PCILO STUDY OF HYDROGEN BOND AND PROTON TRANSFER IN SYSTEMS 1-METHYLTHYMINE–ACETAMIDE AND 1-METHYLTHYMINE–ACETIC ACID

Milan REMKO

Pharmaceutical Faculty,
Comenius University, 880 34 Bratislava

Received August 19th, 1980

Complexes containing two hydrogen bonds of the systems 1-methylthymine–acetamide and 1-methylthymine–acetic acid have been studied by the quantum-chemical PCILO method. In accordance with experiment our PCILO calculations have shown that acetic acid forms stronger hydrogen bonds than acetamide with 1-methylthymine. Further the PCILO method has been used to study of double proton transfer in O—H···O and N—H···O bonds of the complexes 1-methylthymine–acetamide and 1-methylthymine–acetic acid. Using equilibrium O···O and N...O distances, the PCILO calculations have given one-minimum proton potential functions. The proton transfer has not been observed. At somewhat longer N···O and O···O distances (0·30 nm) the PCILO calculations indicate a second minimum as a shoulder.

Direct interaction by hydrogen bonds belongs among the basic mechanisms which can contribute to understanding of specificity of nucleic acids besides proteins and enzymes. Amino acids and bases of nucleic acids have various polar groups able to form hydrogen bonds. Each polar group of the amino acid side chain can form hydrogen bonds with all the four bases. This peculiarity led Seeman and coworkers[1] and Hélène[2,3] to the conclusion that a single hydrogen bond is inadequate for unambiguous identification of any base or pair of bases. But the model studies[1,2] presume that a pair of bases can be precisely identified, if two hydrogen bonds are formed. Interaction of carboxylic acids or amide groups of polypeptides with the bases of nucleic acids can result in formation of such complexes involving two hydrogen bonds.

Possibility of formation of the hydrogen-bonded complexes between the bases of nucleic acids and both amides and carboxylic acids was studied experimentaly in the works[4–8]. The present paper gives the results of quantum-chemical calculations of hydrogen bonds and proton transfer in the model systems 1-methylthymine–acetamide and 1-methylthymine–acetic acid.

Calculation Method and Geometry

The original PCILO method[9] was used for the calculations of equilibrium geometry, hydrogen bond energy, as well as the proton potential functions. Geometry of the complexes studied (Fig. 1) was optimized with respect to the following parameters: the distances r_{N-H}, r_{O-H}, $R_{O...N}$, $R_{O...O}$, linearity of the X—H···O (X = N, O) bonds being presumed in the calculations.

The interaction energy of two hydrogen bonds (E_{HB}) of the complexes studied was calculated

as a difference between the total energy of the hydrogen-bonded complexes and that of the isolated molecules:

$$E_{HB} = E_{(MIN)} - E_{\infty} \qquad (1)$$

For the calculations we used the experimental geometry of the monomers[10,11]. The calculations were carried out with a Siemens 4004/150 computer in Computer Centre of Comenius University using the program QCPE No 220 (ref.[12]).

RESULTS AND DISCUSSION

Energy of hydrogen bond. Table I gives the equilibrium geometry, energy of hydrogen bonds, and the dipole moments of the studied systems calculated by the PCILO method.

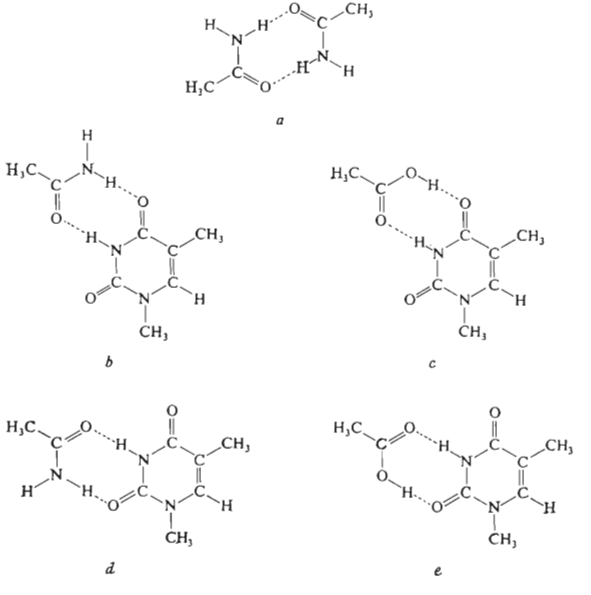

FIG. 1
Molecular Arrangement of the Complexes Studied

First we studied hydrogen bond in acetamide dimer. According to the experimental studies[7] liquid acetamide is associated in cyclic dimers. Our PCILO calculations of the cyclic dimer of acetamide (Fig. 1) showed that the hydrogen bonds in this dimer have medium strength, the interaction energy being 23·71 kJ/mol per one hydrogen bond. With 1-methylthemine, acetamide can form two types of complexes having two hydrogen bonds (the complexes *b* and *d*, Fig. 1). According to the PCILO calculations the complex *b* is more stable (Table I), the calculated interaction energy of this complex being lower than that found in the cyclic dimer of acetamide by 2·4 kJ/mol. A similar trend in relative stability of complexes of the cyclic acetamide dimer and the structurally similar system of 1-cyclohexyluracil–acetamide was found in NMR measurements of Lancelot and Hélène[7].

Carboxylic acids can interact (in similar way as amides) with the bases of nucleic acids through hydrogen bonds. Therefore, our further PCILO studies were concerned with the model system 1-methylthylamine–acetic acid. Pure carboxylic acids themselves associate to cyclic dimers[13]. The work[14] gives a PCILO-calculated interaction energy of the cyclic dimer of acetic acid to be 71·83 kJ/mol. The both complexes *c* and *e* of the system 1-methylthymine–acetic acid (Table I) have the interaction energies somewhat lower than that found for the cyclic dimer of acetic acid. Similarly to the case of acetamide, acetic acid also forms a more stable hydrogen-bonded complex with the hydrogen bonds bound to 3 and 4 positions of 1-methylthymine (the complex *c*, Fig. 1).

Comparison of the hydrogen-bonding properties of acetamide and acetic acid in their interaction with the said base of nucleic acids–1-methylthymine–shows (Table I) that acetic acid forms with 1-methylthymine a stronger complex than acet-

TABLE I

PCILO Equilibrium Geometry, Hydrogen Bond Energy and Dipole Moments of the Complexes Studied

Complex	r_{N-H}, nm	r_{O-H}, nm	$R_{N...O}$, nm	$R_{O...O}$, nm	E_{HB}[a], kJ/mol	$\mu \cdot 10^{29}$ C m
a	0·108		0·273		47·42	0
b	0·11	0·11	0·273	0·273	45·04	1·20
c	0·11	0·11	0·263	0·263	64·25	1·22
d	0·109	0·109	0·268	0·268	36·83	1·56
e	0·109	0·109	0·269	0·269	62·66	2·16

[a] Energy of two hydrogen bonds.

amide by about 1/3. The same trends in comparison of relative stability of model complexes acetamide–base and acetic acid–base of nucleic acid were also observed experimentally[6,7].

Proton transfer. Both semi-empirical and *ab initio* calculations of the proton potential functions of one proton transfer between neutral molecules lead to the conclusion that there is only an one-minimum potential function for the proton at the most stable intermolecular conformation[15]. Calculations of model systems of formic acid[16] indicate that a two-minimum potential can be expected in the case of simultaneous transfer of two protons in the direction of the hydrogen bonds. Similar conclusions were arrived at also by Scheiner and Kern[17,18] in their theoretical studies of the proton transfer between DNA base pairs.

From this point of view our further studies by the PCILO method were focused on calculation of the proton potential functions of simultaneous proton transfer in the complexes *b* and *c* of the systems 1-methylthymine–acetamide and 1-methylthymine–acetic acid. Possibility of such proton transfer was predicted experimentally[6] in the case of a system 6-ethyladenine–butanoic acid. The results of the PCILO calculations of the proton potential functions of the *b* and *c* complexes are given in Figs 2

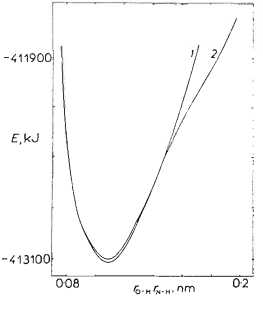

FIG. 2

PCILO Proton Potential Functions for the Proton Transfer in Complex *b* of System 1-Methylthymine–Acetamide

1 The equilibrium distance $R_{O\cdots N}$, *2* $R_{O\cdots N} = 0{\cdot}30$ nm.

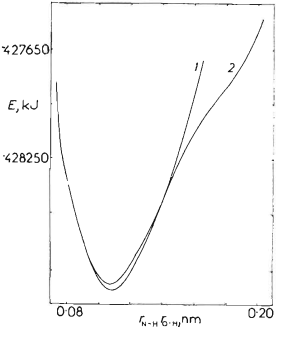

FIG. 3

PCILO Proton Potential Functions for the Proton Transfer in Complex *c* of System 1-Methylthymine–Acetic Acid

1 The equilibrium distance $R_{O\cdots O}$ and $R_{N\cdots O}$, *2* $R_{O\cdots O} = R_{N\cdots O} = 0{\cdot}30$ nm.

and 3. The potential functions were calculated for the simultaneous proton transfer along the hydrogen bonds between the proton donor and the proton acceptor at fixed geometries and intermolecular distances. In the both cases studied we could find only one-minimum potential curves by the PCILO calculations at the equilibrium O···O and N···O distances (curves *1*, Figs 2 and 3). The proton transfer was not observed. A second minimum was observed as a shoulder at somewhat longer O...O and N···O distances (0·30 nm) (curves 2, Figs 2 and 3). However, it must not be forgotten that semi-empirical methods can reproduce the proton potential functions semi-quantitatively at best[15]. Calculations of realistic proton potential functions necessitate the *ab initio* calculations with extended bases, and also it is necessary to consider, in some way, a part of the correlation energy[15]. Earlier calculations of the proton potential curves showed that transfer of one proton in one bond[19–23] or simultaneous transfer of two protons in two hydrogen bonds[18,24] are accompanied by significant fluctuations of the X···Y distances. These conclusions are also confirmed by the PCILO calculations carried out for simultaneous proton transfer at two X···O distances (X = N, O) in the *b* and *c* complexes of the systems 1-methylthymine–acetamide and 1-methylthymine–acetic acid.

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Translated by J. Panchartek.