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ORIGINAL PAPER

Investigation of the intermolecular proton transfer in the supersystems adenine-methanol/ethanol/i-propanol: MP2 and DFT levels study

Vassil B. Delchev · Ivan G. Shterev · Hans Mikosch · Nikolay T. Kochev

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Abstract Twelve H-bonded supersystems constructed between the adenine tautomers and methanol, ethanol, and i-propanol were studied at the B3LYP and MP2 levels of theory using 6-311G(d,p) and 6-311++G(d,p) basis functions. The thermodynamic parameters of the complex formations were calculated in order to estimate the exact stability of the supersystems. It was proven that the calculated energy barriers of the alcohol-assisted proton transfers are about 60% lower than those of the intramolecular proton transfers in adenine found earlier (Gu and Leszczynski in J Phys Chem A 103: 2744–2750, 1999).

Keywords Adenine · Density functional methods · H-bonding · MP2 calculations · Proton transfer

Introduction

The hydration of the DNA/RNA bases plays an important role in the biological functions and structure of biopolymers. There are theoretical investigations revealing that the nucleic acid bases could form hydrated complexes with a different number of water molecules [2–6]. The water molecules can be involved in tautomerizations (intermolecular proton transfers) of bases, thus they considerably lessen the energy barrier of the proton transfers [6–10].

Adenine is one of the purine nucleic acid bases. The structure of the polyhydrated adenine molecule has been studied at the B3LYP/6-31G(d) level of theory [11]. Four complexes including 12,13,14, and 16 water molecules have been an object of the study. The calculations have shown that the location of water molecules on one side of the adenine molecule leads to a significant deformation of the nucleobase structure [11].

Gu and *Leszczynski* [1] have investigated the intermolecular proton transfer in adenine (amino - imine tautomerism) assisted by one water molecule. They obtained lower energy barriers of the water-assisted proton transfers as compared to the intramolecular proton movement. Furthermore, they have found that the inclusion of quantum mechanical tunneling effects drastically increases the proton transfer rate in adenine. It would be interesting to know, how other small protic molecules (like the lower alcohols - methanol, ethanol, and i-propanol) would change the energy barrier of the amino - imino tautomeric conversions in adenine.

The energy of the guanine and adenine water complexes have been studied at B3LYP/6-31+G(d,p) with respect to their protonation and deprotonation enthalpies [12]. According to this investigation, the complex formation with water causes a moderate change of the pyramidal character of the amino group. This change has been estimated by the deviation of the sum of the angles around the nitrogen atom (ΣAH) from 360°.

The purpose of the current study is to study the possible ways for H-bonding between adenine and methanol/ethanol/i-propanol in order to find out the energy barriers of the

V. B. Delchev (✉) · N. T. Kochev
Computer Chemistry group, University of Plovdiv,
Plovdiv 4000, Bulgaria
e-mail: vdelchev@pu.acad.bg

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

H. Mikosch
Institute of Chemical Technologies and Analytics,
Technical University Vienna,
Getreidemarkt 9,
1060 Wien, Austria

alcohol-assisted proton transfers of the amino - imino tautomerism. The calculations were performed at the B3LYP [13–15] level of theory using the 6-311G(d,p) basis functions.

In the investigations of *Mebel*, *Morokuma*, *Lin* [16] and *Gu*, *Leszczynski* [1] it has been demonstrated and shown that the geometries and frequencies of the molecules calculated at the B3LYP/6-311G(d,p) level agree well with experiment. Moreover, the data for the water-assisted proton transfers in adenine [1] can be compared directly with the results discussed in this study.

The B3LYP optimized geometries and energies of a large number of organic molecules have been found to be very close to those found with the computationally more expensive MP2 method [17]. It has been established [18] that higher-order electron correlation corrections for H-bonding energies are usually small. There is no guarantee that the higher-order terms are negligible, but there is a substantial degree of compensation of errors for H-bonding [19]. Despite that we decided to carry out this investigation with the B3LYP functional and MP2 method.

Sponer and *Hobza* [20] have revealed that the diffuse functions do not provide a significant improvement for the description of the hydrogen bonding. However, the inclusion of such functions drastically increases the computational time. A detailed description of the basis sets and the correlation energy has been given also in the work of *Handy* and *Cohen* [21].

Computational method

The calculations in the current paper were performed by means of the GAUSSIAN 98 and GAMESS 6.4 program packages [22, 23], at B3LYP and MP2 theoretical levels with 6-311G(d,p) and 6-311++G(d,p) basis functions. The structures were optimized (using only the 6-311G(d,p) basis set) in the ground state by standard gradient procedure with no symmetry restrictions. Frequency calculations were performed to prove that the resulting stationary points are real energy minima (without imaginary frequencies in their vibration spectra). Further, QST2 computations were performed to find the transition states between two minima. Single-point computations were carried out at both levels with 6-311++G(d,p) basis set.

The combination B3LYP/6-311G(d,p) was applied to estimate the bonding energies (ΔE_b) and BSSE for each supersystem. They were calculated according to the equations given in [24–26].

$$\Delta E_b = E_{complex} - \left(E'_A + E'_{Alc}\right) \text{ and } \Delta(BSSE) = \sum_i^n \left(E_{m_i} - E'_{m_i}\right),$$

where $E_{complex}$ is the energy of the complex (supersystem); $E'_A\left(E'_{Alc}\right)$ is the energy of adenine (alcohol) calculated with "ghost" orbitals of the other monomer; E_{m_i} are the energies of the individual monomers frozen in their aggregate geometries, found by single-point calculations.

The adenine - alcohol interaction energy (ΔE_{int},) was calculated as the difference between the energies of the complex and isolated molecules of adenine and alcohol;

$$\Delta E_{int} = E_{complex} - (E_A + E_{Alc}),$$

where E_A and E_{Alc} are the optimized energies of a given adenine tautomer and alcohol.

The calculated energies of the supersystems could not be used for the stability discussion of the supersystems because the lower energy of a certain H-bonded complex may come from the lower energy of the adenine tautomer included into it. Therefore, a much more accurate estimation of the stability could be achieved using the ΔG^o_{298} values of all complex formations.

The Onsager's continuum model (B3LYP) was applied for the solvent effect prediction on the H-bonded complexes in an appropriate environment. In spite of a limited number of effects included it this method it was used in the current paper as the simplest and most time-saving continuum model included in GAUSSIAN 98. One of the goals of the paper is a demonstration of the rough approach included in the Onsager's method. For example, the Onsager's model is not able to predict the possibility for H-bonding between adenine and a given alcohol. Thus, the paper pretends to reveal the discrete interactions between adenine and surrounding medium (solvent - methanol, ethanol, i-propanol here) that cannot be achieved with any continuum model implemented in GAUSSIAN 98 and GAMESS 6.4.

Results and discussion

The optimized (B3LYP and MP2 with 6-311G(d,p)) structures of the supersystems are shown in Fig. 1.

For all amino adenine supersystems (at both levels) the shortest intermolecular hydrogen bond H(16)....N(1) is calculated in the complex $A^{iPr}_{am}N(9)H\left(1.933\,Å - B3LYP,\right.$ and $\left.1.932\,Å - MP2\right)$. In some supersystems either H-bond is longer than 2 Å, but the other one is rather short, which implies a compensation effect. Most probably, the lengths of the two H-bonds in one supersystem are a result of the spatial hindrance between the amino group of adenine and the alkyl residue of alcohols.

The shortest H-bonds in all imino adenine supersystems are formed between the alcoholic hydrogen and the imino adenine nitrogen (B3LYP). However, the MP2 calculations predicted nearly equal distances H(15)....N(13) and H(16)....O(17). These results show that the relation "H-bond - complex

stability" can not be explicitly defined. In each imino adenine supersystem the two bonds are comparatively short (<2 Å) and similar by length.

The pyramidal properties of the amino group (nonplanarity) in the amino adenine supersystems were evaluated by the deviation of the sum of the angles (ΣAH) around the nitrogen atom from 360° [12]. The B3LYP values of ΣAH of all amino adenine supersystems are: $A_{am}^{Me}N(9)H - 358.7°$; $A_{am}^{Me}N(7)H - 349.4°$; $A_{am}^{Et}N(9)H - 359.0°$; $A_{am}^{Et}N(7)H - 349.5°$; $A_{am}^{iPr}N(9)H - 360.0$; $A_{am}^{iPr}N(7)H - 351.6°$. It can be seen that only in the supersystem $A_{am}^{iPr}N(9)H$ the sp^2 hybridization of N (13) is pronounced. Pyramidal behavior of the amino group is well pronounced in the complexes $A_{am}^{Me}N(7)H$; $A_{am}^{Et}N(7)H$; and finally in $A_{am}^{iPr}N(7)H$. In the adenine N(9)H and N(7)H monomers ΣAH are correspondingly 358.7° and 344.0°. In other words, the complexations of the amino adenine tautomers with one alcohol molecule reduce the pyramidal character of the amino group. Thus, the complexations facilitate the conjugation of N(13) with the aromatic rings.

The lowest energy has been found for the isomer $A_{am}N(9)H$ at the B3LYP level of theory using the standard valence triple-ζ basis set augmented with six d-type and three p-type polarization functions, 6-311G(d,p). On the other hand, the highest energy has been calculated for the tautomer $A_{im}N(7)H$ $\left(E_{A_{im}N(7)H} - E_{A_{am}N(9)H} = 70\,kj\,mol^{-1}\right)$ [1]. Therefore, it is expected of the complexes containing

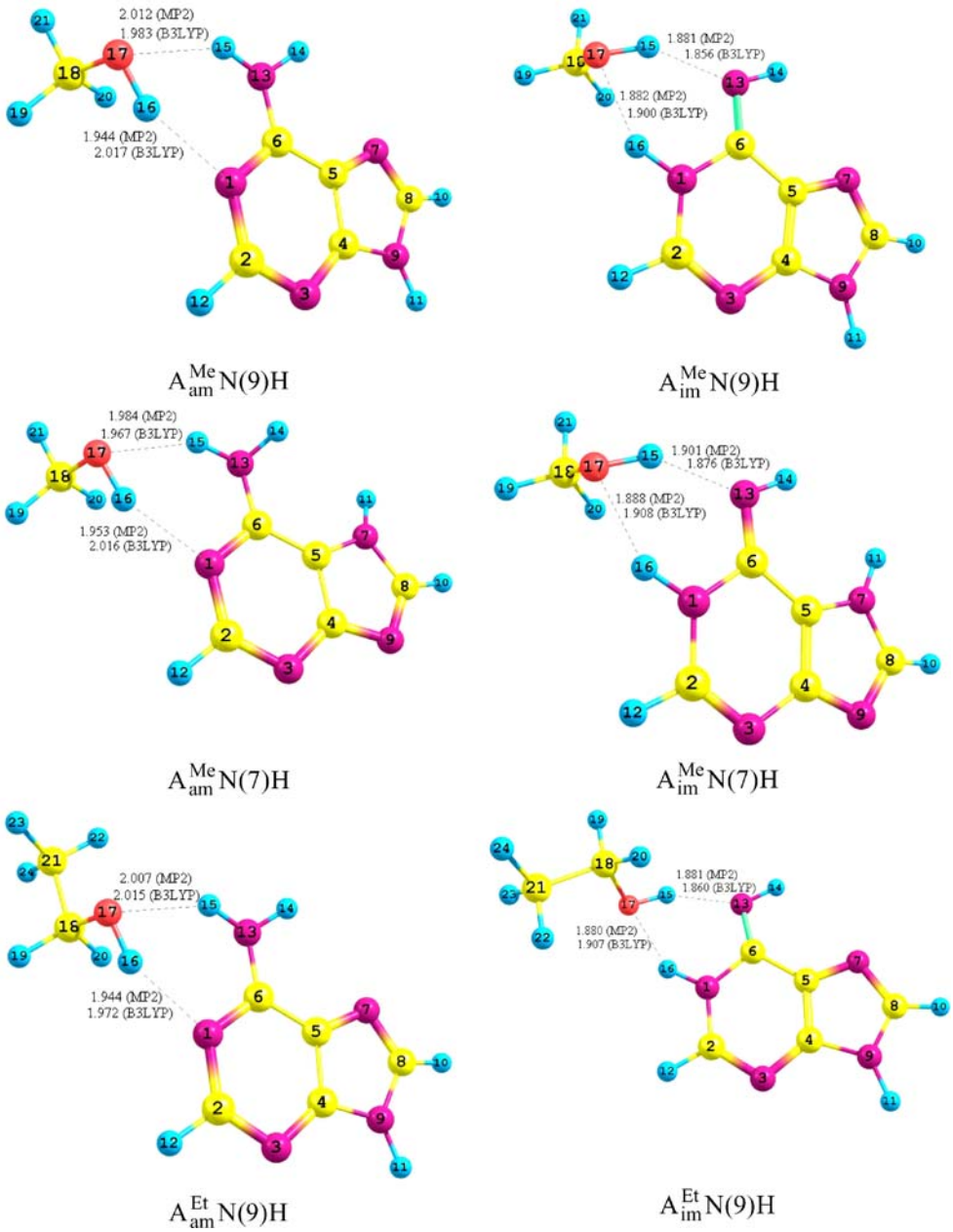

Fig. 1 Optimized structures of the supersystems between methanol/ethanol/i-propanol and adenine

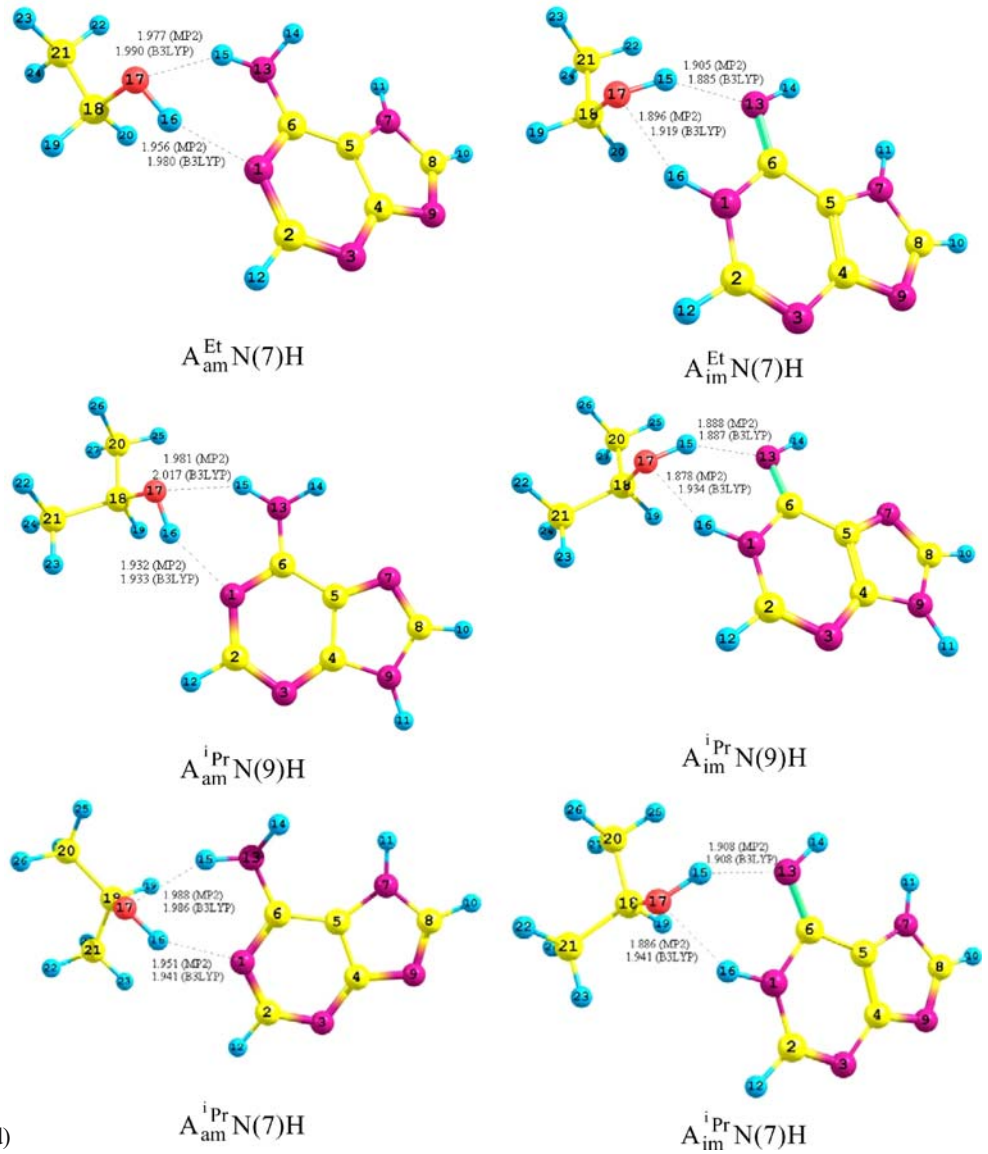

Fig. 1 (continued)

the tautomer $A_{am}N(9)H$ to have low energy and those in which the tautomer $A_{im}N(7)H$ is included - high energy. However, this does not mean that the complexes with the lowest energy are the most stable ones, because the lower energy is due only to the adenine monomer (as mentioned in the Computational method section).

The calculated energies at the B3LYP and MP2 theoretical levels are listed in Table 1.

The B3LYP data show that the inclusion of diffuse functions in the basis set causes a slight energy reduction.

Higher energies were calculated for the supersystems that contain the $A_{im}N(7)H$ tautomer. For example (B3LYP): $E_{A_{im}^{Me}N(7)H} - E_{A_{am}^{Me}N(9)H} = 57\,kJ\,mol^{-1}$; $E_{A_{im}^{Et}N(7)H} - E_{A_{am}^{Et}N(9)_H} = 56\,kJ\,mol^{-1}$; and $E_{A_{im}^{iPr}N(7)H} - E_{A_{am}^{iPr}N(9)H} = 63\,kJ\,mol^{-1}$.

The usage of the Onsager's continuum model (B3LYP) for the solvent effect prediction in an appropriate environment led to a reduction of the energies of the supersystems (3–14 kJ mol^{-1}). It is interesting to mention than the largest reduction is achieved (ΔE_S, Table 1) in the supersystems containing the amino adenine N(7)H tautomer. Otherwise, the energy reduction in solvents is rather small. Such results were expected because almost all continuum models account only for a limited number of effects (e.g., electrostatic interactions between adenine and alcohols). Furthermore, the energy of a certain supersystem including solvent energy depends on the cavity size predicted at a given theoretical level.

Thermodynamic parameters of the complex formations

The thermodynamic and bonding analyses are performed in order to throw light upon the stability of the supersystems and their discrete interactions (by H-bonds) with alcoholic environment.

The calculated (B3LYP) thermodynamic and bonding properties of the supersystems are listed in Table 2.

The values of the standard enthalpies show that all complex formations are enthalpically favored (exothermic). The values of $T\Delta S^{o}_{298}$ imply large entropy changes during the complex formations. In some cases, the high negative values of $T\Delta S^{o}_{298}$ determine the positive values of ΔG^{o}_{298}. For example, the formations of several amino adenine supersystems require larger entropy than energy changes (in other words $\left|T\Delta S^{o}_{298}\right| > \left|\Delta H^{o}_{298}\right|$). Therefore, these complex formations are thermodynamically disfavored $\left(\Delta G^{o}_{298} > 0\right)$. One exception is the formation of $A^{iPr}_{am}N(7)H$, whose ΔG^{o}_{298} value is equal to −2 kJ mol^{-1}. In three cases $\left|T\Delta S^{o}_{298}\right| = \left|\Delta H^{o}_{298}\right|$. Those are the complex formations of $A^{Me}_{am}N(7)H, A^{Et}_{am}N(9)H$, and $A^{Et}_{am}N(7)H$ that are in equilibrium $\left(\Delta G^{o}_{298} = 0\right)$.

All complex formations of imino adenine supersystems are thermodynamically favored. They are accompanied with significant energy changes rather than entropy ones $\left(\left|T\Delta S^{o}_{298}\right| < \left|\Delta G^{o}_{298}\right|\right)$. This reflects on the bonding and interaction energies, which are larger for the complex formations of imino adenine supersystems as compared to the amino adenine ones. Using the ΔG^{o}_{298} values the supersystems follow the next stability pattern:

$$A^{Me}_{im}N(9)H > A^{Et}_{im}N(9)H > A^{Me}_{im}N(7)H > A^{Et}_{im}N(7)H = A^{iPr}_{im}N(9)H > A^{iPr}_{im}N(7)H >$$
$$> A^{iPr}_{am}N(7)H > A^{Me}_{am}N(7)H = A^{Et}_{am}N(9)H = A^{Et}_{am}N(7)H > A^{Me}_{am}N(9)H = A^{iPr}_{am}N(9)H$$

This pattern shows that the supersystem $A^{Me}_{im}N(9)H$ is the most stable one, which is in a full agreement with the H-bond lengths and strengths discussed above. Perhaps, the high stability of the imino adenine supersystems relates with the shortest H-bonds calculated in this complexes.

Among all amino adenine supersystems the complex $A^{iPr}_{am}N(7)H$ seems to be the most stable one, followed by the complexes $A^{Me}_{am}N(7)H, A^{Et}_{am}N(9)H$ and $A^{Et}_{am}N(7)H$. Obviously, the tautomer $A_{am}N(7)H$ should be abundant in alcoholic solution, which is in agreement with previously published experimental data [27–29].

Based on the large dipole moment of adenine and most polar methanol (ε_{MeOH}=32.63, ε_{EtOH}=24.55, $\varepsilon_{i\text{-}PrOH}$= 18.30) the highest stability of the methanol containing supersystems was expected. Moreover, the more polar imino adenine tautomer is $A_{am}N(9)H$ (μ=3.686 D), and the least polar amino adenine one is $A_{am}N(9)$ H ($\mu = 2.395$ D). Obviously, the polarity of adenine tautomers corresponds to the aforementioned stability pattern.

The absolute values of ΔE_{int} (Table 2) and those of ΔE_S (Table 1) show that the electrostatic interactions (continuum) are negligible as compared to H-bonding (discrete) interactions between adenine and alcohols. This demonstrates the rough approximation in which all continuum models (in particular Onsager's method) work.

The large values of ΔE_{int} and ΔE_b show that all H-bonds in the supersystems are strong. Their contribution to the heats effects of the complex formations is large and determines the major part of the energy changes during the complex formations.

BSSEs are comparatively large for all supersystems. This is the reason why the bonding energies and the bonding energies without BSSE (ΔE_{int}) differ considerably (see Table 2). It has been established that ΔBSSE for several guanine - water and guanine - methanol supersystems are in the interval 4.8–5.9 kJ mol^{-1} (found at the B3LYP/6-31+G* level [30]). The large ΔBSSE were expected because the entropy (deforma-

Table 1 Calculated energies of the supersystems, a. u

Super-system	B3LYP/6-311G(d,p)			MP2/6-311G(d,p)	[a]B3LYP/6-311++G(d,p)	[a]MP2/6-311++G(d,p)
	E	E_o	ΔE_S			
$A^{Me}_{am}N(9)H$	−583.215082	−583.049275	4	−581.633830	−583.229442	−581.635019
$A^{Me}_{im}N(9)H$	−583.202868	−583.036437	4	−581.619515	−583.217071	−581.619818
$A^{Me}_{am}N(7)H$	−583.201397	−583.036024	14	−581.621052	−583.216360	−581.622774
$A^{Me}_{im}N(7)H$	−583.193410	−583.027590	9	−581.609402	−583.208357	−581.610612
$A^{Et}_{am}N(9)H$	−622.545052	−622.351000	5	−620.835669	−622.558761	−620.835662
$A^{Et}_{im}N(9)H$	−622.533062	−622.338206	4	−620.821341	−622.546662	−620.820407
$A^{Et}_{am}N(7)H$	−622.531364	−622.337698	13	−620.822901	−622.545662	−620.823382
$A^{Et}_{im}N(7)H$	−622.523805	−622.329528	6	−620.811687	−622.538026	−620.8115005
$A^{iPr}_{am}N(9)H$	−661.875832	−661.653954	3	−660.038469	−661.889746	−660.037693
$A^{iPr}_{im}N(9)H$	−661.861005	−661.638802	3	−660.025085	−661.874792	−660.023297
$A^{iPr}_{am}N(7)H$	−661.862001	−661.640794	10	−660.026618	−661.876595	−660.026103
$A^{iPr}_{im}N(7)H$	−661.851817	−661.630179	6	−660.014980	−661.866331	−660.014155

[a] Single-point calculations.

ΔE_S - relative reduction of energy in solvent (Onsager's model), kJ mol^{-1}

Table 2 Interaction energies, and thermodynamic properties of the supersystems and complex formations (in kJ mol^{-1}), all in the gas phase (B3LYP/6-311G(d,p))

Super-system	ΔE_b	ΔE_{int}	ΔBSSE	ΔH^o_{298}	ΔG^o_{298}	$T\Delta S^o_{298}$
$A^{Me}_{am}N(9)H$	−35	−48	17	−41	2	−43
$A^{Me}_{im}N(9)H$	−52	−65	17	−58	−16	−42
$A^{Me}_{am}N(7)H$	−35	−49	17	−41	0	−41
$A^{Me}_{im}N(7)H$	−48	−62	17	−55	−12	−43
$A^{Et}_{am}N(9)H$	−34	−47	17	−39	0	−39
$A^{Et}_{im}N(9)H$	−51	−64	17	−57	−14	−43
$A^{Et}_{am}N(7)H$	−34	−47	17	−40	0	−40
$A^{Et}_{im}N(7)H$	−47	−61	16	−54	−11	−43
$A^{iPr}_{am}N(9)H$	−37	−48	15	−41	2	−43
$A^{iPr}_{im}N(9)H$	−49	−58	15	−52	−11	−41
$A^{iPr}_{am}N(7)H$	−38	−48	15	−41	−2	−39
$A^{iPr}_{im}N(7)H$	−46	−55	15	−49	−7	−42

tion) changes during the complex formations are considerably large. They significantly contribute to the values of ΔE_{int} and respectively to BSSE.

Intermolecular proton transfer

The intramolecular proton transfer in adenine has investigated and discussed at B3LYP/6-311(d,p) level of theory [1, 31]. Very high energy barriers have been found [31] for this kind of proton transfer (over 200 kJ mol^{-1}).

The energy barriers of the intermolecular proton transfers in adenine assisted by alcohol molecule (methanol, ethanol, i-propanol) are given in Table 3.

We were not able to compute the vibrational spectrum of the transition state of the proton transfer $A^{iPr}_{am}N(7)H \rightleftarrows A^{iPr}_{im}N(7)H$ for the following reason: Several times the frequency calculations failed without final result to be reached even when tight and very tight convergence criteria were used.

All proton transfers are endoergic (endothermic) reactions, which, according to the *Leffler - Hammond* postulate [32, 33] means that all transition states are "late" or "product-like" [34].

As seen in Table 3, the energy barriers of the alcohol-assisted proton transfers undergo a considerable reduction, as the adenine N(7)H proton transfers (intra- and inter-) have less lower energy barriers than the energy barriers of the adenine N(9) ones. In other words, the proton transfers in the adenine N(7)H tautomer occur easier with the smallest positive value of ΔG^o_{298}.

In the adenine N(9)H tautomers alcohol-assisted proton transfers have on the average 59% and 68% (forward and reverse reaction) lower energy barriers than those of intramolecular proton transfers [1]. With respect to the adenine N(7)H tautomer, alcohol-assisted proton transfers have on the average 60% and 65% lower energy barriers than the intramolecular proton transfers. Thus, the energy barrier reduction of the reverse reactions is larger.

Table 3 Energy barriers and thermodynamic properties of the intermolecular proton transfers (kJ mol^{-1})

Proton transfer	B3LYP/6-311G(d,p)					MP2/6-311G (d,p)		*B3LYP/6-311++G (d,p)		*MP2/6-311++G (d,p	
	1	**2**	ΔH^o_{298}	ΔG^o_{298}	$T\Delta S^o_{298}$	**1**	**2**	**1**	**2**	**1**	**2**
$A_{am}N(9)H \rightleftarrows A_{im}N(9)H$	201 [a]	152 [a]	49 [a]	53 [a]	−4 [a]	–	–	–	–	–	–
$A_{am}N(7)H \rightleftarrows A_{im}N(7)H$	193 [a]	159 [a]	34 [a]	35 [a]	−1 [a]	–	–	–	–	–	–
$A^{W}_{am}N(9)H \rightleftarrows A^{W}_{im}N(9)H$	86 [a]	50 [a]	36 [a]	39 [a]	−3 [a]	–	–	–	–	–	–
$A^{W}_{am}N(7)H \rightleftarrows A^{W}_{im}N(7)H$	80 [a]	56 [a]	24 [a]	27 [a]	−3 [a]	–	–	–	–	–	–
$A^{Me}_{am}N(9)H \rightleftarrows A^{Me}_{im}N(9)H$	81	49	33	35	−2	91	54	82	50	88	48
$A^{Me}_{am}N(7)H \rightleftarrows A^{Me}_{im}N(7)H$	75	54	21	23	−2	89	58	76	55	84	52
$A^{Et}_{am}N(9)H \rightleftarrows A^{Et}_{im}N(9)H$	81	49	32	39	−7	91	53	83	51	88	48
$A^{Et}_{am}N(7)H \rightleftarrows A^{Et}_{im}N(7)H$	75	55	20	24	−4	89	60	76	55	85	54
$A^{iPr}_{am}N(9)H \rightleftarrows A^{iPr}_{im}N(9)H$	86	47	37	40	−3	92	57	87	48	87	50
$A^{iPr}_{am}N(7)H \rightleftarrows A^{iPr}_{im}N(7)H$	80	53	27	30	−3	92	61	81	54	86	54

1: forward; **2**: reverse; * data resulted from single-point calculations; [a] data taken from ref. [1]

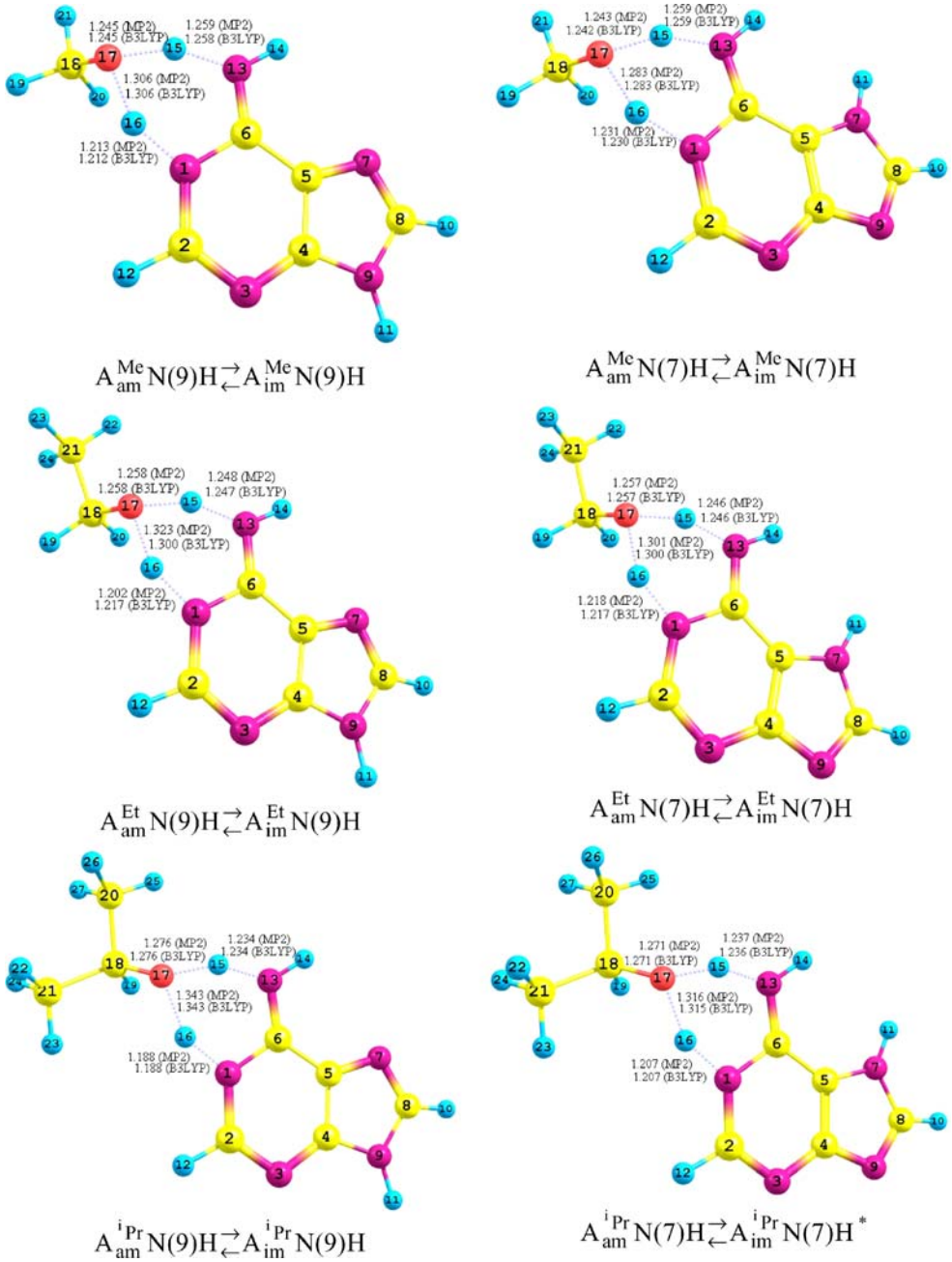

Fig. 2 The transition states of the alcohol-assisted proton transfers

The transition states of the intermolecular proton transfers were optimized as first order saddle points on the corresponding energy hypersurface - for each transition state one imaginary frequency was calculated in the vibration spectrum. The form of this vibration explicitly shows the proton exchange between the adenine and alcohol molecules.

The structures of the transition states are illustrated in Fig. 2.

As one can see (Fig. 2), the proton exchange occurs in the plane of adenine molecule. We believe that, this in-plane motion of protons is one of the reasons for the reduction of the energy barriers of the intermolecular H-transfers as compared to the intramolecular ones. The next major reason is that the intermolecular proton transfers are accompanied with a break of one weak H-bond and a formation of another one. These simultaneous processes ensure better and uniformly distribution of the electron density during the H-transfer. Possibly for this the imaginary frequencies of the intramolecular H-transfers have higher absolute values than the intermolecular ones. The larger negative imaginary frequencies imply larger energy barriers of the H-transfers since the transition states would

be unstable. Thus, from the transition state the reaction will have larger negative energy gradient downhill toward the reactants (amino) or products (imino).

Conclusions

The performed theoretical calculations at the B3LYP and MP2 levels of theory with 6-311G(d,p) and 6-311++G(d,p) basis functions led to the following major conclusions:

1. The H-bonding between alcohols and the amino adenine tautomers leads to the reduction of the pyramidal behavior of the amino group. In other words, the complexations facilitate the conjugation of N(13) with the aromatic rings.
2. All formations of the imino adenine supersystems are thermodynamically favored, with considerable heat effects and negative ΔG^{o}_{298} values. The thermodynamic analysis showed that the supersystem $A^{Me}_{im}N(9)H$ is the most stable complex. In other words the imino adenine tautomer should be abundant in alcoholic media.
3. Comparing the values of ΔE_{int} (resulted by discrete interactions adenine -alcohol) and those of ΔE_S (resulted by electrostatic interactions adenine -alcohol) it could be concluded that the first type of interactions are more important for studying the influence of solvents on the dissolved molecule. Unfortunately, the discrete interactions cannot be predicted by any continuum model.
4. The calculated energy barriers of the alcohol-assisted proton transfers are about 60% lower than those of the intramolecular H-transfer in adenine [1].

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