

Ground state intermolecular proton transfer in the supersystems thymine–(H₂O)_n and thymine–(CH₃OH)_n, n=1,2: a theoretical study

Vassil B. Delchev · Ivan G. Shterev

Received: 7 May 2008 / Accepted: 8 July 2008 / Published online: 10 December 2008
© Springer-Verlag 2008

Abstract Twelve binary and eight ternary supersystems between thymine and methanol, and water were investigated in the ground state at the B3LYP and MP2 levels of theory using B3LYP/6-311++G(d,p) basis functions. The thermodynamics of complex formations and the mechanisms of intermolecular proton transfers were clarified in order to find out the most stable H-bonded system. It was established that the energy barriers of the water/methanol-assisted proton transfers are several times lower than those of the intramolecular proton transfers in the DNA/RNA bases. The X-ray powder spectra of thymine, and this precrystallized from water and methanol showed that water molecules are incorporated in the crystal lattice of thymine forming H-bridges between thymine molecules.

Keywords DFT calculations · H-Bonding · MP2 calculations · Rietveld method · Thymine · X-ray analysis

Introduction

Thymine is one of the more important DNA and RNA pyrimidine bases, resembling uracil but with a methyl group at a 5th position. The most interesting reactions of thymine are those that concern its biologic role in living

organisms. They can be divided into two major groups: thermal and photochemical reactions. As an example for an important photochemical reaction is the photo-cyclodimerization of two thymine molecules. A lot of papers have been dedicated on this process [1–3]. Interesting ground state or thermal reaction (as well as photochemical) is the proton transfer one. There are two basic mechanisms for this reaction to occur: intermolecularly or intramolecularly. The first mechanism is connected with the participation of a small protic molecule (more commonly water molecule), which exchanges protons with thymine. Intramolecular proton transfer describes the motion of a single proton in the frames of the thymine molecule.

Intramolecular proton transfer in tautomers of thymine radical cation and its hydrated complexes with one water molecule has been investigated at the B3LYP/6-311++G(d,p) level of theory [4]. It has been shown that the presence of water significantly lowers the energy barrier of the proton transfer in thymine cation.

The DNA cytosine-C5 methyltransferase M. Hha I flips its target base out of the DNA helix during interaction with the substrate sequence GCGC. It has been found that in cases when the target cytosine is replaced with thymine (GTGC), KMnO₄ proved an efficient probe for positive display of flipped-out thymines [5]. In such position thymine residue can exchange protons with surrounding media (most commonly water).

The Raman spectra of thymine and thymidine have been investigated, with visible excitation, in eight and nine solvents respectively [6]. No evidence of deprotonation in the different solvents has been observed for either thymine or thymidine. Correlations of the observed frequency shifts of specific vibrational modes with characteristic properties of the solvent for both thymine and thymidine have shown a significant correlation with acceptor and donor numbers,

V. B. Delchev (✉)
Department Physical Chemistry, University of Plovdiv,
Plovdiv, Bulgaria
e-mail: vdelchev@uni-plovdiv.bg

I. G. Shterev
Department Physical and Inorganic Chemistry,
University of Food Technologies,
Plovdiv, Bulgaria

measures of the hydrogen-bonding ability of the solvent, in both thymine and thymidine. These results have been interpreted in terms of hydrogen-bonding interactions between the N-H protons of the thymine base and lone pairs of electrons on the solvent molecules and between the solvent hydrogens and lone pairs on C=O sites. The solvent-dependent intensity in vibrational bands of thymine between 1500 and 1800 cm^{-1} indicates a strong interaction between thymine and solvent at the C=O and N-H sites that leads to separation of the C=O stretches from the C=C stretch [6].

Unfortunately, there are no investigations on the comparative study of H-bonding between thymine and water and methanol molecule(s) and its influence on the thermodynamics of complex formations and mechanisms of intermolecular proton transfers. The goal of this investigation is to fill this scientific gap.

Methods

The X-ray powder spectra of thymine (FLUKA), and thymine precrystallized from methanol and water were recorded on a TUR-MA-62 apparatus, working tension of 32 kV, Cu-antecathod, $\lambda_{\alpha 1} = 1.5405 \text{ \AA}$, $\lambda_{\alpha 2} = 1.5443 \text{ \AA}$, $\bar{\lambda}_{\alpha 2} = 1.5424 \text{ \AA}$, and a step of 0.02° .

Small amounts of uracil were hot-dissolved in $\sim 70\text{--}80 \text{ cm}^3$ water/methanol until saturated solution was obtained. After boiling to the volume of 20 cm^3 the solutions were cooled 60 h at $+5^\circ\text{C}$. White crystals of thymine were filtered. The röntgenograms of the moist thymine samples were recorded. Then the samples were heated to dry ~ 1 hour at 60°C , and again the powder diffraction spectra were recorded.

The ground state optimizations (by standard gradient procedure with no symmetry restrictions) of the supersystems were performed at the B3LYP/6-311++G(d,p) theoretical level by means of the Gaussian 03 program [7]. Subsequent single-point calculations were carried out at the MP2 level with the same basis set and the program GAMESS [8]. Even lower basis sets, as for example 6-31+G(d), has shown a sufficient accuracy in calculating H-bonds and energy parameters of DNA bases and other bioorganic compounds [9–11].

Furthermore, frequency calculations were carried out to prove that the resulting stationary points are real energy minima (without imaginary frequencies in their vibration spectra). It has been demonstrated that the B3LYP functional yielded accurate normal mode frequencies for intermolecular interactions compared with experiment [12]. Each transition state located between two minima was found by using the QST2 procedure (included in Gaussian 03).

The bonding energies (ΔE_b) and BSSE for each supersystem were calculated using the equations [13–15]

$$\Delta E_b = E_{SS} - \sum_{i=1}^n E'_{m_i}, \Delta(\text{BSSE}) = \sum_{i=1}^n (E_{m_i}^{\text{SP}} - E'_{m_i}),$$

where E_{SS} is the energy of the complex (supersystem); E'_{m_i} is the energy of i -th monomer in the supersystem calculated with “ghost” orbitals of the remaining monomer(s); $E_{m_i}^{\text{SP}}$ are the energies of the individual monomers frozen in their aggregate geometries, found by single-point calculations.

The interaction energy was calculated by the equation:

$$\Delta E_{\text{int}} = E_{SS} - \sum_{i=1}^n E_{m_i},$$

where E_{m_i} are the energies of isolated monomers found by preliminary optimizations.

The energy ΔE was calculated using the equation:

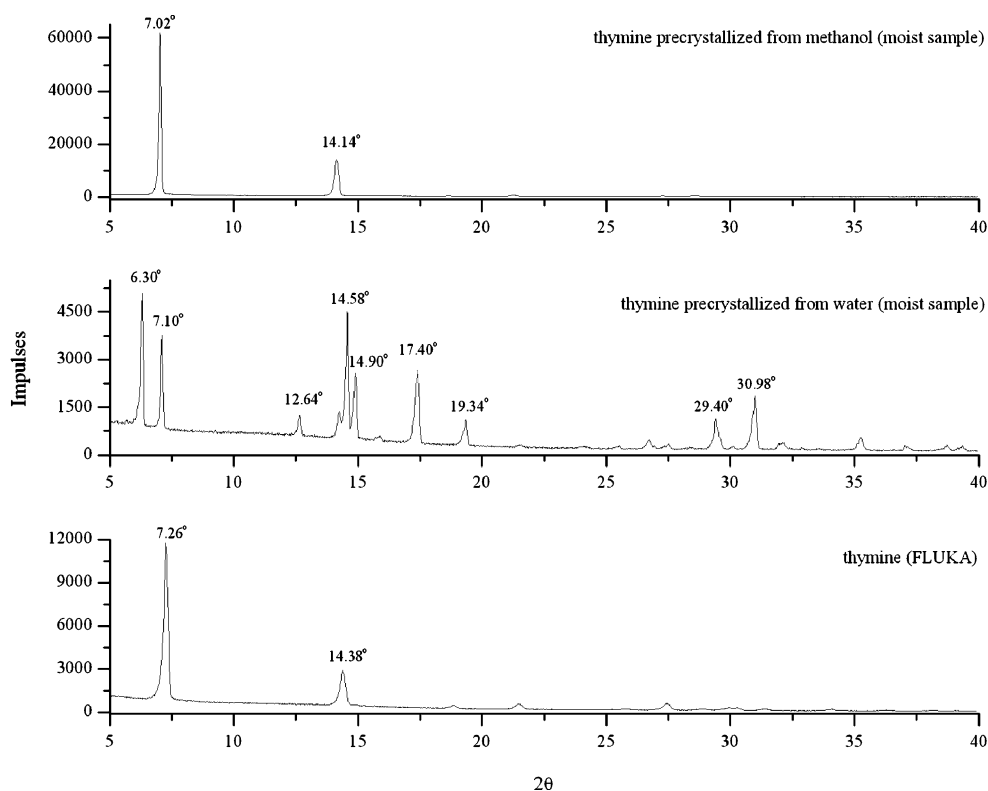
$$\Delta E = E_{SS} - \sum_{i=1}^n E_{m_i}^{\text{SP}}.$$

Results and discussion

X-ray diffraction study of thymine

Our preliminary investigations started with the record of the X-ray diffraction spectra of thymine (FLUKA), and thymine precrystallized from water and methanol (moist and dry sample). The röntgenograms recorded are depicted in Fig. 1.

Thymine can form hydrate crystal clusters and the crystal structure of thymine monohydrate has been established [16]. As one can see in Fig. 1, water-precrytallized thymine has a rather distinguished röntgenogram. No doubt, the water molecules are involved in the crystal lattice of thymine forming H-bridges between its molecules. One can say that the water molecules serve as linking agents between the different proton donating and accepting atoms of thymine molecules. In pure thymine the interplanar spacing (d) is 13.532 \AA ($2\theta = 7.26^\circ$) and 6.843 \AA ($2\theta = 14.38^\circ$). Perhaps, the large spacing between the crystal planes is due to the space hindrance between the methyl groups of the thymine molecules. However, water-precrytallized thymine is polymorphous and a crystal lattice with $d = 3.201 \text{ \AA}$ ($2\theta = 30.98^\circ$) is observed. In other words, linking water drastically improves the base stacking in crystals due to the H-bonds formed. In some cases those H-bonds are formed in a manner taking away the crystal

Fig. 1 X-ray powder diffraction spectra of thymine

planes: $d=15.592 \text{ \AA}$ ($2\theta=6.30^\circ$) and $d=13.837 \text{ \AA}$ ($2\theta=7.10^\circ$). May be those water molecules are bound (through only one H-bond) to the end proton donating and accepting atoms in thymine crystal lattice and due to the space hindrance the crystal planes take away.

The same reason caused a remote of the crystal planes in thymine precrystallized from methanol: $d=13.9952 \text{ \AA}$ ($2\theta=7.02^\circ$) and $d=6.959 \text{ \AA}$ ($2\theta=14.14^\circ$). The impossibility of methanol to form cross-linking bridges between the crystal planes is responsible for the spectrum depicted in Fig. 1. It is seen that thymine and this precrystallized from methanol form almost isomorphous crystals.

The dried at 60°C thymine (~ 1 hour) showed an absence of water and methanol.

The crystal structure of pure thymine was established by Rietveld refinement method and the X-ray powder spectrum of pure thymine (FLUKA), recorded at a step of 0.02° . The Powder Cell 2.4 program [17] was applied. As a model (monoclinic crystal) we chose the lattice constants: $a=12.85 \text{ \AA}$, $b=6.826 \text{ \AA}$, $c=6.728 \text{ \AA}$; $\alpha=\gamma=90.00^\circ$, $\beta=104.66^\circ$; and a space group of $P2_1/c$ [18]. The initial fractional coordinates (x, y, z) of the thymine model were obtained by the calculated (B3LYP) Cartesian coordinates (X, Y, Z) of the oxo form of thymine (isomer **A**, see below): $x=X/a$, $y=Y/b$, $z=Z/c$. The refined crystal structure of thymine is depicted in Fig. 2.

Rietveld refinement method showed a slight change in the crystal lattice constants (Fig. 2). Respectively, the

parameters a , c , and β are slightly increased, whereas the parameter c is insignificantly reduced. This method predicted a reasonable model of the thymine oxo form with a lot of possibilities for H-bonding with water and methanol (see Fig. 3)

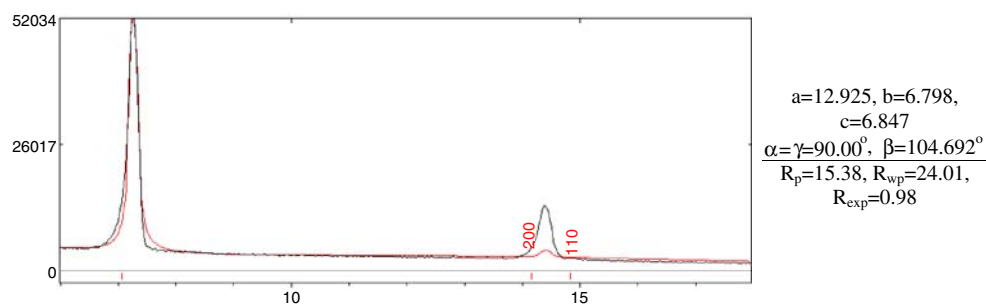
Structures of thymine monomers, binary and ternary systems

Five functional and conformational isomers of thymine were initially optimized at the B3LYP/6-311++G(d,p) theoretical level. Subsequent single-point calculations were carried out at the MP2 level using the same basis set. The calculated energy and thermodynamic parameters are listed in Table 1, and their optimized structures are depicted in Fig. 4.

The B3LYP and MP2 calculations unequivocally show that the isomer **A** (oxo thymine) is energetically the most stable form of thymine. The two methods give contradictory data on the energy stability of the remaining forms. For example, the B3LYP calculations predicted that tautomer **D** is more stable than **B**. Conversely, the MP2 energies show **B** to be more stable than **D** one.

It is seen that the B3LYP functional is a reasonable choice for studying such tautomers, the more so as several investigations of aromatic systems have revealed that geometries and frequencies of the molecules calculated at the B3LYP level agree well with experiment [19, 20].

Fig. 2 Refined (Rietveld) powder diffraction spectrum of thymine and lattice parameters



Moreover, the MP2 and B3LYP calculated energies do not confirm the results reported in Ref. [21], according to which the B3LYP obtained energies of a great number of organic molecules have been found to be very close to those calculated with the more expensive and time-consuming MP2 method.

The isomers (Fig. 4) were subsequently used in a complexation with one water molecule and again with methanol molecule (through H-bonds) in appropriate positions for intermolecular H-transfer. The obtained geometries of these supersystems are illustrated in Scheme 1.

It was found, in the water dimers, that the intermolecular H-bonds are shorter than the internuclear distances in the monomers given in Fig. 4. Therefore, it is expected for intermolecular proton transfer to occur more easily (lower energy barriers) than the intramolecular one. The formation of supersystem **A_W** from tautomer **A** and water is accompanied with a slight distortion of the pyrimidine aromatic ring and oxygens. For example, the dihedral angle $N_1C_2N_3C_4$ is changed from 0.0° (**A**) to 0.2° (**A_W**), the angle $O_8C_2N_3C_4$ - from 180.0° (**A**) to -179.7° (**A_W**). These values in the supersystem **A1_W** reach -0.4° and -179.6° (distorted in opposite directions as compared to the supersystem **A_W**) correspondingly. Maximal distortion of

the angle $O_7C_6N_1C_2$ is achieved in the supersystem **A2_W** (179.5° ; in the tautomer **A** it is 180.0°).

With respect to the pyrimidine ring and oxygens, tautomer **B** has planar structure. However, the H-bonding with water (as in the supersystem **B_W**) causes a disturbance of the planar geometry: the angle $N_1C_2N_3C_4$ is changed to 0.5° , and the angle $O_8C_2N_3C_4$ - to -179.4° .

The formation of the supersystem **C_W** from tautomer **C** and water is accompanied with the largest ring distortions: the dihedral angle $N_1C_2N_3C_4$ in tautomer **C** is 0.0° , whereas in the supersystem **C_W** it is 2.6° , the angles $O_7C_6N_1C_2$ and $O_8C_2N_3C_4$ in **C** are respectively 180.0° and 179.9° ; in **C_W** they are 178.1° and -177.3° . In other words, the aromatic character of the pyrimidine ring in this supersystem is in a lesser degree pronounced as compared to the remaining supersystems.

With regard to the methanol-containing supersystems one can say that the formation of the supersystem **A2_M** is connected with the largest distortion of the angle $N_1C_2N_3C_4$; its value in the supersystem is 3.0° . In general, it can be concluded that the H-bonding of methanol to the oxo thymine tautomer causes a significant distortion of the aromatic ring as compared to water. Perhaps, the reason is the steric hindrance of the methyl residue in methanol.

Thermodynamics of the complex formations

The bonding parameters and the thermodynamic functions of the complex formations are listed in Table 2.

With regards to the binary supersystems, one can see that, despite the lowest energies of complexes which contain the oxo form of thymine (**A**), the bonding parameters of the systems containing tautomers **B**, **C** and **D** are significantly higher (by absolute value). It means that these binary systems are rather stable; the H-bonds between the monomers are stronger than those between the thymine oxo form and water/methanol. Comparing all values of these bonding parameters one can expect the system **C_M** to be the most stable one. This can be seen also from the values of ΔG_{298}^0 . In this case the equilibrium (see K_p values) of the complex formation process is pronouncedly shifted towards the binary system **C_M**. The formations of the supersystems that do not

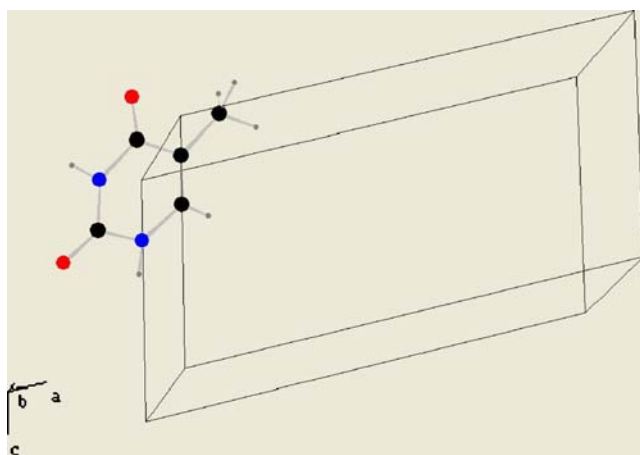


Fig. 3 Rietveld method predicted crystal structure of thymine

Table 1 Energies, thermodynamic properties (hartree) and relative energies (kJ.mol⁻¹)

System	B3LYP				MP2	
	E	H	G	E _{rel}	E	E _{rel}
A	-454.275747	-454.152665	-454.194100	0	-453.108895	0
B	-454.254633	-454.131929	-454.173119	55	-453.103272	15
C	-454.245191	-454.122734	-454.164181	80	-453.044960	168
D	-454.257587	-454.134924	-454.176049	48	-453.060719	127
E	-454.252934	-454.130259	-454.171199	60	-453.067897	108
Binary supersystems						
A_W	-530.748499	-530.597671	-530.646120	7	-529.366314	3
A_{1W}	-530.751087	-530.600126	-530.648330	0	-529.367508	0
A_{2W}	-530.747838	-530.596995	-530.645442	9	-529.365135	6
B_W	-530.732946	-530.582373	-530.629651	48	-529.350673	44
C_W	-530.725227	-530.574943	-530.622338	68	-529.343953	62
D_W	-530.735379	-530.584817	-530.631957	41	-529.354838	33
A_M	-570.054678	-569.873687	-569.927104	7	-568.537125	6
A_{1M}	-570.057396	-569.879238	-569.929123	0	-568.539431	0
A_{2M}	-570.053504	-569.872463	-569.926066	10	-568.536141	9
B_M	-570.039141	-569.858440	-569.910544	48	-568.531993	20
C_M	-570.031820	-569.851481	-569.903944	67	-568.516796	59
D_M	-570.042243	-569.861594	-569.913628	40	-568.527525	31
Ternary supersystems						
A_{2W}	-607.224082	-607.045454	-607.100814	0	-605.724934	0
B_{2W}	-607.209472	-607.031149	-607.085432	38	-605.648033	202
D_{2W}	-607.205919	-607.027537	-607.082848	48	-605.645831	208
E_{2W}	-607.203053	-607.024896	-607.079205	55	-605.646755	205
A_{2M}	-685.836977	-685.598004	-685.663152	0	-684.005879	0
B_{2M}	-685.822749	-685.584093	-685.648382	37	-683.993498	33
D_{2M}	-685.822650	-685.585254	-685.647630	38	-683.965525	106
E_{2M}	-685.817731	-685.579286	-685.643414	51	-683.993394	33

contain the thymine oxo form are thermodynamically favoured processes (for them ΔG_{298}^0 is negative).

As the values in Table 2 show, the complex formations are accompanied with large steric (entropy) changes ($T\Delta S_{298}^0$ are large) due to the mutual orientation of the interacting molecules to form a certain supersystem. This does not mean that the interacting molecules undergo any distortions. The last follows from the close values of ΔE_b and ΔE_{int} or ΔE and ΔE_{int} .

Basing on the ΔE_b values we propose the following stability pattern of the binary systems:

$$C_M > C_W > B_M = D_M > B_W > D_W > A_{1M} \\ = A_{1W} > A_M = A_W > A_{2W} > A_{2M}.$$

As expected, the bonding parameters of the ternary supersystems are about two times higher. These finding automatically leads to about two times higher basis set superposition errors, as can be seen in Table 2. The most stable ternary supersystem is **B_{2M}**. All ternary supersystems that contain the oxo thymine form have much lower stability than all remaining. This fact shows that the

stability of one H-bonded supersystem does not come from the low energies of the separate monomers involved in H-bonding.

Following the values of ΔE_b , we propose the stability pattern:

$$B_{2M} > B_{2W} > D_{2M} > E_{2M} > E_{2W} > D_{2W} > A_{2M} > A_{2W}.$$

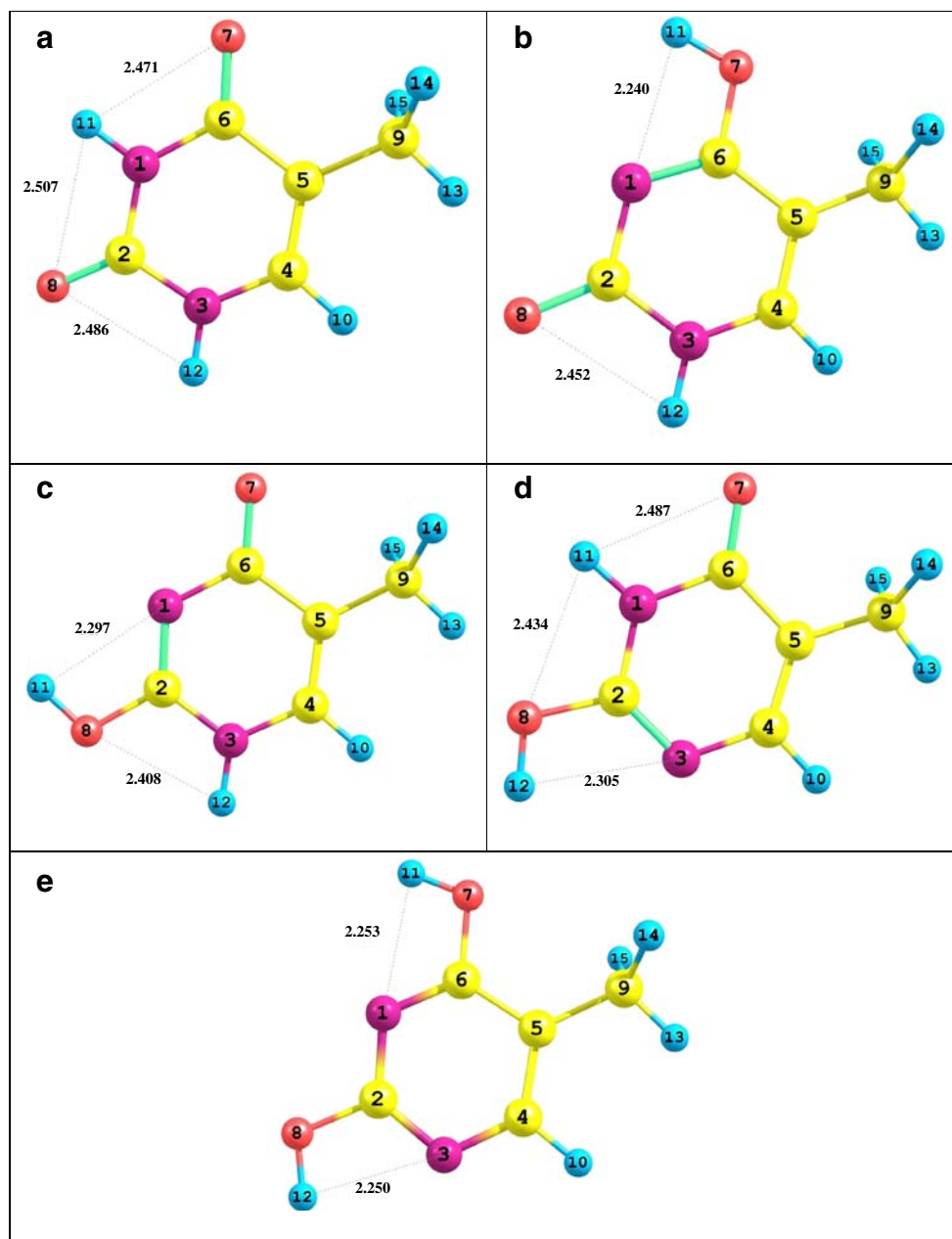
Obviously, the methanol molecule(s) are able to oust the water molecules and to form competitively more stable H-bonded systems with thymine.

All complex formations are enthalpically favoured, whereas only two of them are thermodynamically favoured: those are the formations of the binary systems **B_{2M}** and **B_{2W}**. As a result, for these supersystems the equilibrium, in the gas phase and standard conditions, is shifted towards the aggregate systems (see K_p values).

Intermolecular proton transfers

The water and methanol-assisted intermolecular proton transfers reveal the discrete interactions between thymine

Fig. 4 Optimized tautomeric forms of thymine



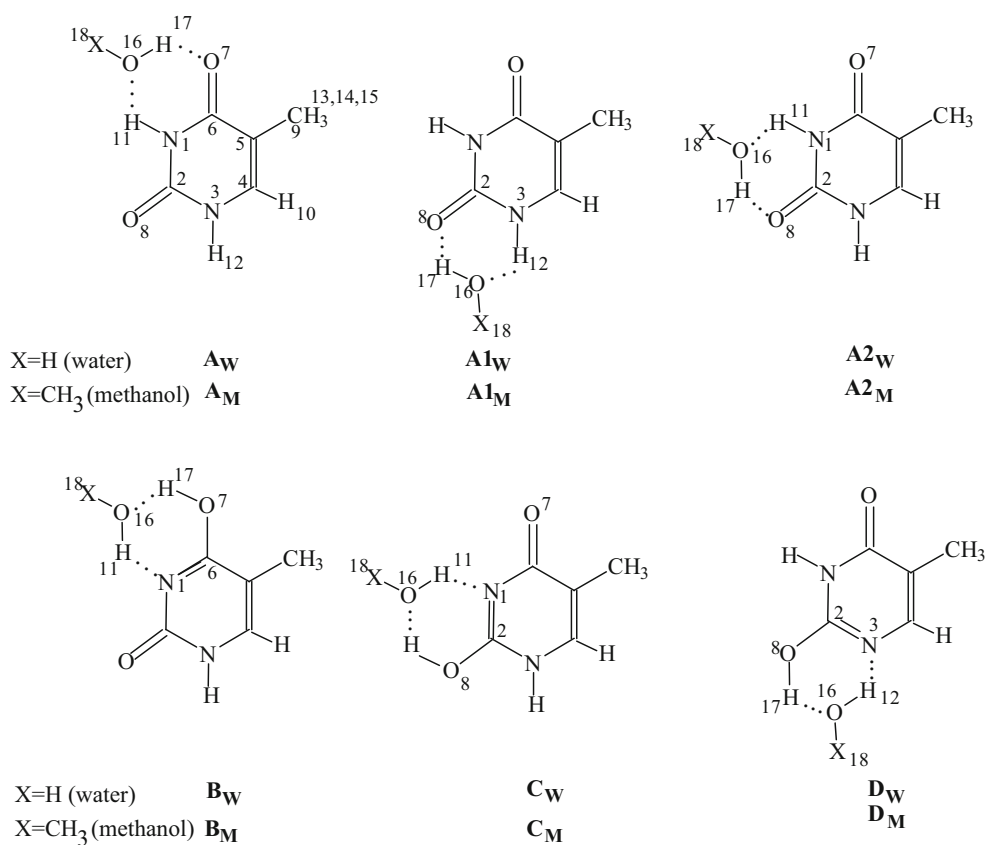
and environment. These discrete interactions change the mechanism of tautomeric conversions in thymine. Water and methanol molecules are directly engaged in the proton exchange processes with the thymine tautomers. No continuum theory for modelling the solvent influence can describe correctly these processes. However, in this study we used the Onsager continuum model only for comparison of the gas phase results with those in water and methanol environment.

The transition states of the intermolecular proton transfers were calculated at the B3LYP/6-311++G(d,p) level, as a first order saddle points with one imaginary frequency in the vibration spectrum of each. This frequency corre-

sponds to a parallel vibration mode along the reaction coordinate. The calculated energy barriers and thermodynamic parameters of these processes are listed in Table 3.

The calculated energy barriers are several times lower than those of the intramolecular proton transfers in the DNA/RNA bases [22–24]. In other words, one can say that the molecules of water and methanol facilitate the H-transfer in thymine. Moreover, they serve as catalysts of these processes.

The data in Table 3 show that the application of Onsager SCRF method does not influence considerably the energy barriers of the transformation. In some cases it favours the proton transfer processes (lessens the energy barrier slightly) and for some reactions the effect is opposite.

Scheme 1 Dimer supersystems
thymine – water/methanol**Table 2** Bonding parameters and thermodynamic properties of the complex formations (kJ mol⁻¹)

Supersystem	Bonding parameters				Thermodynamic parameters			
	ΔE_b	ΔE_{int}	ΔE	$\Delta BSSE$	ΔH_{298}^0	ΔG_{298}^0	$T\Delta S_{298}^0$	K_p
Binary supersystems								
A_W	-36	-37	-39	3	-30	9	-39	0.03
A1_W	-43	-44	-46	3	-37	3	-40	0.30
A2_W	-34	-36	-38	3	-29	11	-40	0.01
B_W	-52	-52	-56	4	-45	-3	-42	3.36
C_W	-58	-56	-62	4	-49	-7	-42	16.87
D_W	-51	-51	-55	4	-43	-1	-42	1.50
A_M	-36	-37	-39	3	-30	10	-40	0.02
A1_M	-43	-44	-46	3	-37	4	-41	0.20
A2_M	-33	-34	-36	3	-27	13	-40	0.01
B_M	-53	-51	-57	4	-44	-2	-42	2.24
C_M	-60	-57	-64	4	-50	-8	-42	25.25
D_M	-53	-52	-57	4	-45	-2	-43	2.24
Ternary supersystems								
A2_W	-80	-82	-86	7	-68	12	-79	0.01
B2_W	-99	-99	-107	7	-85	-3	-82	3.64
D2_W	-82	-82	-89	8	-67	11	-79	0.01
E2_W	-87	-87	-95	8	-73	8	-81	0.04
A2_M	-81	-82	-86	5	-68	12	-80	0.01
B2_M	-102	-100	-108	7	-86	-5	-82	6.67
D2_M	-94	-92	-100	6	-81	5	-86	0.13
E2_M	-92	-91	-100	7	-86	3	-89	0.26

K_p – equilibrium constant of the complex formation (Pa⁻¹ for dimers and Pa⁻² for trimers)

Table 3 Energy barriers (ϵ) and thermodynamic parameters (B3LYP) of the ground state intermolecular proton transfers ($\text{kJ}\cdot\text{mol}^{-1}$)

Proton transfer	Energy barriers				ΔH_{298}^0	ΔG_{298}^0	$T\Delta S_{298}^0$
	1	2	1*	2*			
$A_W \rightleftharpoons B_W$	85	44	87	45	40.2	43.2	-3.0
$A_{1W} \rightleftharpoons D_W$	85	44	91	45	40.2	43.0	-2.8
$A_{2W} \rightleftharpoons C_W$	95	36	97	36	57.9	60.7	-2.8
$A_M \rightleftharpoons B_M$	79	38	81	42	40.0	43.5	-3.5
$A_{1M} \rightleftharpoons D_M$	78	39	72	33	38.5	40.7	-2.2
$A_{2M} \rightleftharpoons C_M$	87	30	94	31	55.1	58.1	-3.0
$A_{2W} \rightleftharpoons B_{2W}$	83	45	83	43	37.6	40.4	-2.8
$A_{2W} \rightleftharpoons D_{2W}$	82	35	82	32	47.1	47.2	-0.1
$D_{2W} \rightleftharpoons E_{2W}$	68	60	68	60	6.9	9.6	-2.7
$B_{2W} \rightleftharpoons E_{2W}$	68	51	67	49	16.4	16.4	0.0
$A_{2M} \rightleftharpoons B_{2M}$	79	41	80	42	36.5	38.8	-2.3
$A_{2M} \rightleftharpoons D_{2M}$	78	40	76	37	33.5	40.8	-7.3
$D_{2M} \rightleftharpoons E_{2M}$	67	54	68	56	15.7	11.1	4.6
$B_{2M} \rightleftharpoons E_{2M}$	66	52	65	52	12.6	13.0	-0.4

1: forward; 2: reverse; 1*: forward, including solvent energy; 2*: reverse, including solvent energy.

In order to clarify better the mechanism of intermolecular proton transfer in the most stable thymine tautomer (A) we performed PES scan of the transformation $A_W \rightleftharpoons B_W$. The two-dimensional PES of the reaction is depicted in Fig. 5.

As reaction coordinates were chosen the distances $H_{11}\dots N_1$ and $H_{17}\dots O_{16}$ that were changed stepwise (with a step of 0.01 Å), 20 times each (441 points were calculated). The constructed PES shows that the proton transfer reaction passes through a low energy barrier. The last is the reason for the “broad” and not so steep reaction path. This finding reconfirms the calculated low energy barriers of the water-assisted proton transfers.

The data in Tab. 3 show that the proton transfer processes occur with small entropy (steric) changes. Moreover, one of the transformations, $B_{2W} \rightleftharpoons E_{2W}$, has a zero change of the entropy. In other words, the energy changes are dominating in these reactions. All transformations are enthalpically disfavoured that means (according to the Leffler-Hammond postulate [25, 26]) that the transition state of each reaction is product-like (or “late”). Its structure is closer to that of the product than of the reactant.

Conclusion

The preliminary analysis of the X-ray powder spectra of thymine and this precrystallized from water and methanol showed that water molecules are incorporated in the crystal lattice of thymine forming H-bridges with its molecules(s). In this way the linking water molecules drastically improve the base stacking in the thymine crystal. This finding was not observed in thymine precrystallized from methanol.

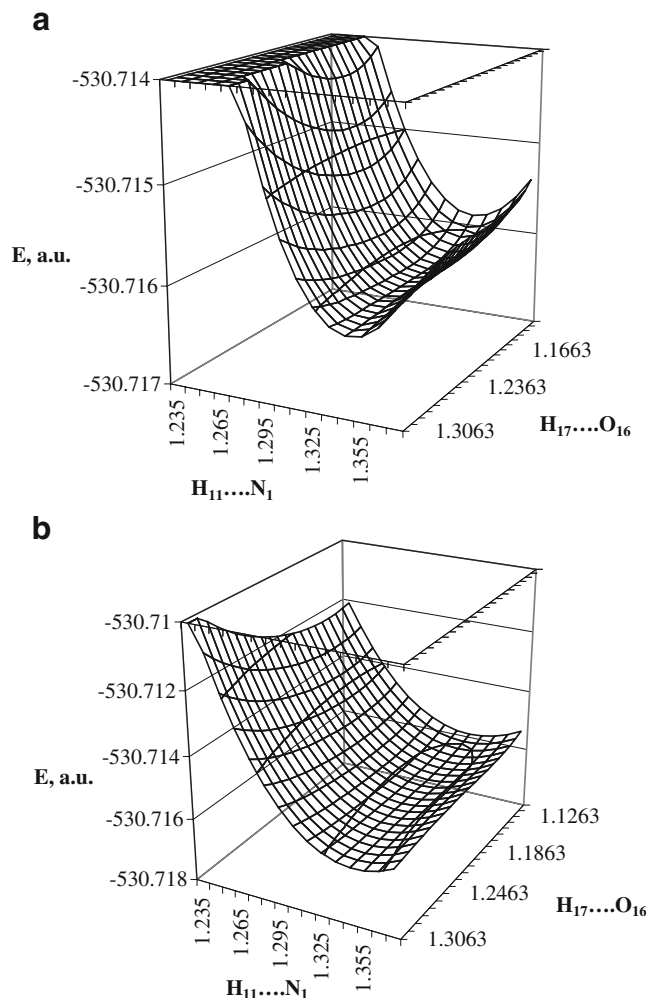


Fig. 5 Two-dimensional PES of the intermolecular proton transfer reaction $A_W B_W$, calculated at the B3LYP/6-311++G(d,p) theoretical level

It was established that the complex formations are accompanied with large steric (entropy) changes ($T\Delta S_{298}^0$ are large), coming from the mutual orientation of the interacting molecules to form a certain supersystem and not from monomer distortions during the complex formations. Conversely, all proton transfers occur with minimal entropy changes.

It was established (by analyzing the bonding parameters of the supersystems) that the most stable complexes are not those containing the oxo thymine tautomer (**A**). Among the binary systems the most stable supersystem is **C_M**, whereas among the ternary systems - the complex **B_{2M}**. This shows that the methanol molecules serve as a better catalyst in the proton transfer processes in thymine. Therefore, methanol can oust the water molecule to form competitively more stable H-bonded system with thymine.

The estimated energy barriers of the water/methanol-assisted proton transfers are several times lower than those of the intramolecular proton transfers in the DNA/RNA bases [22–24].

Acknowledgements We thank the National Science Fund (Ministry of Education and Science of Bulgaria) for the financial support (Project “Young Scientists – Chemistry – 1504”).

References

- Durbeej B, Eriksson LA (2002) *J Photochem Photobiol Chem* 152:95–101 doi:10.1016/S1010-6030(02)00180-6
- Boggio-Pasqua M, Groenhof G, Schäfer LV, Grubmüller RMA (2007) *J Am Chem Soc* 129:10996–10997 doi:10.1021/ja073628j
- Blancafort L, Migani A (2007) *J Am Chem Soc* 129:14540–14541 doi:10.1021/ja074734o
- Kim NJ (2006) *Bull Korean Chem Soc* 27:1009–1014
- Serva S, Weinhold E, Roberts RJ, Klimasauskas S (1998) *Nucleic Acids Research*. University Press, Oxford
- Beyere L, Arboleda P, Monga V, Loppnow GR (2004) *Can J Chem* 82(6):1092–1101 doi:10.1139/v04-052
- Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA Jr, Vreven T, Kudin KN, urant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani S, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA, Gaussian, Inc., Pittsburgh PA, Gaussian 03, Revision B.05, 2003
- Schmidt MW, Baldrige KK, Boatz JA, Elbert ST, Gordon MS, Jensen JH et al. (1993) *J Comput Chem* 14:1347–1363 doi:10.1002/jcc.540141112
- Li X, Cai Z, Sevilla MD (2002) *J Phys Chem A* 106:9345–9351 doi:10.1021/jp021322n
- Li X, Cai Z, Sevilla MD (2001) *J Phys Chem B* 105:10115–10123 doi:10.1021/jp012364z
- van Mourik T (2004) *Phys Chem Chem Phys* 6:2827–2837 doi:10.1039/b315520j
- Müller A, Losada M, Leutwyler S (2004) *J Phys Chem A* 108:157–165 doi:10.1021/jp0361024
- Boys SF, Bernadi F (1970) *Mol Phys* 19:553–566 doi:10.1080/00268977000101561
- Hobza P, Zahradnik R (1989) *Intermolecular Complexes*. Mir Press, Moscow (in Russian)
- Simon S, Duran M, Dannenberg JJ (1999) *J Phys Chem A* 103:1640–1643 doi:10.1021/jp9842188
- Gerdil R (1961) *Acta Crystallogr* 14(4):333–344 doi:10.1107/S0365110X61001182
- Kraus W, Nolze G (2000) *Powder Cell* 2.4 for Windows
- Welton J, McCarthy G (1988) North Dakota State University, USA, ICDD Grant-in-Aid.
- Gu J, Leszczynski J (1999) *J Phys Chem A* 103:2744–2750 doi:10.1021/jp982713y
- Mebel AM, Morokuma K, Lin CM (1995) *J Chem Phys* 103:7414–7421 doi:10.1063/1.470313
- van Mourik T, Emson LE (2002) *Phys Chem Chem Phys* 4:5863–5871 doi:10.1039/b207565b
- Delchev VB, Mikosch H (2006) *J Mol Model* 12:229–236 doi:10.1007/s00894-005-0022-x
- Shterev IG, Delchev VB (2006) *Scientific papers of the University of Plovdiv* 34:105–111
- Delchev VB, Shterev IG, Mikosch H, Kochev NT (2007) *J Mol Model* 13:1001–1008 doi:10.1007/s00894-007-0226-3
- Hammond GS (1955) *J Am Chem Soc* 77:334–338 doi:10.1021/ja01607a027
- Leffler JE (1953) *Science* 117:340–341 doi:10.1126/science.117.3039.340