# Enthalpies of Hydration of *N*-Methylacetamide by One, Two, and Three Waters and the Effect upon the C═O Stretching Frequency. An Ab Initio DFT Study

**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*

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DFT calculations at the B3LYP/D95++(d,p) level of clusters of *N*-methylacetamide (NMA) with one, two, and three waters that were geometrically optimized on the counterpoise-corrected potential energy surfaces show that the gas-phase enthalpy of the interactions of NMA with three waters is −14.11 kcal/mol. Since the interactions between the three waters is 0.99 kcal/mol, the interaction enthalpy would become −15.10 if these interactions were subtracted. The internal geometry of the NMA molecule is sensitive to the degree of hydration, as are the H-bond lengths. Changes in the internal bond lengths with degree of hydration are approximately additive. The calculated C═O stretching frequencies correlate extremely well with the calculated C═O bond lengths, which suggests that the solvent effect upon this stretch could not be a purely electrostatic interaction. The calculated C═O stretch for NMA solvated by three waters in the gas phase agrees very well with that experimentally observed in aqueous solution.

Solvation remains an important aspect of thermodynamic analyses of peptide conformations. For example, experimental data on the enthalpies and free energies of folding often depend on the differential solvation enthalpies and entropies of peptides in their folded and unfolded states. To evaluate the differences in solvation by water (hydration), various schemes have been devised. One approach that has been popular with biochemists is the so-called inventory of H-bonds, in which the number of H-bonds is counted and each assigned the same energy.[1] However, the H-bonding energy of a water to an N−H bond should clearly be different from that to a C═O bond. Also, combinations of the H-bonding energies may not be additive. The inventory approach usually assumes that water forms a single H-bond to both the C═O and the N−H bonds. However, C═O bonds are double H-bond acceptors (as are other oxygens, such as that of water). Furthermore, there is significant confusion in the biochemical literature with respect to the manner in which ab initio molecular orbital calculations can be converted into enthalpies to be compared with experimental values. To properly convert calculated H-bonding energies into enthalpies, corrections must be made for the basis set superposition error (BSSE),[2] for vibrational levels and the proper Boltzmann distribution over them. One most usually corrects for BSSE using the counterpoise (CP) correction,[3,4] typically as a single point correction on the preoptimized geometry. However, CP modifies the potential energy surface (PES), which lowers the CP correction, generally lengthens H-bonds, and red-shifts the stretches associated with breaking the H-bonds. A general procedure for optimizing the geometry on the CP corrected PES allows for properly accounting for BSSE with respect to energies, geometries, and vibrations, as well as any other property that can be formulated as a derivative of the energy.[5]

*N*-Methylacetamide (NMA) is the smallest model for a peptide that contains the C−C and C−N bonds that connect amino acid residues within a peptide chain. As such, it is an appropriate model for estimating the energies of hydration of the H-bonding donor and acceptor sites for peptides using accurate quantum mechanical methods. In the course of writing a review chapter,[6] it has become apparent to this author that, despite the fact that values for these energies are often estimated and used by biochemists, and that there have been several MO calculations on the interaction of NMA with specific water molecules,[7−15] there are no accurate molecular orbital values for the enthalpies of the complete hydration in the current literature. The best values are those contained in the compilation published by Rablen;[8] however, this contains only two monohydrated structures for *trans*-NMA, both with single waters hydrating the different acceptor positions on the C═O but not the N−H bond. The purpose of this paper is to provide that information.

The experimental heat of solution of NMA in water has been reported by several groups.[16,17] The experimental determination by Della Gatta et al. of −17.6 kcal/mol is most relevant to this work as it is referenced to the gas phase.[18]

## Computational Details

The molecular orbital calculations were performed at the density functional theory (DFT) level using the Gaussian 03 program,[19] the B3LYP hybrid functional, and the D95++(d,p) basis set. This method combines Becke's three-parameter functional[20] with the nonlocal correlation provided by the correlation functional of Lee et al.[21] The complexes were completely optimized without any geometric restraints, and vibrational frequencies were calculated on the CP-optimized PES[5] using the harmonic approximation as programmed in Gaussian 03. We have shown this level of theory to be extremely accurate for the energy of the water dimer.[22] All calculated frequencies are real, indicating true minima. The enthalpies and free energies were calculated from the CP-corrected vibrations, which provide better vibrational frequencies than those on the normal (uncorrected) surface.

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* Corresponding author. E-mail: jdannenberg@gc.cuny.edu.

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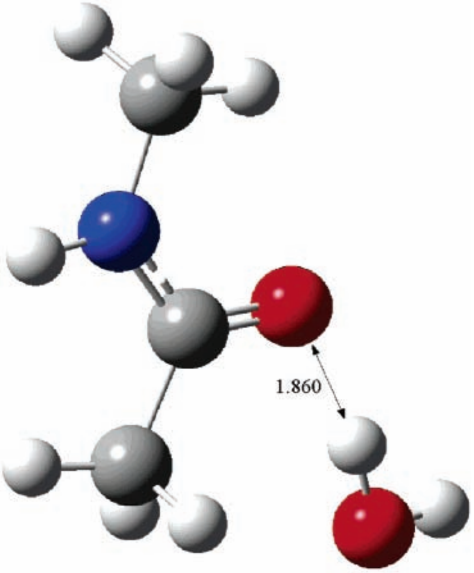

**Figure 1.** NMA1WO1.

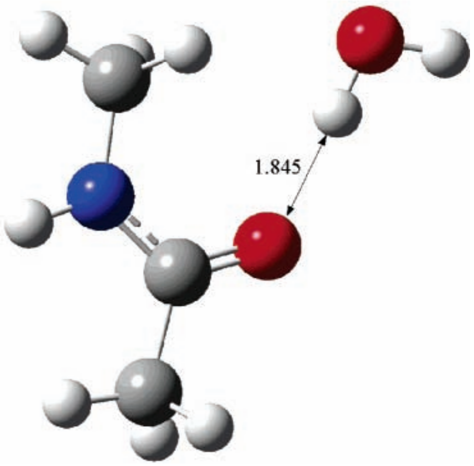

**Figure 2.** NMA1WOb.

Water−water interactions were calculated using frozen geometries taken from the optimized structures by simply removing the atoms of NMA. These single point calculations included the CP correction. Only energies could be calculated in this manner, as the geometries do not represent stationary points on the potential energy surfaces, precluding meaningful vibrational calculations. Thus, the enthalpies of interaction corrected for water−water interactions are essentially a hybrid of the interaction enthalpy corrected by a water−water interaction energy.

## Results and Discussion

The resulting structures of the various hydration complexes considered are depicted in Figures 1−7, while energetic and structural data are collected in Tables 1 and 2. Both energies and enthalpies of interaction are presented in the tables. Unless otherwise noted, the values that we use in the discussion shall refer to the enthalpies. We shall present the results for single, double, and triple hydrations individually and then discuss them in general.

**Hydration by a Single Water Molecule.** The hydration enthalpies for a single water are significantly greater for interaction with the C═O bond than the N−H bond by almost a factor of 2, while hydration of the C═O bond with the water near the *N*-methyl is slightly less stabilizing than at the other hydration position. The optimized geometries for both monohydrated structures at the C═O bond have the water molecule coplanar with the heavy atoms of NMA, while that hydrated at the N−H bond has the water molecule perpendicular. The H-bond lengths (H···O or H···N) are in the inverse order of H-bond strength. H···N distances are generally longer than H···O distances, in any case, due to the larger atomic radius of N than O. All three hydrating interactions result in lengthening of the C═O bond and shortening of the C−N bonds in NMA. The largest change in the C═O distance occurs in NMA1WOa, while the largest change in the N−H distance occurs in NMA1WOb, while hydration at N (NMA1WN) induces the smallest change in each of the bond distances.

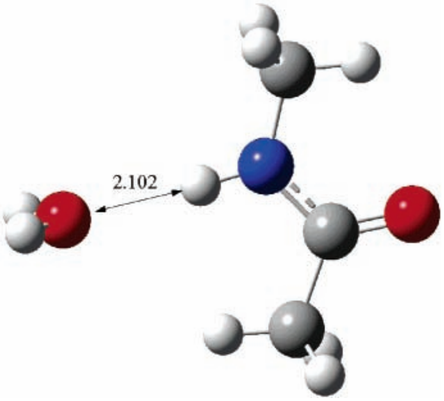

**Figure 3.** NMA1WN.

**Hydration by Two Water Molecules.** Hydration by two molecules of water at the two H-bonding acceptor positions of the C═O bond (NMA2Wab) provides the greatest stabilization of the dihydrated NMAs, which is not surprising considering that single hydrations at each of these positions are more stabilizing than hydration at the N−H bond. The dihydrated NMA2WNOa is marginally more stable than NMA2WNOb, as might be expected from the observation than NMA1WOa is slightly more stable than NMA1WOb.

When two or more waters interact with the NMA, one must consider the cooperative effect of the interactions. We shall approach the cooperativity in two different ways: (1) we shall consider the cooperativity to be the stabilization of NMA by *N* waters less than the sum of the individual stabilizations of each water or (2) we can correct the first definition by subtracting the interactions between the water molecules. By the first definition, the interactions defined by NMA2WNOa and NMA2WNOb are both cooperative (by 0.55 and 0.69 kcal/mol, respectively), while the interaction defined by NMA2WOab is anticooperative (by 0.90 kcal/mol). However, when one corrects for the water−water interactions, all three complexes are seen to be cooperative (by 0.61, 0.71, and 0.19 kcal/mol, respectively). The difference is due to the observations that the two waters in NMA2WNOa and NMA2WNOb hardly interact, while the two in NMA2WOab repel each other by 1.14 kcal/mol.

When two waters interact with NMA, the changes in the C═O and C−N bond lengths become significantly larger than for interactions with single waters. In fact, the changes in these bond lengths from isolated NMA are essentially additive for all three dihydrated NMAs. On the other hand, the H-bonds become shorter for both NMA2WNOa and NMA2WNOb but longer for NMA2WOab. These observations agree with the observed cooperativity of the H-bond interactions, as tempered by the significant repulsions between the waters of NMA2WOab. Another significant difference between the mono- and dihydrated

**TABLE 1: Hydration Energies and Enthalpies of NMA with One, Two, and Three Water Molecules**

| | interaction | | cooperativity | | water−water | corrected for water−water | | |
|---|---|---|---|---|---|---|---|---|
| species | Δ*E* | Δ*H* | Δ*E* | Δ*H* | interaction[a] | Δ*E* | Δ*H* | cooperativity |
| NMA1WOa | −7.36 | −5.63 | | | | | | |
| NMA1WOb | −7.12 | −5.37 | | | | | | |
| NMA1WN | −4.38 | −2.89 | | | | | | |
| NMA2WNOa | −12.32 | −9.07 | −0.58 | −0.55 | 0.03 | −12.93 | −9.68 | −0.61 |
| NMA2WNOb | −12.21 | −8.95 | −0.71 | −0.69 | 0.00 | −12.91 | −9.66 | −0.71 |
| NMA2WOab | −13.52 | −10.09 | 0.95 | 0.90 | 1.14 | −13.71 | −10.28 | −0.19 |
| NMA3W | −19.09 | −14.11 | −0.23 | −0.22 | 0.99 | −20.31 | −15.33 | −1.22 |

[a] Interaction energy of the water molecules with the NMA removed.

**TABLE 2: Selected Distances (Å)[a]**

| | O···H | | | O···N or O···O | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| species | NH | COa | COb | NH | COa | COb | C═O | C−N | scaled 1/λ (cm$^{-1}$) |
| NMA | | | | | | | 1.230 | 1.372 | 1692.3 |
| NMA1WOa | | | 1.845 | | | 2.811 | 1.239 | 1.364 | 1663.2 |
| NMA1WOb | | 1.860 | | | 2.837 | | 1.238 | 1.360 | 1668.8 |
| NMA1WN | 2.102 | | | 3.117 | | | 1.233 | 1.368 | 1682.0 |
| NMA2WNOa | 2.072 | | 1.822 | 3.087 | | 2.798 | 1.242 | 1.359 | 1659.0 |
| NMA2WNOb | 2.061 | 1.842 | | 3.075 | 2.823 | | 1.241 | 1.355 | 1654.2 |
| NMA2WOab | | 1.893 | 1.872 | | 2.863 | | 1.248 | 1.353 | 1638.0 |
| NMA3W | 2.035 | 1.873 | 1.851 | 3.050 | 2.848 | 2.823 | 1.251 | 1.348 | 1629.9 |

[a] COa and COb designate the two H-bonding acceptor positions (see figures).

structures is that, while the optimized geometries of the former all have the two waters on the C═O bond in the plane of the heavy atoms of NMA, this no longer holds for NMA2WOab, where each water bends out of the plane in opposite directions.

**Hydration by Three Water Molecules.** We considered only one triply hydrated structure, NMA3W, which contains all three of the H-bonds previously discussed individually and in pairs. The enthalpy of hydration for this structure is −14.11 kcal/mol, which is −0.23 kcal/mol stronger than the sum of the three individual hydrations at each of the positions. The water−water interactions are 0.99 kcal/mol, so that the hydration energy becomes −15.10 kcal/mol when corrected for these interactions that do not exist in the individually hydrated species. When corrected for these interactions, the cooperative component of the triple hydration increases from −0.23 to −1.22 kcal/mol.

The differences in the C═O and C−N bond distances from those in isolated NMA increase over those noted for the dihydrated species. They continue to be additive in that they are very close (within about 0.0011 Å) to the sums of the differences calculated for each monohydrated species in each of the two bond distances. The changes in the H-bond distances (H···O) upon going from the di- to trihydrated species are close to additive. The N−H···O distance was changed by −0.030 and −0.042 Å (over that of NMA1WN) in the two dihydrated species that have such an H-bond. The corresponding distance is changed by −0.067 Å in the NMA3W. The analogous values for the other two H-bonds are −0.018, 0.033, and 0.013 (for that in NMA1WOa) and −0.022, 0.027, and 0.006 (for that in NMA1WOb).

Interestingly, the water−water interactions are less repulsive (by 0.52 kcal/mol) than the sum of the three pairs of interactions. For the waters fixed in the orientations, they take in the three dihydrated examples discussed previously. Thus, cooperative interactions between the water molecules influence the calculated hydration energies. The water−water cooperativity probably diminishes the cooperative component for the hydration calculated previously (−1.22 kcal/mol) as the individual NMA−water interactions would be expected to weaken somewhat as a tradeoff to the energetic benefit of lowering the (overall) repulsion between the three waters. The O···O distances that define the relative water−water positions are all significantly shorter in NMA3W than the corresponding values for the three dihydrated species (see green distances in Figures 4−7).

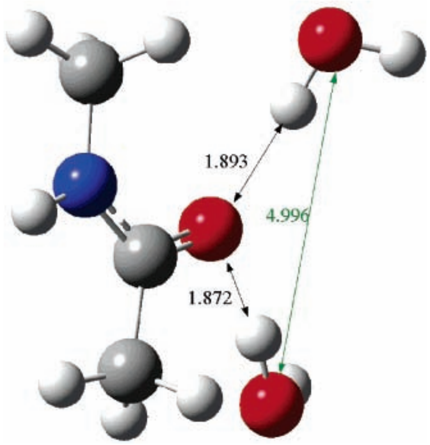

**Figure 4.** NMA2WNOa.

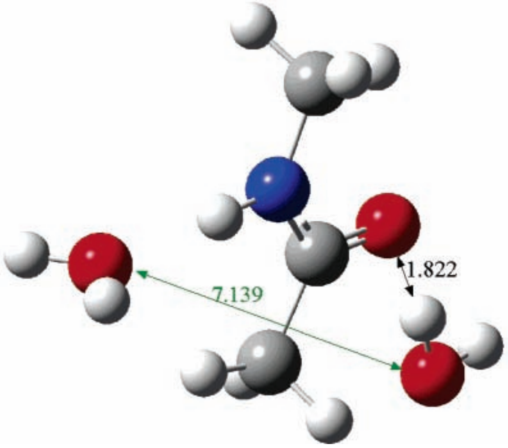

**Figure 5.** NMA2WNOb.

Comparison with experiment requires estimating the solvation enthalpy of the amide group of NMA as the three water molecules explicitly considered interact only with this functional

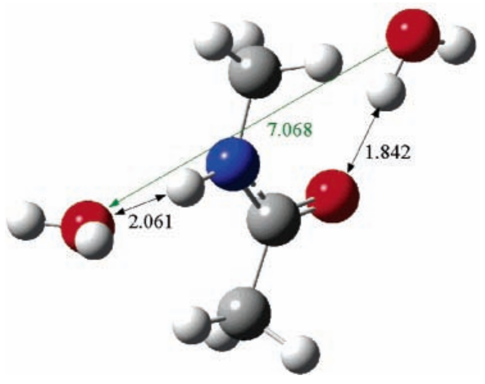

**Figure 6.** NMA2WOab.

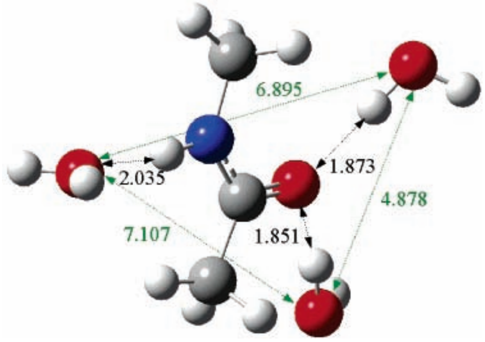

**Figure 7.** NMA3W.

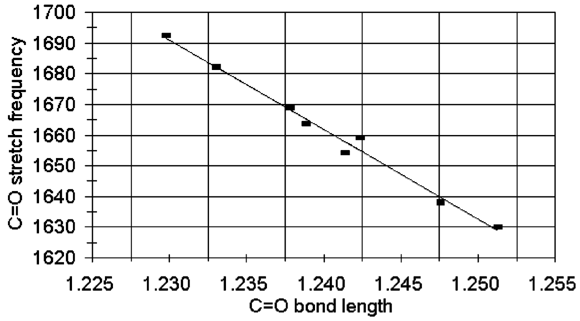

**Figure 8.** Plot (scaled by 0.965) of C═O frequencies, 1/$\lambda$ (cm$^{-1}$) vs optimized C═O bond lengths (Å) for NMA and all hydrated species. The line is a least-squares fit with a 0.994 correlation.

group. Presumably, there should be an additional component of the hydration energy directly related to the interactions with the rest of the molecule, which we have not considered in this study. The experimental report of Della Gatta et al. includes the hydration enthalpies of several differently substituted amides.[18] From the results of these studies, they obtained the hydration enthalpies of the amide functional group. The values they obtained for different amide groups range from −11.6 to −14.7 kcal/mol, while the value obtained for the amide group of NMA was −13.0 kcal/mol. Privalov, who used an average value for the enthalpy of hydration of the amide group of −14.2 kcal/mol,[23] which was obtained from the same data published by Della Gatta, did not include the data for three of the nine *N*-alkylamides originally considered (including NMA). Baldwin reports a value of −11.5 kcal/mol for the polar contribution to the enthalpy of solution.[24] The calculated value of −14.1 kcal/mol for the $\Delta H$ of interaction of NMA with three discrete water molecules (or −15.3 kcal/mol if one removes the interactions between the three waters) is surprisingly close to the experimental value. While this observation superficially suggests that the enthalpic effects of bulk water are unimportant, it is more likely that those effects that further stabilize the NMA3W structure are roughly canceled by those that destabilize the pure liquid by making a cavity for this structure. Since the water molecules that discretely solvate NMA3W would otherwise H-bond to others in pure liquid water, those H-bonds would need to be broken to form the new H-bonds in NMA3W. Water−water H-bonds in the pure liquid can be estimated to have enthalpies that are half the $\Delta H_{\text{vaporization}}$ at 298 K or −4.9 kcal/mol. Since 1.5 water H-bonds must be broken to form 3 H-bonds to the amide group, this would cost 7.3 kcal/mol, about half the $\Delta H$ calculated for NMA3W. Since two of the three waters attached to the amide group participate as H-bond donors and one as an acceptor, another water that was an acceptor in one of the water−water H-bonds remains unaccounted. Since one cannot break half a H-bond, this other water presumably interacts in some other way with the solute (via a C−H···O) H-bond or remains unsatisfied. Since the half C−H···O interaction is likely to be smaller in magnitude than the remaining half water−water H-bond, the energetic cost of 7.3 kcal/mol for breaking the water−water H-bonds to form those to the amide should be taken as a lower limit. The cavitation energy is often partially attributed to an unfavorable entropy contribution to the free energy. While this attribution has been recently questioned,[6] further discussion that is beyond the scope of this paper is clearly required.

**Carbonyl Stretches.** The coupled C═O stretches of the amide moieties comprise the amide I infrared bands of peptides and proteins. Since we had necessarily calculated the vibrational frequencies to compute the enthalpies, we present the frequencies (more correctly, 1/$\lambda$), for the C═O stretch as a function of the level of hydration. The infrared frequencies of NMA and the effect of solvation upon them have been studied by several groups. The values in Table 2 and Figure 8 have been scaled using a scaling factor of 0.965, which we have used in previous calculations.[25,26] The correlation between the C═O bond lengths and the stretching frequencies can be seen to be excellent. Furthermore, the scaled amide I frequency for NMA3W of 1630 cm$^{-1}$ is in good agreement with several observations of this frequency in aqueous solution of 1625,[27] 1626 (with a water-coupled subband at 1646),[28] and 1628[29] cm$^{-1}$. The complete analysis of the vibrations of NMA is complex and will not be reviewed here as it has been adequately covered in the literature.[9,11,27−46] We wish simply to note that the calculated amide I frequency of NMA solvated with only three waters is in good agreement with the experimentally observed value in aqueous solution and that the C═O bond lengths correlate very well with these frequencies.

The observations that (1) cooperative interactions are present in the interactions of NMA with two or three water molecules, (2) the cooperativity extends to the interactions between the three water molecules in the NMA3W structure, and (3) the correlation of the C═O bond lengths with the amide I stretching frequencies for all the aggregates considered in this study, combined with the observation the agreement of the amide I stretch with those reported for hydrated NMA, reinforce the importance of looking beyond the electrostatic component of H-bonding. The correlation of the amide I stretch with C═O distance would not be a consequence of electrostatic interactions as the C═O distance would not change upon solvation in a purely electrostatic model. Thus, this observation is clearly inconsistent with such a model.

Cooperativity in hydration of amides[10,14,47−49] and in H-bonding between amides[47,48,50−58] has long been established. Nevertheless, the observation that the interaction of only three discrete waters with NMA reasonably reproduces both the experimentally observed enthalpy of solution of the amide moiety and the amide I stretching frequency is a surprise.

## Conclusions

The hydration of NMA by three discrete water molecules provides a good estimate of both the hydration enthalpy of the amide functional group as well as its amide I stretching frequency. Cooperativity provides part of the stabilizing interaction of NMA with more than one water molecule, while reducing the repulsive interactions between the three water molecules in the solvent shell.

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