QUANTUM-CHEMICAL STUDY OF N-METHYLACETAMIDE AND N,N-DIMETHYLACETAMIDE AS MODELS FOR PEPTIDIC BOND IN HYDROGEN-BOND INTERACTION WITH WATER, METHANOL AND PHENOL

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Dedicated to Professor RNDr Ľ. Krasnec on the occasion of his 70th birthday.

The PCILO quantum-chemical method with geometry optimization has been used to study rotation barriers of methyl groups in N-methylacetamide and N,N-dimethylacetamide. In all the cases studied, the eclipsed conformation have been found to be the most stable. *Cis* form of N-methylacetamide is less stable than the corresponding *trans* form by 2·0 kJ mol^{-1}. Moreover, the PCILO method has been used to study linear *n*-mers ($n = 4$) of N-methylacetamide. On going from the dimer to tri- and tetramers, the hydrogen-bond energies have been found non-additive, and positive cooperativity has been observed. Finally, hydrogen-bond complexes have been studied which were formed by C=O groups of N-methylacetamide and N,N-dimethylacetamide with water, methanol or phenol as proton-donors. The said proton-donors have been found to act as breakers of inter-peptide hydrogen bonds N—H···O=C. The hydrogen bonds formed by methanol are somewhat stronger than those formed by water, In accordance with experiment, the strongest hydrogen bonds with the studied proton-acceptors are formed by phenol.

The existence of hydrogen bonds between peptide groups in proteins, polypeptides, oligopeptides, and amino acids is generally known[1,2]. In proteins the hydrogen bonds formed between the peptidic groups play an important role in stabilization of configuration of the macromolecules and contribute decisively to their secondary structure[3,4]. In biological systems the protein macromolecules are surrounded predominantly by water medium. Experimental studies[2,5,6] of association of simple amides in various solvents showed that the solvents having proton-donor groups can break the hydrogen bonds between the peptides in favour of formation of hydrogen bonds between C=O group of the peptide and solvent.

The aim of this work was a quantum-chemical study of hydrogen-bond properties of N-methylacetamide and N,N-dimethylacetamide – realistic models of peptidic group. First we studied the conformational properties of these compounds. Using the complexes of N-methylacetamide, we studied hydrogen bonds similar to those involved in formation of secondary structure of proteins. Finally, quantum-chemical calculations were carried out of intermolecular hydrogen bonds formed between carbonyl groups of N-methyl- or N,N-dimethylacetamide and water, methanol or phenol. Water represents the medium in which natural polypeptides exist pre-

dominantly. Methanol and phenol represent models of aliphatic and aromatic proton-donor OH groups of amino acids residues present in proteins which are supposed to be able to form hydrogen bonds with adjacent segments of peptide chain, contributing thus to structure stabilization[4].

Method of Calculation and Geometry

Equilibrium geometry and interaction energy of the studied complexes were calculated by the PCILO method[7] (Figs 1, 2). The calculations were carried out with the optimized geometry of the monomers (Table I). As the PCILO method is known[8] to give, *e.g.* for N-methylacetamide, the non-planar conformer as the most stable, which contradicts experiment[9-11], we carried out an only limited optimization, optimizing only bond lengths and bond angles of the studied compounds.

The geometry of the studied complexes was only optimized with respect to H···O distance, which made it possible to overcome some inconsistencies of the PCILO method applied to study of intermolecular interactions. It is known[12] that full optimization of hydrogen-bond systems gives not only the energy-surface minima corresponding to hydrogen-bond complexes but also those corresponding to unrealistic "bonds" of the types lone electron pair/lone electron pair or lone electron pair/π bond. In the calculations of equilibrium geometry of the complexes, the O—H···O and N—H···O bonds were presumed to be linear (Figs 1, 2). All the complexes studied were presumed to be planar with C_s symmetry. The hydrogen bond energy E_{HB} was defined as the difference between total energy of the isolated molecules and total energy of the hydrogen-bond complex:

$$E_{HB} = E(R_\infty) - E(R_{min}) \qquad (1)$$

The average hydrogen-bond energy E_D was calculated from the relation:

$$E_D = (\text{energy of monomers} - \text{energy of complex}) \,.\, h^{-1} \,, \qquad (2)$$

where h means number of hydrogen bonds.

The calculations were carred out with a Siemens 4004/150 computer (Computer Centre, Comenius University) using the programs QCPE Nos 220 and 272.

RESULTS AND DISCUSSION

Conformation study of N-*methylacetamide and* N,N-*dimethylacetamide.* First we studied the energy curves of rotation around the peptidic bond (γ angle, Fig. 3) for N-methyl- and N,N-dimethylacetamide. In the both cases the energy curves show two minima (at 0° and 180°) and two maxima (at 90° and 270°). The energy barrier found for N-methylacetamide (50·8 kJ mol^{-1}) was higher than that for N,N-dimethylacetamide (43 mol^{-1}). A similar relation was described[13] in the case of rotational barriers of methyl derivatives of formamide. *Cis* form of N-methylacetamide is, by our calculations, less stable by 2·0 kJ mol^{-1}.

Sawaryn & Yadav carried out both *ab initio* and semiempirical calculations[14] of N-methylacetamide using the experimental geometry[11]. Using the PCILO method, they found the *cis* form of N-methylacetamide less stable by 5 kJ mol^{-1} and the

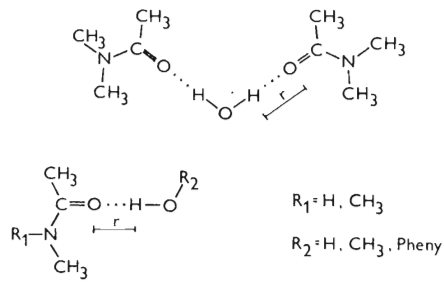

FIG. 1

Molecular arrangement of the studied complexes of N-methylacetamide and N,N-dimethylacetamide

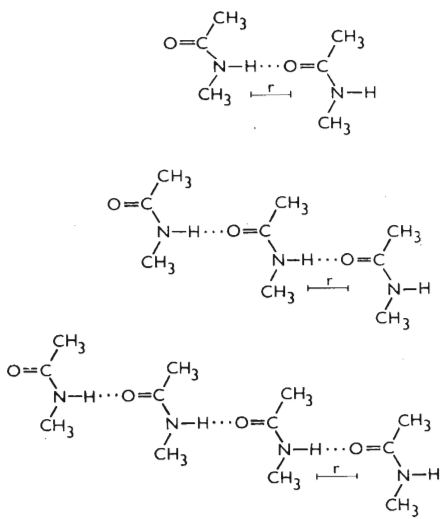

FIG. 2

Model of hydrogen bonds in open *n*-mers of N-methylacetamide

height of the *trans-cis* rotation barrier equal to 59·6 kJ mol^{-1}. Similar PCILO calculations[13] using the experimental geometry found the energy barrier of *trans-cis* rotation of N-methylacetamide equal to 53·6 kJ mol^{-1}. The difference between our

Table I
The PCILO-optimized geometry of the compounds studied

Bond lengths, nm		Bond angles, °	
		N-methylacetamide[a]	
1—2	0·142	1—2—3	120·6
2—3	0·137	2—3—4	118·2
3—4	0·128	2—3—5	119·3
3—5	0·146	3—5—10	110·3
2—6	0·107	3—2—6	107·5
1—9	0·113	9—1—2	110·3
5—10	0·113		
		N,N-dimethylacetamide[b]	
1—2	0·141	1—2—3	120·6
1—9	0·113	3—2—6	118·4
2—3	0·139	2—3—4	119·0
2—6	0·143	2—3—5	119·5
3—4	0·128	3—5—10	110·2
3—5	0·146	2—6—15	110·2
5—10	0·113	9—1—2	110·2
6—15	0·113		
		Water	
O—H	0·104	H—O—H	102·5
		Methanol	
C—O	0·138	H—O—C	104·8
C—H	0·113	H—C—O	108·8
O—H	0·105		
		Phenol	
$C_{arom}—C_{arom}$	0·139	$(C—C—C)_{arom}$	120·0
$C_{arom}—O$	0·137	$C_{arom}—C_{arom}—O$	123·6
$C_{arom}—H$	0·113	$C_{arom}—O—H$	107·0
O—H	0·104		

[a,b] The numbering of atoms is the same as that in Fig. 3.

PCILO-calculated values of N-methylacetamide and those given in refs[13,14] is due obviously to different geometries used in the calculations.

Experimental values[15-18] of rotational barriers of *trans-cis* rotation of substituted amides are found within the interval from 60 to 100 kJ mol^{-1}. The found enthalpy[19] of the *cis-trans* equilibrium is 4·2 kJ mol^{-1}.

The energy curves of rotation around the C-methyl bonds (α angle, Fig. 3) have three-fold symmetry with three equivalent minima (at 0°, 120°, and 240°) and three equivalent maxima (at 60°, 180°, and 300°). A substantially higher energy barrier (10·8 kJ mol^{-1}) was calculated for N,N-dimethylacetamide as compared with the value calculated for N-methylacetamide (2·3 kJ mol^{-1}).

As far as the rotation around N-methyl bonds is concerned (β and δ rotation angles, Fig. 3), the found rotational barriers have three-fold symmetry with the minima at 0°, 120°, and 240° and maxima at 60°, 180°, and 300°. For the rotation around N_2—C_1 bond of N-methylacetamide the heights of energy maxima lie within the interval from 2·5 to 3·0 kJ mol^{-1}. A somewhat greater energy barrier (3·8 kJ . . mol^{-1}) was found for similar rotation of CH_3 group in N,N-dimethylacetamide. The barrier height in N_2—C_6 bond of N,N-dimethylacetamide has the value of 4·7 kJ . . mol^{-1}. The difference from the rotational barrier of the N_2—C_1 bond is obviously due to steric effects.

From the PCILO calculations carried out for rotational barriers of CH_3 groups of N-methylacetamide and N,N-dimethylacetamide it follows that the most stable conformations found in all the cases are the eclipsed ones (Fig. 3, $\alpha = \beta = \delta = 0°$). These results agree with the *ab initio* calculations of the conformations of N-methylacetamide[20,35] and the PRDDO calculations[21] using the optimized geometry of N-

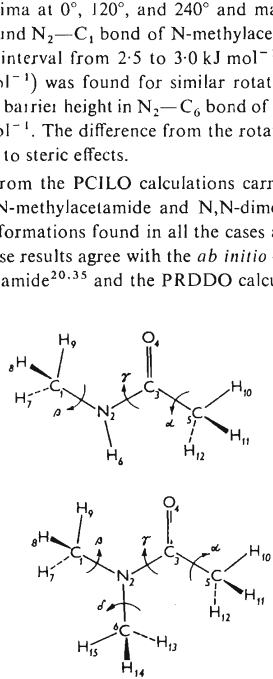

FIG. 3

Rotation angles and numbering of atoms in N-methylacetamide and N,N-dimethylacetamide

-methylacetamide. On the contrary, the PCILO calculations of N-methylacetamide[13] and *ab initio* calculations of N-methylformamide[22] found the opposed conformation for the rotation around the C—N bond. The latter works, however, used the idealized geometry involving the C—N bond lengths equal to 0·13 nm. Our PCILO-optimized geometry involves the N_2-C_3 bond length equal to 0·137 nm, which leads to the eclipsed conformation as the most stable.

Self-association of N-methylacetamide. So far the quantum-chemical approaches to study of forces determining the secondary structure of proteins were limited to study of N—H···O interpeptide hydrogen bonds only, these bonds being predominantly studied in dimers[21,23-29]. However, in secondary structure of proteins there are series of hydrogen bonds connecting the individual peptide units. The hydrogen-bonded oligomers of formamide modelling such hydrogen bonds were studied in refs[30-33]. We modelled a series of interpeptide hydrogen bonds of the protein secondary structure with linear N-methylacetamide oligomers (Fig. 2), the amide representing a simple realistic peptide model.

Table II gives the equilibrium geometries, hydrogen bond energies, average hydrogen bond energies, and percentage of cooperativity in the studied *n*-mers ($n = 4$) of N-methylacetamide. The PCILO calculations of N-methylacetamide with experimental and the optimized geometries showed that the optimization caused an increase in the interaction energy of the dimer. The hydrogen bond energies are not additive on going from the dimer to trimer and tetramer being increased with number of hydrogen bonds. Thus positive cooperativity was observed in linear *n*-mers. The in-

TABLE II

Equilibrium geometries, hydrogen bond energies, and average hydrogen bond energies of N--methylacetamide oligomers

N-methylacetamide	$R_{O...H}$ nm	E_{HB} kJ/mol	Number of H-bonds	E_D kJ/mol	% Coop.[a]
Dimer	0·165 (0·170)[b]	22·79 (19·00)	1	22·79	
Trimer	0·165	25·50	2	24·14	5·92
Tetramer	0·165	26·28	3	24·85	2·94
			∝	26·45	

[a] The cooperativity percentage is defined as percentual increase in average hydrogen bond energy of the *n*-mer as compared with the value of $(n-1)$-mer; [b] the numbers in brackets are results of the calculations involving experimental geometry of N-methylacetamide[11].

crease of hydrogen bond energy, however, is not monotonous, the maximum energy per one hydrogen bond being reached at the number of hydrogen bonds 3 – 5.

Fig. 4 presents the dependence of reciprocal value of the average hydrogen bond energy *vs* reciprocal value of number of hydrogen bonds. The dependence is almost linear and allows the extrapolation to $h = \infty$. A similar linear dependence was found[32] in study of linear formamide oligomers and in a study[34] of linear *n*-mers ($n = 6$) of methanol. On the contrary, the PCILO calculations[30] of formamide oligomers predicted the hydrogen bond additivity in contrast to our results. The extrapolation to $h = \infty$ gives the average hydrogen bond energy 26·45 kJ mol^{-1} for an infinitely long hydrogen-bonded chain of N-methylacetamide, which agrees well with the value 27·5 kJ mol^{-1} found in ref.[32] for E_D of an infinitely long formamide chain.

TABLE III

The calculated equilibrium geometry, interaction energy, and dipole moments of the studied complexes of N-methylacetamide and N,N-dimethylacetamide

System	$R_{O...H}$ nm	E_{HB} kJ/mol	$\mu \cdot 10^{29}$ Cm
N-Methylacetamide–N-methylacetamide	0·165	22·79	2·55
N-Methylacetamide–water	0·160	27·49	1·85
N-Methylacetamide–methanol	0·160	27·75	1·81
N-Methylacetamide–phenol	0·155	34·44	1·67
N,N-Dimethylacetamide–water	0·160	26·58	1·72
N,N-Dimethylacetamide–methanol	0·160	27·14	1·69
N,N-Dimethylacetamide–phenol	0·155	33·65	1·56

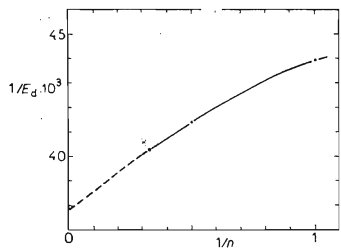

FIG. 4

Doubly reciprocal dependence between the data given in Table II

Heteroassociation of N-*methylacetamide and* N,N-*dimethylacetamide.* Table III gives the PCILO-calculated hydrogen bond energies of interactions of carbonyl group of N-methylacetamide or N,N-dimethylacetamide with water, methanol, or phenol. In all the cases studied, the found hydrogen bonds type O—H···O=C were stronger as compared with hydrogen bond energy of type N—H···O=C in the linear dimer of N-methylacetamide. Thus water and polar alcoholic and phenolic OH groups act as breakers of interpeptidic hydrogen bonds. The alcoholic OH group forms with C=O groups of N-methylacetamide and N,N-dimethylacetamide hydrogen bonds which are somewhat stronger than those formed by OH group of water. The strongest hydrogen bonds, however, are formed with the studied proton-acceptors by phenolic OH group. The same trend was also found experimentally in a study of interaction of N,N-disubstituted amides with the mentioned proton-donors[6].

In the case of N,N-dimethylacetamide we studied, besides the 1 : 1 system N,N-dimethylacetamide–water, the 2 : 1 complex, too (Fig. 1). The latter was obtained by addition of a molecule of N,N-dimethylacetamide to the optimized 1 : 1 system dimethylacetamide–water. The calculated energy of the „second" hydrogen bond was somewhat lower (21·38 kJ bol^{-1}) at the equilibrium $R_{O...H}$ distance equal to 0·160 nm.

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