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Quantum Mechanical Studies of Environmental Effects on Biomolecules

VIII. Hydration of Acetamide

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An *ab initio* study of acetamide and its hydrated species is presented. The structural features, the molecular potential and the hydration scheme are compared to those of other substituted amides. The first hydration shell is likely to contain only three directly bound water molecules.

Key words: Acetamide, hydration of ~

1. Introduction

In the previous paper of this series [1], we have used the supermolecule approach [2] to determine the hydration properties of urea. We present here the corresponding results concerning acetamide in view of a comparison with urea, particularly from the point of view of their effect on the movement of water in the mammalian kidney [3].

The computations were made by the *ab initio* SCF LCAO procedure, using the same ($7s$, $3p/3s$) atomic Gaussian basis contracted to a minimal set, as in Ref. [1]. For the geometry of acetamide we have adopted that of the stable rhombohedral structure [4] (the molecule deviates slightly from planarity, see footnote to Table 2).

We have first computed the molecular electrostatic potential to help a preliminary search in the proton attracting regions. Interaction of acetamide with one water molecule was then studied in detail, and completion of the first solvation shell was performed as usual [2].

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2. Structure and Molecular Potential

Figure 1 shows the Mulliken population analysis, the main characteristics of which are compared to those of formamide and urea [1] in Table 1: the qualitative features of the electron distribution are here similar to those of formamide, in particular the inequivalence of the two NH_2 protons (which is reversed in urea).

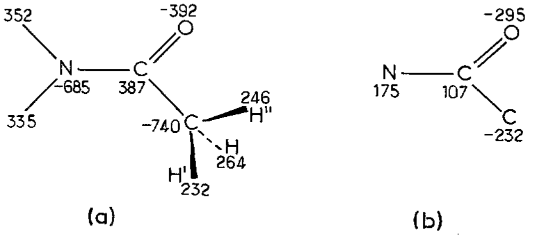


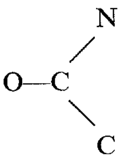
Fig. 1. Mulliken population analysis of acetamide ($10^{-3} e$). The out-of-plane coordinates of H, H′, H″, are −2.051, 0.756 and 0.505 a.u. respectively

Table 1. Comparison of atomic charges and of the global charges on the NH_2CO fragment in formamide, acetamide, and urea (10^{-3} e)

	Total	π	H_c[a]	H_t[a]	N	C	O	π_N	σ_O
F	−194	0	337	321	−639	170	−383	199	−89
A	+2	−13	352	335	−685	387	−392	175	−97
U	+56	−126	415	504	−975	536	−423	126	−51

[a] H_c, H_t are *cis* and *trans* to the CO bond respectively.

It is seen that the NH_2CO fragment, globally negative in formamide, looses its global charge to the CH_3 group in acetamide, with a small return in the π-system by hyperconjugation. Analogous but stronger effects were seen in urea. In both cases, the presence of the second substituent on the carbon atom decreases the conjugation of the first NH_2 group. The global charge of the oxygen atom increases in the order *F*, *A*, *U* whereas the corresponding σ population decreases.

The molecular potential of acetamide in the  $O{-}C(N)(C)$ plane, in a perpendicular section containing the C–N bond, and in a plane parallel to the first one at 2.5 a.u. are given in Figs. 2a, 2b and 2c respectively.

The most attractive region is in the molecular plane with a potential minimum in the direction making an angle of 18° with the C–O bond. The value of the minimum (−65.7 kcal/mole) is slightly less favorable than those of formamide, N-methylacetamide [5] and urea in the same region (67.1, 66.5, 68.5 respectively). Another minimum (−65.5 kcal/mole) exists in the direction making an angle of 30° with the C–O bond on the other side. In the perpendicular section containing C–N, two

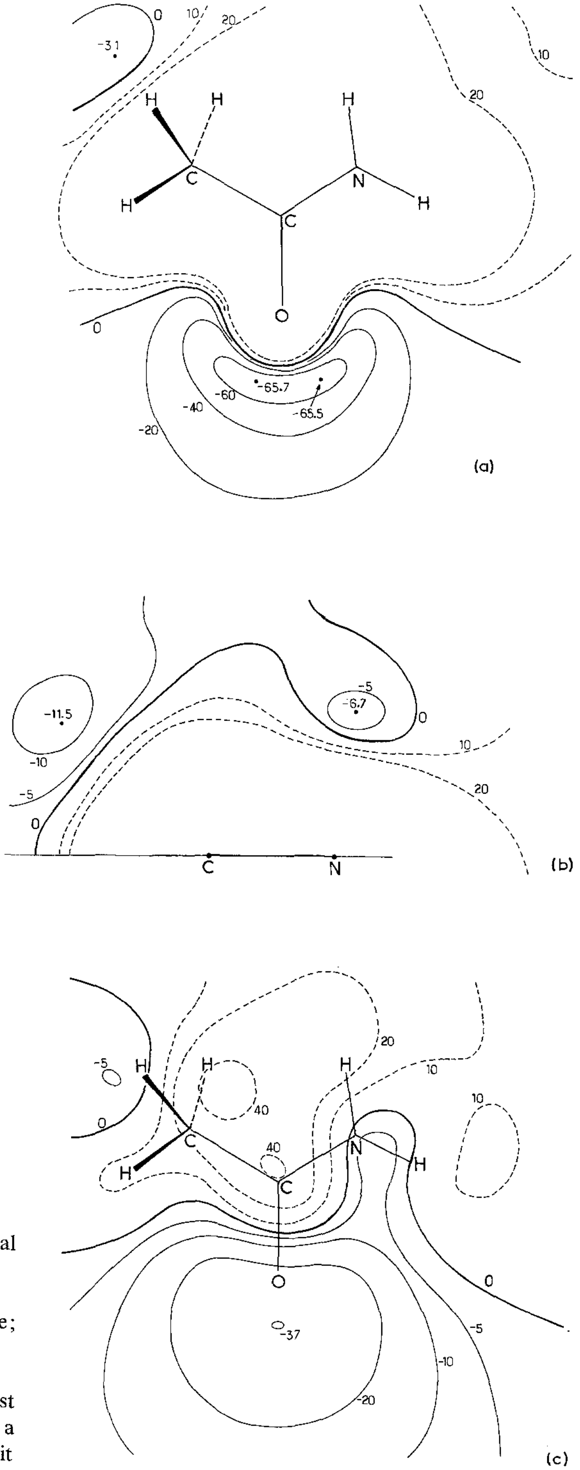
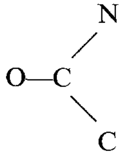


Fig. 2. Molecular electrostatic potential of acetamide (a) in the $\mathrm{OC}\begin{array}{l}\diagup\mathrm{N}\\ \diagdown\mathrm{C}\end{array}$ plane; (b) in a plane perpendicular to the first and containing the NC bond; (c) in a plane parallel to the first at 2.5 a.u. of it

secondary minima (−6.7 kcal/mole, −11.5 kcal/mole) are seen, whose values are slightly larger than those of urea in this region. In a plane parallel to the  $O{-}C\begin{smallmatrix}N\\C\end{smallmatrix}$ plane, at 2.5 a.u. a repulsive region exists above (and symmetrically below) the carbon and the hydrogens of the methyl group. Furthermore a new feature appears in Figs. 2a and 2b, namely the existence of a small but definite attractive zone outside the methyl group. The possibility of existence of such zones has been found for hydrocarbons [6] but, until now, not in heteroatomic molecules.

3. Hydration

As in Ref. [1] the oxygen of water, O_W, is defined by polar coordinates R, θ, φ with respect to the N or O atom to which water is bound, the polar axis being either CO or NH. $\varphi = 0$ or 180° when O_W is in the molecular plane. η, ξ, and ζ are local axes centered at O_W: η along the polar axis towards O or N, ξ perpendicular to it in the plane of the solute, ζ forming with them a direct system. For CO binding, η is along one O_WH bond; for NH binding it bissects the water molecule.

The regions *I*, *II*, *III*, *IV* are defined as in formamide (see Fig. 3). Table 2 gives the characteristics of the most stable positions of the water molecule in a monohydrate in each region and Fig. 3 shows the lability characteristics of the monohydrate.

The most stable monohydrate occurs in region *I* at $\theta = 75°$, $\varphi = 0$, $R = 2.8$ Å (same position as for urea but smaller energy). $R = 2.85$ Å does not change much the energy.

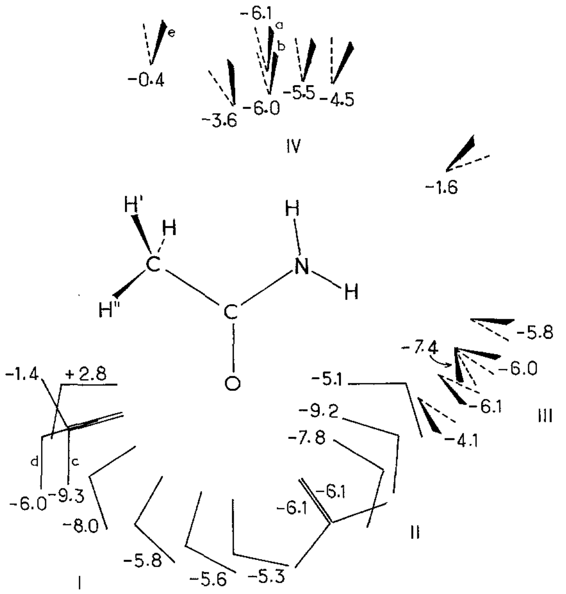


Fig. 3. In-plane monohydration of acetamide. (a) NO = 2.85 Å; (b) NO = 2.80 Å; (c) OO = 2.85 Å; (d) OO = 3.30 Å; (e) CO = 3.25 Å

Table 2. Geometries and binding energy of the monohydrates of acetamide at four preferred positions

Region	R	θ	φ	ξ	η	ζ	$-\Delta E$
I	2.80	75	0	0	0	0	−9.3
II	2.80	75	0	0	0	0	−9.2
III	2.85	0	0[a]	0	0	−60	−7.2
IV	2.85	0	180[a]	0	0	0	−6.0

[a] The polar axes are in the directions of the NH bonds which are slightly out of the OCN plane. (6°, 4 above for *III* and 5°, 7 below for *IV*).

The most stable position in region (*II*) is symmetrical to (*I*) with respect to the C–O bond. A very little decrease of the stabilization energy is observed (−9.3 kcal/mole to −9.2 kcal/mole). These values are somewhat less than those obtained for urea but nearly equal to those obtained for formamide and larger than those of N-methylacetamide [7].

The most stable hydrate in region *III* has characteristics similar to those of urea. Finally the most stable adduct in region *IV* corresponds to a smaller stabilization energy than in urea (6.4 instead of 8.4 kcal/mole). The energy of water–water interaction in the same basis set being −6.6 kcal/mole in a dimer, the formation of a stable hydrate of acetamide in region *IV* does not appear advantageous and it seems likely that this position will be occupied only occasionally [7].

It is clear from the isopotential maps that other regions both in-plane and out of plane would be unfavorable for fixation of water.

Table 3 compares the energies of monohydration in formamide, acetamide, N-methylacetamide [8] and urea. It appears from this table that the average values are in the order $U > A \simeq F > NMA$.

Considerations of Tables 2 and 3 suggests interesting remarks: the binding of water to the *cis* NH bond is more favorable than to NH_t in *F* and *A*, the preference being reversed in urea, following the trends observed above in the net charges on the proton involved in the hydrogen bond. Similar proportionalities between ΔE and q_H were observed in other cases for a same proton acceptor [9]. However this

Table 3. Comparison of the energies of monohydration in sites *I* to *IV* in formamide, acetamide, N-methylacetamide and urea

Site	*F*	*A*	*NMA*	*U*
C=O (*I*)	−9.2	−9.3	−7.6	−10.2
C=O (*II*)	−9.0	−9.2	−6.4	−10.2
NH_c (*III*)	−8.2	−7.2	—	−7.4
NH_t (*IV*)	−7.1	−6.1	−6.0	−8.4

kind of correlation can be only very partial and must be used with extreme caution because they are only partial reflection of a more complex reality as shown for instance by the fact that the ΔE in acetamide are smaller than in formamide for both NH_c and NH_t although both q_H are larger in the first molecule. Along a similar line one observes that the binding to the carbonyl oxygen increases in *F*, *A*, *U*, in apparent agreement with the increase in the global charge on the oxygen but the correlation breaks down for N-methyl-acetamide where the oxygen net charge (-0.388) is similar to that in *F* and *A* while the binding energy is appreciably smaller, showing the importance of the *whole* molecular structure in determining the strength of the hydrogen bond.

Fig. 4 gives the net charges of the monohydrates of acetamide in the four preferred positions as well as the global charge transfers to water (*I*, *II*) or from it (*III*, *IV*). The trends are similar to those observed in other cases [1, 10].

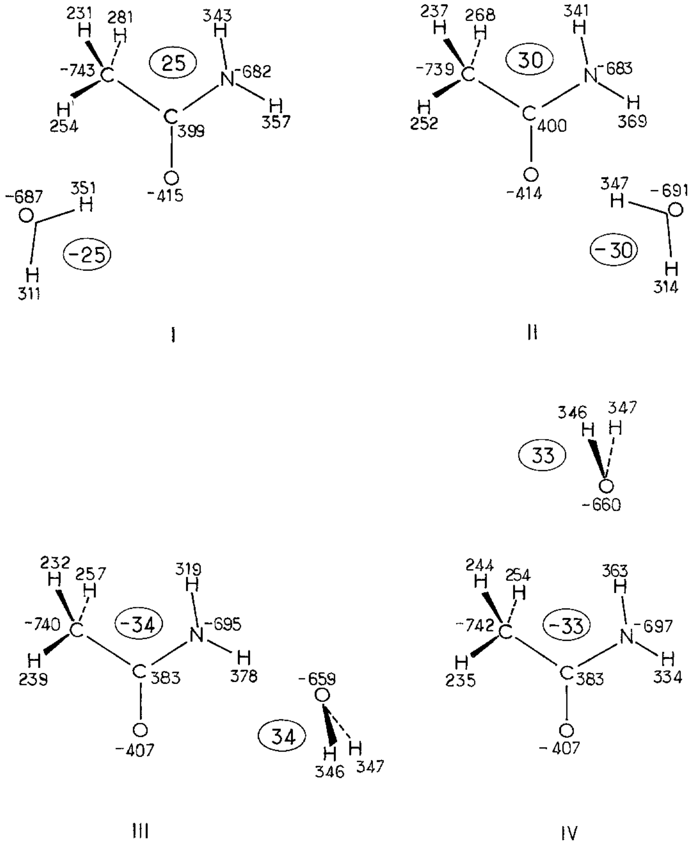


Fig. 4. Mulliken populations in four monohydrates of acetamide ($10^{-3}e$). The circled number is the global charge transfer. (The net charges in isolated water are +326 on H, −652 on O)

Building up the first hydration shell was performed step by step with reoptimization: the results concerning two intermediate dihydrates are given in Fig. 5. It is seen that the simultaneous occupation of positions *I* and *II* does not bring about an appreciable repulsion. Thus the trihydrate was computed occupying simultaneously the three positions. This yields an average energy of 9.4 kcal/mole. The net charge distribution in the trihydrate is given in Fig. 6.

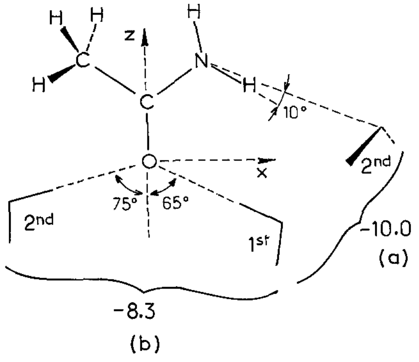


Fig. 5. Geometries and stabilization energies per water molecule for two dihydrates. (For water in position *III*, O_W is in the OCN plane and the hydrogens have the coordinates 6.686, 0.466, 0.625 and 7.333, −1.808, 2.234 a.u. respectively.)

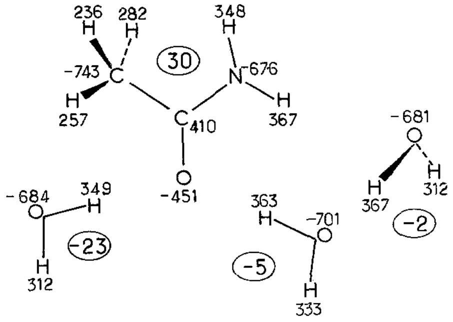


Fig. 6. Mulliken populations in the trihydrate (notations as in Fig. 4)

4. Conclusion

On the whole it appears that the number of water molecules directly bound to acetamide in the first hydration shell is three, with a possibility of occasional loose binding in a fourth position, whereas a shell of five water molecules may bind directly to urea. This may be related to the behavior of the two molecules in the mammalian kidney, where acetamide seems to have a qualitatively similar, but less effective, effect than urea on the absorption of water [3].

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