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Relationes

Quantum Mechanical Studies of Environmental Effects on Biomolecules

IV. Hydration of N-Methylacetamide

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Ab initio SCF calculations on the hydration of N-methylacetamide are reported and compared to the results previously obtained for formamide. The hydration energies are all slightly decreased. The angular positions of the two carbonyl sites are brought closer to the CO axis and the orientation of the water molecule on the NH site remains very flexible in spite of the α methyl group.

Key words: Hydration of peptide bond – N-Methylacetamide hydration

In a previous paper [1] we have investigated extensively by an SCF *ab initio* procedure the possible hydration sites of formamide and characterized four essential monohydrates in the positions visualized on Fig. 1. We have now extended our study to *trans*-N methyl acetamide which should be more representative than formamide itself of the situation of the peptide bond in proteins. We have used the geometry and the most stable methyl configurations determined in a recent study of the barriers to internal rotation in a series of amides [2]. The basis set utilized is the same as that used for formamide

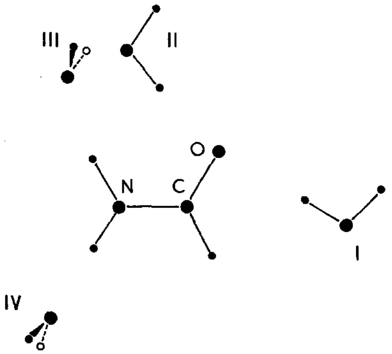

Fig. 1. The stable hydration sites of formamide

Table 1. Geometry and energy characteristics of the stable hydrates of *trans* N-methylacetamide as compared to those of formamide[a]

Hydrate	R (Å)[b]	$\theta°$[c]	ΔE (kcal/mole)[d]
I	2.81	70	7.6
	2.81	88	9.2 (9.4)
II	2.81	40	6.4
	2.81	72	8.5 (9.1)
IV	2.85	0	6.0
	2.85	0	7.1 (7.1)

[a] first line: N-Methylacetamide; second line: formamide.
[b] distance O–O or O–N.
[c] θ: polar angle.
[d] The values in parentheses refer to the most stable configuration of H_2O in the position considered, for the case of formamide (non-linearity of the hydrogen bond; see paper I for details).

and the computations were performed using the program Gaussian 70 in a foreign basis [3]. A preliminary search of the most probable hydration sites was made using the electrostatic model of Bonaccorsi *et al.* [4] and a further optimization was performed by an exact computation as in Paper I. Table 1 summarizes the angular and energy characteristics of the three monohydrates found, and Fig. 2 shows the variations in the hydrogen bond energy for a rotation around the carbonyl bond (in the plane of the peptide link) on both sides of the CO axis, compared to the same rotation in formamide.

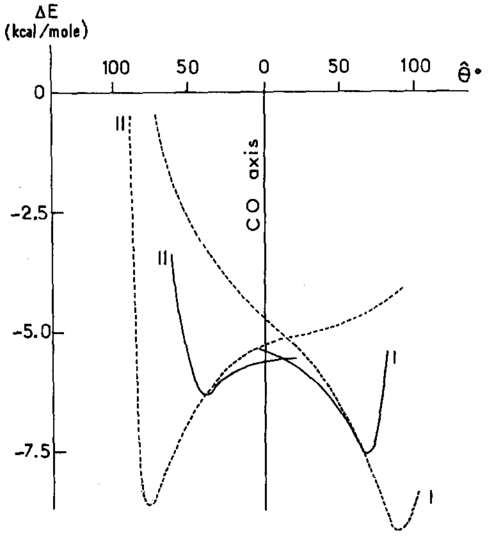

Fig. 2. Variation of the hydrogen bond energy when the water molecule rotates in the peptide plane around the carbonyl oxygen in formamide (— — —) and N-methylacetamide (———). The labels I and II identify the positions of the non-hydrogen bonded hydrogen atom of water (see Fig. 1)

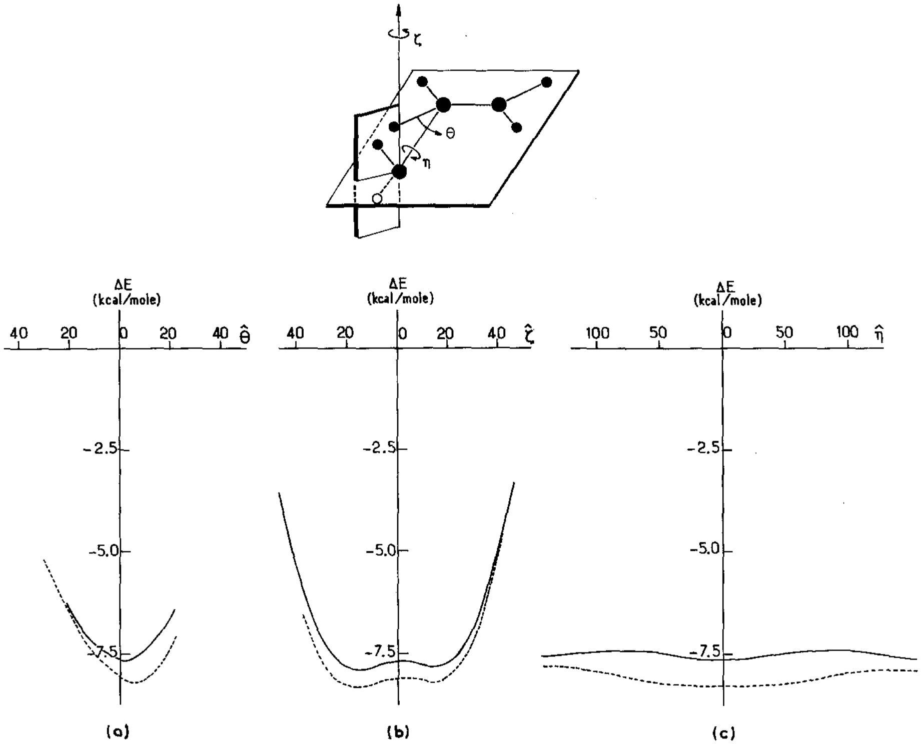

Fig. 3. Variations of the conformational energy for association IV in formamide (— — —) and N-methylacetamide (———). a) rotation $\hat{\theta}$; b) rotation $\hat{\zeta}$; c) rotation $\hat{\eta}$, as indicated in the drawing at the top of the figure

This set of results indicate that:

a) the stabilization energies are all slightly decreased with respect to the unsubstituted molecule, but remain appreciable and in the same relative order, the favorable position remaining on the C_α side of the CO bond. The equilibrium distances are practically not modified.

b) The positions of the most stable adducts on the carbonyl are both shifted closer to the CO axis. The shape of the corresponding angular variation is similar to that found in formamide although less steep particularly on the site *trans* to the NH bond. The approach of water in the neighbourhood of the CO axis is only a little less favorable than in formamide. Moreover, the position of the second hydrogen of the water molecule itself in this region is practically indifferent (as seen by the closeness of the two curves near their crossing point), still more than in formamide. This may be a favorable factor easing the approach of the water molecule along a ridge of the potential surface.

As concerns the hydration site on the NH bond, we have observed in the case of formamide that this position (*trans* to C=O) was quite flexible as far as the orientation of the water molecule is concerned. It was interesting to test if this flexibility was maintained in the more crowded methyl-substituted compound.

Figures 3a, b, c depict various possible rotations of the water molecule starting from the configuration in which it sits perpendicularly to the peptide plane with its bissectrix along the NH bond. (The curves have been drawn using the electrostatic model only since this has been proved to parallel the SCF curves for the corresponding rotations in formamide). It is seen that they do not differ substantially from those of the unsubstituted compound: like in formamide, the water molecule bound to this NH bond prefers to have its oxygen nearly in line with N and H, but then its bissectrix may rotate easily on each side of the NH axis and furthermore the rotation around the NH axis itself is practically free.

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