.53)	OCC	124.4 (122)
	CN	1.410 (1.36)	CNH	121.9 (107) ^d
	NH	1.013 (1.02) ^d	CNH'	120.0 (107) ^d
	NH'	1.014 (1.02) ^d	HC''H	108.8
	C''H''	1.086 (1.09) ^d	CC''H''	109.6 (109.5) ^d
Methylacetamide	CO	1.221	OCN	121.8
	CC''	1.544	OCC''	124.5
	CN	1.411	CNC'	121.4 (117) ^e
	NC'	1.462 (1.44) ^e	CNH	119.8
	NH	1.015	HC'H	108.3
	C'H'	1.091	NC'H'	109.4
	C''H''	1.086	HC''H''	109.2
		CC''H''	108.9	

^a Molecular C_s symmetry and local C_3 symmetry assumed for the methyl groups. Experimental values given in parentheses have been taken from L. E. Sutton, "Tables of Interatomic Distances and Configurations in Molecules and Ions", The Chemical Society, London, 1965. ^b See Figure 1 for labeling. ^c Formamide data taken from ref 15. ^d Assumed values. ^e Dimensions of acetamide part assumed to be the same as those for acetamide.

tures reported in Table I. In methylformamide and methylacetamide, the methyl group is "s-cis" to the carbonyl group, giving the OCNH "trans" structure found in biological molecules. The conformations of the methyl groups which are shown in Figure 1 correspond to the lowest energy conformations in methylformamide and acetamide, as determined by Pople et al.¹⁴ The same conformations have been used in methylacetamide. The optimized geometries of formamide¹⁵ and of water¹⁶ have been reported previously, and have been used in this study.

Geometry Optimization of Dimers. With the restriction that the optimized geometries of the monomers be held rigid, the structures of the hydrogen-bonded complexes have been optimized in an intermolecular coordinate system to ± 0.01 Å in R , the intermolecular A-B distance measured along the A-H...B hydrogen bond, and, where possible, to $\pm 1^\circ$ in each of

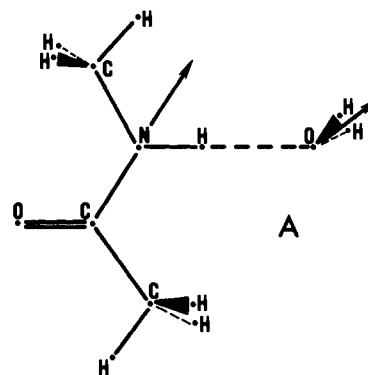


Figure 2. The methylacetamide-water dimer A, with principal axes "cis" with respect to the intermolecular line.

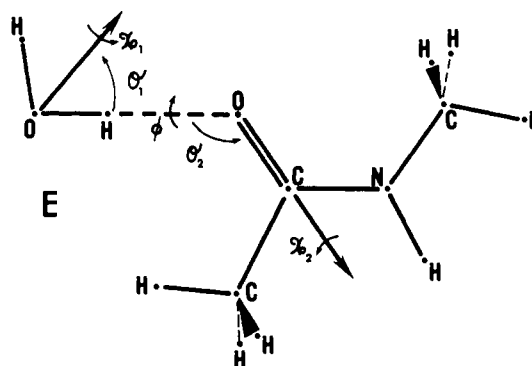


Figure 3. The methylacetamide-water dimer E. Intermolecular coordinates and principal axes are shown.

five intermolecular angles. These angles are defined with reference to the intermolecular A-B line and the principal axes of the proton donor and proton acceptor molecules. For convenience, the principal axis of an amide proton donor molecule has been chosen as the bisector of the H-N-H angle in formamide and acetamide, and of the corresponding H-N-C angle in methylformamide and methylacetamide, with origin at the nitrogen, as shown in Figure 2. When the amide molecule is the proton acceptor, the principal axis has been chosen coincident with the carbonyl CO bond, with origin at the oxygen, as illustrated in Figure 3. For water, the principal axis is the C_2 symmetry axis. In the intermolecular coordinate system, the angle θ_1 is the angle between the principal axis of the proton donor molecule and the intermolecular line, while the angle χ_1 measures rotation of the proton donor molecule about its own principal axis. Angles θ_2 and χ_2 refer to the proton acceptor molecule, and are defined analogously to θ_1 and χ_1 , respectively. The fifth angle ϕ measures rotation of the principal axis of the proton acceptor molecule about the intermolecular A-B line. These angles are shown in Figure 3. The stabilization energy (hydrogen bond energy) of an equilibrium dimer is computed at that point on the intermolecular surface at which the intermolecular coordinates have their optimized values, as the difference between the total dimer energy and the energies of the isolated monomers. In this study, two regions of the intermolecular surfaces have been investigated for equilibrium structures. In one of these, the amide molecule is the proton donor molecule, and N-H...O hydrogen bonds formed through the N-H proton "s-trans" to CO are found in dimers labeled A and B. In the other, the amide molecule is the proton acceptor molecule, and O-H...O hydrogen bonds are found in dimers labeled E and F.¹⁷

Trimers. The 2:1 water-amide trimers have been constructed from the rigid optimized dimers. Three different types

have been examined. In the first, the amide molecule is the central molecule in the trimer, acting as a proton donor through the N-H proton and a proton acceptor through the carbonyl oxygen. These trimers are identified in terms of the corresponding dimers as A-E, B-E, A-F, and B-F. Thus, trimer A-E is one in which the amide molecule is a proton donor to one water molecule as in dimer A of Figure 2, and a proton acceptor as in dimer E of Figure 3. A second set of trimers, defined as AWW-A and AWW-B, are those in which the amide molecule is the proton donor to a hydrogen bonded water dimer, forming an N-H...O-H...O chain of hydrogen bonds. In AWW-A, the hydrogen-bonded amide and water molecules have the relative orientation found in dimer A. The hydrogen-bonded water dimer is the equilibrium dimer reported previously.¹⁸ In the third set of trimers WWA-E and WWA-F, the water dimer is the proton donor and the amide molecule is the proton acceptor as in dimers E and F, respectively, with the formation of an O-H...O-H...O chain of hydrogen bonds. All calculations reported in this paper have been performed in double precision on an IBM 370/145 computer.

Results and Discussion

A Model for Dimer Structures. In previous papers of this series the general hybridization model (GHM) has been introduced and used as a model for equilibrium structures of hydrogen-bonded dimers.^{7,8,19} This model describes the idealized hydrogen bond as one which arises when a directed lone pair of electrons on the proton acceptor atom takes part in the formation of a linear hydrogen bond. The directed lone pair of electrons is necessary to provide a region of high electron density at the proton acceptor site. Qualitatively, this region coincides with one of the lone pair hybrid orbital directions. The linear hydrogen bond is formed when the proton lies along the A-B line, and is necessary for the close approach of the negatively charged atoms A and B which form the A-H...B hydrogen bond. In GHM, the directed lone pair of electrons is viewed as the factor which is primarily responsible for determining the orientation of the proton acceptor molecule, as described by the intermolecular coordinates θ_2 and χ_2 . In terms of this model, idealized values of θ_2 and χ_2 are 125 and 90°, respectively, when water is the proton acceptor molecule. For a carbonyl proton acceptor molecule, χ_2 values of 0 or 180° and θ_2 values of 120° are anticipated. The linear hydrogen bond determines the orientation of the proton donor molecule, described by coordinates θ_1 and χ_1 . Since the optimized value of the coordinate θ_1 necessary for a linear hydrogen bond varies as the proton donor molecule changes, the angle θ_1' has been introduced as a direct measure of the angle between the A-H bond and the intermolecular A-B line. In dimers, values of θ_1' and χ_1 equal to 0° correspond to a linear A-H...B hydrogen bond.

There has been a considerable amount of discussion in the literature concerning models for dimer structures in general, and the directionality of the hydrogen bond (as indicated by the angle θ_2) in particular.¹⁹⁻²² For the most part, it has been recognized in these discussions that the θ_2 potential curve may be somewhat flat near the minimum, so that variations in this coordinate may correspond to small energy changes. As noted above, the general hybridization model emphasizes the need for a directed lone pair of electrons as the primary factor in determining the orientation of the proton acceptor molecule. However, secondary factors such as dipole-dipole and long-range interactions also influence the structure of the dimer, particularly with respect to the orientation of the proton acceptor molecule. If these secondary factors assume increased importance, then distortions of the dimer structure from the idealized GHM structure may be anticipated.

The influence of secondary factors on dimer structures was

first illustrated in a study of the basis set dependence of the structure of the water dimer, where a correlation was observed between the computed value of the dipole moment of the water molecule and the optimized value of the angle θ_2 in the water dimer.²³ This correlation suggests that as the dipole moment increases, the dipole-dipole interaction assumes increased importance, with the result that the proton acceptor molecule rotates away from the proton donor (θ_2 increases) in order to provide for a more favorable distribution of charge ($\theta_2 = 180^\circ$ provides the $\delta - \dots\delta + \dots\delta - \dots\delta +$ arrangement along the intermolecular line). This, of course, occurs with a concomitant loss of the directed lone pair.

A test of the appropriateness of a model such as GHM can be made by comparing the model with experimental data. For this comparison, it is most appropriate to use gas-phase experimental data. Recently, the structure of the gas-phase water dimer has been reported by Dyke and Muentner, who concluded that in this dimer, the hydrogen-bonded proton lies along the oxygen-oxygen line, and the hydrogen bond forms in one of the tetrahedral directions with respect to the proton acceptor atom.²⁴ This structure is in agreement with the idealized GHM structure. Moreover, the value of the angle θ_2 computed with the STO-3G basis set (123°) is in excellent agreement with the value determined experimentally (122°). It is important to note here that the STO-3G value of the water dipole moment of 1.71 D is also in fairly good agreement with the experimental value of 1.85 D.²⁵ Thus, it seems appropriate to use GHM as a model for dimers formed from first-row elements, provided that it is recognized that this is an idealized model, and that secondary factors may lead to distortions of the idealized dimer structure. Indeed, as illustrated in previous papers of this series and as shown below, using GHM as a reference provides a framework for evaluating the influence of these factors on equilibrium structures.

Given that the orientation of the proton donor and proton acceptor molecules is determined primarily by the requirements of the directed lone pair and the linear hydrogen bond, the dimer structure is still not completely specified, since the proton acceptor molecule may rotate about the intermolecular line (the ϕ rotation) while keeping the hydrogen bond essentially intact. Once again, it is the secondary factors of dipole-dipole and long-range interactions which influence the nature of the ϕ coordinate, and determine where along this coordinate equilibrium structures are found.

When describing the structure of the water dimer, Dyke and Muentner labeled it a "trans" structure to indicate that the external nonhydrogen bonded proton of the donor molecule is "trans" to the hydrogens of the proton acceptor molecule with respect to the oxygen-oxygen line.²⁴ The computed equilibrium structure of the water dimer has a "trans" structure, as indicated by a value of 180° for the ϕ coordinate. The "trans" arrangement provides for the most favorable alignment of the dipole moments of the proton donor and proton acceptor molecules within the structural requirements of the directed lone pair and the linear hydrogen bond. Along the ϕ coordinate an energy maximum is found at $\phi = 0^\circ$, where a nearly parallel alignment of dipoles occurs.

In previous papers in this series, it has been shown that the ϕ coordinate may exhibit a definite minimum and maximum, as in the water dimer, or it may be relatively flat, so that the ϕ rotation is essentially free. In the former case, either the dipole alignment changes significantly as the proton acceptor molecule rotates about the intermolecular line, or somewhere along the ϕ coordinate long-range interactions assume increased importance. In the latter case, the angle between the intermolecular line and the dipole moment vector of either the proton donor or the proton acceptor molecule is small, so that rotation of the proton acceptor molecule about this line does not bring about significant changes in the relative orientation

Table II. Structures and Energies of Equilibrium Dimers

	$R, \text{\AA}$	θ_1', deg^a	χ_1, deg	θ_2, deg	χ_2, deg	ϕ, deg	$\Delta E, \text{au}^b$
Type A ^c							
Formamide	2.75	0	0	132	90	0	-0.010 22
Methylformamide	2.76	0	0	132	90	0	-0.009 77
Acetamide	2.76	-1	0	130	90	0	-0.009 54
Methylacetamide	2.77	-1	0	131	90	0	-0.009 18
Type B ^c							
Formamide	2.75	1	0	132	90	180	-0.010 14
Methylformamide	2.76	1	0	132	90	180	-0.009 74
Acetamide	2.77	0	0	134	90	180	-0.009 21
Methylacetamide	2.78	-1	0	135	90	180	-0.008 90
Type E ^d							
Formamide	2.78	0	0	117	0	180	-0.008 07
Methylformamide	2.78	0	0	117	0	180	-0.008 27
Acetamide	2.77	1	0	121	0	180	-0.008 73
Methylacetamide	2.77	1	0	121	0	180	-0.008 91
Type F ^d							
Formamide	2.74	23	0	95	180	180	-0.010 12
Methylformamide	2.81	-1	0	135	180	180	-0.007 69
Acetamide	2.71	20	0	98	180	180	-0.010 46
Methylacetamide	2.80	-2	0	138	180	180	-0.008 06

^a $\theta_1' = \theta_1 - \angle_{\text{HAX}}/2$, and is a direct measure of the linearity ($\theta_1' = 0^\circ$) or nonlinearity of the hydrogen bond. ^b ΔE is the intermolecular (hydrogen bond) energy. 1 au = 627.49 kcal/mol. ^c Types A and B have the amide molecule as the proton donor, with water as the proton acceptor. ^d Types E and F have the amide molecule as the proton acceptor, with water as the proton donor.

of the dipole moment vectors. The influence of secondary factors will again be evident in the features of the ϕ potential curves in the amide-water dimers.

Amides as Proton Donors. Structures. The structures of the hydrogen-bonded formamide-water, methylformamide-water, acetamide-water, and methylacetamide-water complexes in which the amide molecule is the proton donor molecule are reported in Table II. Two equilibrium structures A and B containing N-H...O hydrogen bonds have been found on the intermolecular surfaces. In A dimers, the principal axes of the proton donor and proton acceptor molecules are "cis" with respect to the intermolecular line ($\phi = 0^\circ$) as shown in Figure 2, while in B dimers, these axes are "trans" ($\phi = 180^\circ$). In both A and B dimers, linear N-H...O hydrogen bonds exist as indicated by the values of the coordinates θ_1' and χ_1 , independent of the presence or absence of methyl groups in the proton donor amide molecules.

In formamide-water dimers, the proton acceptor water molecule is rotated away from the proton donor formamide molecule, as indicated by the θ_2 coordinate, which is about 10° larger than in the water dimer. Methyl substitution in the proton donor molecule does not alter this orientation of the proton acceptor water molecule to any significant extent, as indicated by the values of the angle θ_2 , which range from 130° to 135° . The distortion of these equilibrium structures from idealized GHM structures may be attributed to an increased importance of the dipole-dipole interaction in these dimers, a result of the large dipole moments (2.64-2.70 D) of the amide molecules.

The orientation of the dipole moment vectors in the amide molecules also influences the nature of the ϕ potential curves in the dimers. In these amides, the angle between the dipole moment vector and the N-H bond varies only from 10° in acetamide to 22° in methylformamide. As a result, two equilibrium amide-water dimers A and B are found along relatively flat ϕ potential curves. These dimers are easily interconverted. The rotational barriers, estimated from the energies of structures described by the intermolecular coordinates of the A dimers but with $\phi = 90^\circ$, are only 0.17, 0.18, 0.24, and 0.25 kcal/mol, when formamide, methylformamide, acetamide, and methylacetamide, respectively, are the proton donor molecules.

Thus, there is essentially free rotation of the proton acceptor water molecule about the intermolecular line in all cases.

From the discussion of the structures of amide-water dimers and from the data of Table II, it is apparent that the structures of these equilibrium dimers which contain N-H...O hydrogen bonds are very similar. It may be concluded, therefore, that methyl substitution at the nitrogen or carbon atom of formamide has little effect on the equilibrium structures of hydrogen-bonded complexes having methyl-substituted formamides as proton donor molecules with water as the proton acceptor. The formamide-water dimers A and B are representative of the set of amide-water dimers.

Amides as Proton Donors. Energies. The stabilization energies of the equilibrium A and B dimers are also reported in Table II. Equilibrium dimers in which the principal axes of the proton donor and proton acceptor molecules are "cis" with respect to the intermolecular line (A dimers) are very slightly more stable than the "trans" dimers (B dimers). Corresponding A and B structures differ by 0.05, 0.02, 0.21, and 0.18 kcal/mol, when formamide, methylformamide, acetamide, and methylacetamide, respectively, are the proton donor molecules. The larger differences are found for the acetamide-water and methylacetamide-water dimers, where in the "trans" structures, the methyl group bonded to the carbon approaches more closely to the proton acceptor molecule, with a slight reduction in stability.

As evident from the data of Table II, methyl substitution leads to a decrease in the stability of dimers in which the amide molecule is the proton donor molecule, although the variation in stability in the series is less than 0.9 kcal/mol. The effect of the methyl group is slightly greater when substitution occurs at the carbon rather than at the nitrogen which is involved in the N-H...O hydrogen bond. Dimethyl substitution leads to a further reduction in stability, although the effect of two methyl groups is less than additive.

Mulliken population data,²⁶ reported in Table III, indicate that methyl substitution reduces the positive charge on the hydrogen atoms which form hydrogen bonds, from +0.196 in formamide to +0.190 and +0.191 e in methylformamide and acetamide, respectively, to +0.186 e in methylacetamide. Since there is a considerable amount of data suggesting that the

Table III. Mulliken Electron Populations

	N			O			H
	Total	π^a	σ	Total	π^a	σ	
Formamide	7.438	1.851	5.587	8.267	1.250	7.017	0.804 ^b
Methylformamide	7.366	1.824	5.542	8.268	1.249	7.019	0.810
Acetamide	7.442	1.862	5.580	8.280	1.264	7.016	0.809 ^b
Methylacetamide	7.371	1.834	5.537	8.280	1.263	7.017	0.814

^a π refers to N and O orbitals perpendicular to the molecular symmetry plane. ^b Hydrogen atoms "s-trans" to CO.

electrostatic interaction is a prime factor in the stabilization of hydrogen-bonded complexes, some correlation may be anticipated between the hydrogen bond energy and the positive charge on the proton in open dimers having the same proton acceptor molecule. It is interesting to note that the effect of methyl substitution on the electron density at the N-H proton is essentially the same whether the methyl group is bonded to the carbon or nitrogen atom. The methylformamide-water and acetamide-water A dimers also have similar stabilization energies of 6.13 and 5.99 kcal/mol, respectively.

Amides as Proton Acceptors. Structures. In those regions of the intermolecular surfaces where water is the proton donor molecule and the amides are proton acceptor molecules, two sets of equilibrium structures containing O-H...O hydrogen bonds have been found, which are labeled E and F in Table II. In both of these, the external non-hydrogen-bonded proton of water is "trans" to the carbonyl group (and the principal axes are also "trans") with respect to the intermolecular line ($\phi = 180^\circ$).²⁷ In E dimers, the hydrogen bond forms on that side of the carbonyl group "trans" to the nitrogen atom ($\chi_2 = 0^\circ$), as illustrated in Figure 3. In F dimers, hydrogen bond formation occurs "cis" to nitrogen ($\chi_2 = 180^\circ$).

The data of Table II indicate that the structures of the amide-water E dimers are similar, and consistent with the idealized structure of the general hybridization model. In particular, linear O-H...O hydrogen bonds exist in these dimers, as indicated by the values of the coordinates θ_1' and χ_1 . These bonds form in a trigonal direction with respect to the proton acceptor oxygen atom, as indicated by the θ_2 values which approach 120° . In addition, the intermolecular distances are within 0.01 Å in these dimers. Thus, methyl substitution in formamide has little effect on the equilibrium structures of amide-water dimers in which the water molecule is hydrogen bonded "trans" to the nitrogen. The structure of the formamide-water E dimer is an appropriate model for the structures of dimers formed with methyl-substituted formamides as proton acceptor molecules.

In the study of the formamide-water dimers, it was observed that when the proton donor water molecule is hydrogen bonded on that side of the carbonyl group "cis" to nitrogen, interaction between the water molecule and the N-H proton "s-cis" to CO leads to an equilibrium cyclic dimer.⁸ In this dimer, F, the intermolecular distance is reduced by 0.04 Å relative to the open dimer E, and the proton acceptor molecule has rotated toward the proton donor, as indicated by the reduced value of the coordinate θ_2 . A nonlinear O-H...O hydrogen bond is present in this dimer, as indicated by the value of 23° for the angle θ_1' . A comparison of the structural data for the acetamide-water dimer F with that of the formamide-water dimer F shows that the acetamide-water dimer is also cyclic. Thus, methyl substitution at the carbon atom does not interfere with cyclization.

Such is not the case when a methyl group is bonded to the nitrogen in the position "s-cis" to CO, as both the methylformamide-water and methylacetamide-water F dimers have open structures. Not only does the presence of the methyl group prevent cyclization, but it also causes the proton acceptor molecule to rotate away from the proton donor. The equilibrium methylformamide-water and methylacetamide-water

F dimers have structures which are distorted relative to the idealized GHM structure (θ_2 values are 135 and 138° , respectively, rather than 120°), indicating that the hydrogen-bonded oxygen lone pair is not optimally oriented. Thus, it is apparent that in dimers in which the water molecule is hydrogen bonded to the carbonyl group in a position "cis" to nitrogen, the presence or absence of a methyl group bonded to the nitrogen "s-cis" to CO has a major effect on the structure of the equilibrium dimer. As a result, the structure of the formamide-water dimer F is not typical of equilibrium structures of these amide-water dimers.

Amides as Proton Acceptors. Energies. The data of Table II indicate that methyl substitution has a stabilizing effect on amide-water dimers which have the amide molecules as proton acceptors in dimers containing O-H...O hydrogen bonds. This is in contrast to the destabilizing effect of methyl substitution on N-H...O hydrogen bond energies. In the open E dimers, the O-H...O bond energy increases from 5.1 kcal/mol in the formamide-water dimer to 5.6 kcal/mol in the methylacetamide-water dimer. Once again, methyl substitution has a smaller effect when it occurs at the nitrogen atom rather than the carbon, as the acetamide-water dimer is more stable than the methylformamide-water dimer. The presence of two methyl groups further enhances the stability of the methylacetamide-water dimer, although the effect of two methyl groups is again less than additive.

Methyl substitution at the nitrogen does not alter the electron density at the oxygen, as evident from a comparison of the oxygen electron populations in formamide and methylformamide, and in acetamide and methylacetamide. The stabilities of the corresponding pairs of amide-water E dimers also differ by only 0.13 and 0.11 kcal/mol, respectively. The greater impact on the carbonyl oxygen occurs when the methyl group is bonded to the carbonyl carbon, as seen from a comparison of the oxygen electron densities in formamide and acetamide. This difference may account in part for the 0.42 kcal/mol increase in the stability of the acetamide-water dimer relative to formamide-water. It should be noted that in open E structures the methyl group stabilizes the acetamide-water dimer relative to the formamide-water dimer to approximately the same extent as it stabilizes the acetaldehyde-water dimer relative to the formaldehyde-water dimer, by 0.46 kcal/mol.⁷

The data of Table II also show that the relative stabilities of corresponding E and F dimers depend on the nature of the interaction between the NH₂ or substituted NH₂ group and the proton donor water molecule when hydrogen bond formation occurs "cis" to nitrogen. When the nitrogen is unsubstituted, then the formation of a second nonlinear N-H...O hydrogen bond and a favorable dipole alignment in the cyclic dimer cause the formamide-water and acetamide-water F dimers to be more stable than the corresponding E dimers. When the nitrogen is methyl substituted "s-cis" to CO, repulsion between the methyl group and the water molecule in the methylformamide-water and methylacetamide-water F dimers reduces the stability of F dimers relative to E. However, even in the F dimers, the generalization that methyl substitution in these amide molecules stabilizes dimers which have the amides as proton acceptor molecules is still apparent, provided

Table IV. Second Derivatives of Intermolecular Energies^a

$\partial^2\epsilon/\partial\chi^2$:	$\partial\chi^2$					
	$\chi = R$	θ_1	χ_1	θ_2	χ_2	ϕ
			Type A ^b			
Formamide	0.026 18	0.053 07	0.053 56	0.008 40	0.014 17	0.000 48
Methylformamide	0.024 95	0.047 45	0.051 98	0.008 16	0.013 87	0.000 56
Acetamide	0.025 51	0.062 28	0.049 83	0.008 62	0.014 10	0.000 54
Methylacetamide	0.024 22	0.064 41	0.048 04	0.007 98	0.013 33	0.000 64
			Type B ^b			
Formamide	0.025 96	0.050 93	0.051 18	0.008 18	0.014 20	0.000 43
Methylformamide	0.025 01	0.047 12	0.049 55	0.008 08	0.013 74	0.000 53
Acetamide	0.023 69	0.075 83	0.046 84	0.007 26	0.012 80	0.000 33
Methylacetamide	0.022 79	0.074 81	0.044 88	0.007 03	0.012 41	0.000 38
			Type E ^c			
Formamide	0.020 69	0.035 84	0.019 55	0.023 38	0.005 30	0.000 90
Methylformamide	0.020 44	0.036 60	0.020 07	0.023 43	0.005 24	0.000 87
Acetamide	0.020 97	0.040 96	0.020 83	0.048 30	0.004 25	0.000 72
Methylacetamide	0.020 75	0.041 66	0.021 31	0.048 25	0.004 27	0.000 79
			Type F ^c			
Formamide	0.020 25	0.055 60	0.016 05	0.892 04	0.030 37	0.002 96
Methylformamide	0.017 67	0.034 37	0.017 56	0.092 48	0.001 86	0.000 89
Acetamide	0.022 79	0.061 59	0.019 04	0.690 18	0.026 39	0.002 54
Methylacetamide	0.018 01	0.035 85	0.018 43	0.089 79	0.001 63	0.000 85

^a In atomic units with angles in radians. ^b See footnote *c* of Table II. ^c See footnote *d* of Table II.

that dimers with the same type of structure are compared. Thus, for the cyclic dimers, acetamide-water is more stable than formamide-water, while for the open structures, the methylacetamide-water dimer F is more stable than the methylformamide-water dimer F.

Force Constants. Some estimates of the rigidity of the dimer structures with respect to distortions along intermolecular coordinates may be obtained by approximating the second derivatives of the dimer energies with respect to these coordinates. The derivatives are approximated as

$$\partial^2\epsilon/\partial\chi^2 \approx [\epsilon(\chi + \Delta) + \epsilon(\chi - \Delta) - 2\epsilon(\chi)]/\Delta^2$$

where $\epsilon(\chi)$ is the intermolecular energy of the equilibrium dimer and $\epsilon(\chi \pm \Delta)$ are intermolecular energies at two points along a particular intermolecular coordinate $\pm\Delta$ away from the optimized value of that coordinate. The Δ values are 0.1 Å for the intermolecular distance and 20° for intermolecular angles. The force constants estimated in this way are reported in Table IV, and are quite useful for comparative purposes. The following generalizations may be made from the data of Table IV.

1. There is a small variation in the rigidity of these dimer structures with respect to changes in intermolecular distances.

2. When the amide molecule is the proton donor molecule, angular force constants for the more stable A dimers are slightly larger than the corresponding force constants for B dimers. Exceptions to this generalization occur only in the θ_1 coordinate for the acetamide-water and methylacetamide-water dimers where increasing θ_1 causes the methyl group bonded to the carbonyl carbon atom to approach the water molecule. This is energetically more unfavorable in the B dimers.

3. Distortions of open dimer structures caused by rotation of the proton donor molecule are easier when an amide molecule is the proton donor (A and B dimers) than when water is the proton donor (E), even when the energies of corresponding B and E dimers are identical, as illustrated by the θ_1 and χ_1 force constants for the methylacetamide-water dimers.

4. In open dimers, distortions associated with bending the proton acceptor molecule toward or away from the proton donor molecule (θ_2 rotations) are easier in dimers A and B,

where water is the proton acceptor molecule, than in E, even though the E dimers are less stable than the corresponding A and B dimers. However, distortions caused by rotating the proton acceptor molecule about its principal axis (the χ_2 rotation) are easier in E dimers than in corresponding A and B dimers.

5. When the water molecule is hydrogen bonded "cis" to nitrogen, the equilibrium F dimers are quite rigid with respect to rotation of the proton acceptor molecule along the θ_2 coordinate, especially when the rotation moves this molecule toward the proton donor. The largest force constants are the θ_2 force constants for the cyclic formamide-water and acetamide-water dimers.

6. In all cases, the loosest intermolecular motion corresponds to rotation of the proton acceptor molecule about the intermolecular line (the ϕ rotation) which, in open dimers, leaves the hydrogen bond essentially intact. As expected, this rotation is more difficult in cyclic dimers.

Comparisons with Previous Results. At this point it is appropriate to compare the results of this study with those of ref 10, where the effect of methyl substitution on the hydration of methylacetamide relative to formamide was also investigated. Specific comparisons are difficult, since different basis sets have been used in these two studies, and, as noted above, the basis set does have some influence on the details of dimer structures. In addition, experimental monomer geometries were used in ref 10, and somewhat different dimer geometries were analyzed. However, some comparisons of general observations made in the two studies are possible, the following being most relevant.

1. Both studies are in agreement that in the amides, two distinct hydration sites exist at the carbonyl oxygen atoms. In ref 10 it was concluded that hydration of this atom in both formamide and methylacetamide is more favorable when the water molecule is "trans" to nitrogen (structure E) rather than "cis" (structure F). This present study supports this generalization provided that both structures E and F are similar. However, in those cases where dimer F is cyclic, it is more stable than the corresponding dimer E.

2. The data of this study suggest that the hydrogen bonds in the amide-water dimers are essentially linear, except in the cyclic structures where two nonlinear hydrogen bonds are

Table V. Energies (au) of 2:1 Water-Amide Complexes^a

	A-E	B-E	A-F	B-F	AWW-A	AWW-B	WWA-E	WWA-F
Formamide ^b								
a. Intermolecular energy	-0.019 64	-0.019 68	-0.020 01	-0.019 39	-0.023 58	-0.023 53	-0.020 90	-0.016 45
b. Binding energy of corresponding dimers	-0.018 29	-0.018 21	-0.020 34	-0.020 26	-0.019 59	-0.019 51	-0.017 44	-0.019 49
c. a - b	-0.001 35	-0.001 47	+0.000 33	+0.000 87	-0.003 99	-0.004 02	-0.003 46	+0.003 04
d. Nonbonded interaction energy	-0.000 06	-0.000 22	+0.000 13	+0.000 71	-0.000 76	-0.000 80	-0.000 50	+0.003 66
e. c - d	-0.001 29	-0.001 25	+0.000 20	+0.000 16	-0.003 23	-0.003 22	-0.002 96	-0.000 62
Methylformamide								
a. Intermolecular energy	-0.019 29	-0.019 41	-0.018 63	-0.018 24	-0.023 11	-0.023 10	-0.021 15	-0.020 38
b. Binding energy of corresponding dimers	-0.018 04	-0.018 01	-0.017 46	-0.017 43	-0.019 14	-0.019 11	-0.017 64	-0.017 06
c. a - b	-0.001 25	-0.001 40	-0.001 17	-0.000 81	-0.003 97	-0.003 99	-0.003 51	-0.003 32
d. Nonbonded interaction energy	-0.000 06	-0.000 23	-0.000 20	+0.000 04	-0.000 76	-0.000 77	-0.000 51	-0.000 46
e. c - d	-0.001 19	-0.001 17	-0.000 97	-0.000 85	-0.003 21	-0.003 22	-0.003 00	-0.002 86
Acetamide								
a. Intermolecular energy	-0.019 53	-0.019 24	-0.020 03	-0.019 06	-0.022 74	-0.022 27	-0.021 63	-0.018 34
b. Binding energy of corresponding dimers	-0.018 27	-0.017 94	-0.020 00	-0.019 67	-0.018 91	-0.018 58	-0.018 10	-0.019 83
c. a - b	-0.001 26	-0.001 30	-0.000 03	+0.000 61	-0.003 83	-0.003 69	-0.003 53	+0.001 49
d. Nonbonded interaction energy	-0.000 07	-0.000 02	+0.000 06	+0.000 57	-0.000 72	-0.000 70	-0.000 41	+0.002 81
e. c - d	-0.001 19	-0.001 28	-0.000 09	+0.000 04	-0.003 11	-0.002 99	-0.003 12	-0.001 32
Methylacetamide								
a. Intermolecular energy	-0.019 26	-0.019 04	-0.018 38	-0.017 71	-0.022 36	-0.021 94	-0.021 86	-0.020 99
b. Binding energy of corresponding dimers	-0.018 09	-0.017 81	-0.017 24	-0.016 96	-0.018 55	-0.018 27	-0.018 27	-0.017 43
c. a - b	-0.001 17	-0.001 23	-0.001 14	-0.000 75	-0.003 81	-0.003 67	-0.003 59	-0.003 56
d. Nonbonded interaction energy	-0.000 06	-0.000 22	-0.000 21	+0.000 02	-0.000 72	-0.000 69	-0.000 42	-0.000 56
e. c - d	-0.001 11	-0.001 01	-0.000 93	-0.000 77	-0.003 09	-0.002 98	-0.003 17	-0.003 00

^a See text for definitions of trimer designations. ^b Data for formamide-water complexes A-E, A-F, B-E, and B-F taken from ref 8.

formed. The structures reported in ref 10 are ones in which the hydrogen bonds deviate from linearity by about 5-10°.

3. Both studies agree that in dimers having the amide molecule as the proton donor molecule, the position of the water molecule is rather flexible, especially with respect to rotation about the intermolecular line, which rotation is essentially free.

4. The most significant difference between the results of the two studies is found in the effect of methyl substitution on dimer stabilization energies. In ref 10 it was concluded that the stabilization energies of methylacetamide-water dimers are slightly decreased relative to the corresponding formamide-water dimers, independent of which molecule is the proton donor. In the present study, methyl substitution has been found to decrease the stabilities of dimers with the amide molecule as the proton donor, but increase the stabilities of open dimers having the amide molecule as the proton acceptor. In ref 10, the amide molecule was found to be a better proton acceptor molecule than water in the formamide-water and methylacetamide-water dimers. In the present study, the amide molecule is generally the better proton donor molecule in open amide-water dimers. However, since methyl substitution has opposite effects on N-H...O and O-H...O hydrogen bond energies, methylacetamide and water are comparable as proton donors in the methylacetamide-water dimers B and E.

Trimers. In part 12 of this series,⁸ an analysis was made of the trimer stabilities and of the nonadditivities of hydrogen bond energies in 2:1 water-formamide complexes in which the formamide molecule is the central molecule, acting as a proton donor through the N-H proton and a proton acceptor through the carbonyl oxygen in trimers A-E, B-E, A-F, and B-F, as defined above. It is of interest to examine the same types of trimers with the methyl-substituted formamides as central molecules, so that the effect of methyl substitution may be determined. The study of trimers has also been expanded to include 2:1 water-amide complexes in which a water dimer is present, with a water molecule the central molecule in the complex, acting either as a proton donor to an amide molecule

in trimers WWA-E and WWA-F which contain O-H...O-H...O chains of hydrogen bonds, or as a proton acceptor in complexes AWW-A and AWW-B, where N-H...O-H...O chains exist. The results of these studies are reported in Table V.

In Table V, the intermolecular energy, computed as the difference between the total trimer energy and the sum of the energies of the three monomers, is reported as entry a. The energies of the two hydrogen bonds in the corresponding dimers are given as entry b. The difference between these energies, which measures the stability of the trimer relative to the two dimers, is entry c. To estimate the nonadditivity of hydrogen bond energies requires that the interaction between the two non-hydrogen-bonded molecules be determined, and that energy is reported in entry d. The nonadditivity of hydrogen bond energies is then the difference c - d, which is reported as entry e.

The following general observations may be made from the data of Table V.

1. In trimers A-E, B-E, AWW-A, AWW-B, and WWA-E, which contain open dimers exclusively, methyl substitution has only a slight effect on trimer stabilization energies relative to the corresponding dimers, and on the nonadditivities of hydrogen bond energies, which vary by less than 0.2 kcal/mol in a series. Methyl substitution in formamide tends to decrease the stabilities of trimers A-E, B-E, AWW-A, and AWW-B relative to the dimers (entry c) and to cause the hydrogen bond energies to deviate from additivity to a smaller extent (entry e). Methyl substitution has opposite effects in trimers WWA-E. These characteristics are apparently related to the fact that methyl substitution tends to destabilize N-H...O hydrogen bonds to a slightly greater extent than it stabilizes O-H...O hydrogen bonds in the amide-water dimers.

2. Open trimers which contain N-H...O-H...O (AWW-A and AWW-B) or O-H...O-H...O (WWA-E) chains of hydrogen bonds have increased stabilities (entry a), are stabilized to a greater extent relative to the corresponding dimers (entry c), and have larger nonadditivities (entry e) than trimers A-E

and B-E, where such chains do not exist. These features may be attributed to the redistribution of electron density which occurs in the central water molecule of the chains where negative charge increases at the proton acceptor oxygen and positive charge increases at the hydrogen-bonded proton. In the open-chain water trimer, this increased stability led to a further reduction in the intermolecular oxygen-oxygen distances.²⁸ A similar reduction in intermolecular distances would be predicted in trimers AWW-A, AWW-B, and WWA-E, and has been found experimentally in O-H...O-H...O chains in carbohydrate crystals.²⁹

3. The N-H...O-H...O chain of hydrogen bonds stabilizes trimers AWW-A and AWW-B relative to the corresponding dimers to a greater extent than the O-H...O-H...O chain of hydrogen bonds stabilizes trimer WWA-E relative to the dimers.

4. The formamide-water and acetamide-water trimers A-F, B-F, and WWA-F which contain cyclic dimer structures are destabilized relative to the corresponding dimers, except for the acetamide-water trimer A-F. In each case, an unfavorable interaction between the non-hydrogen-bonded molecules contributes to trimer destabilization. This suggests that the presence of cyclic dimers is not conducive to the formation of hydrogen-bonded networks.

5. When the methyl group is bonded to the nitrogen as in methylformamide and methylacetamide, trimers A-F, B-F, and WWA-F have open structures. These trimers are more stable than the pair of corresponding dimers, and are characterized by hydrogen bonds which are stronger than those of the dimers. However, these trimers are somewhat less favorable than the corresponding open trimers A-E, B-E, and WWA-E, respectively.

Conclusions

The following general conclusions are supported by the data obtained in this study.

1. Methyl substitution in formamide has little effect on the equilibrium structures of amide-water dimers which have the amide molecule as the proton donor, and on those dimers which have the amide molecule as the proton acceptor when hydrogen bond formation occurs on that side of the carbonyl oxygen "trans" to nitrogen. However, when hydrogen bonding occurs "cis" to nitrogen, the presence or absence of a methyl group "s-cis" to CO has a major influence on the equilibrium dimer structure. Thus, while the formamide-water and acetamide-water dimers have cyclic structures, the methylformamide-water and methylacetamide-water dimers have distorted open structures.

2. Methyl substitution decreases the stabilities of amide-water dimers which have the amide molecule as the proton donor molecule, and increases to a slightly lesser extent the stabilities of open dimers which have the amide molecule as the proton acceptor.

3. In open amide-water dimers which have the amide molecule as the proton acceptor molecule, hydrogen bond formation "trans" to nitrogen is more favorable than "cis" hydrogen bond formation.

4. The presence of a single methyl group tends to change the stabilization energy of an amide-water dimer relative to formamide-water to a greater extent when methyl substitution occurs at the carbonyl carbon rather than at the nitrogen. Substitution of methyl groups at both sites causes a greater change in stabilization energies, although the effect of two methyl groups is less than additive.

5. In 2:1 water-amide trimers with open structures, the trimer stabilization energies relative to the corresponding dimers and the nonadditivities of hydrogen bond energies do not vary significantly as the amide molecule changes. Thus, methyl substitution in formamide has little effect on these properties.

6. Open 2:1 water-amide trimers which contain the amide molecule either as a proton donor molecule or as a proton acceptor molecule, and which therefore contain N-H...O-H...O or O-H...O-H...O chains of hydrogen bonds, respectively, have increased stabilities and larger nonadditivities of hydrogen bond energies than trimers in which the amide molecule is the central molecule in the structure, acting as both a proton donor through the N-H proton and a proton acceptor through the carbonyl oxygen. The increased stabilities of the former trimers may be associated with the existence of uninterrupted chains of hydrogen bonds, and with the redistribution of electron density which occurs in the central molecule of the chains.

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