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QUANTUM-CHEMICAL ANALYSIS OF GEOMETRIC AND ENERGETIC CHARACTERISTICS OF HETERO ASSOCIATES m⁹Ade·m¹Ura IN MAIN TAUTOMERIC FORM

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For the first time, on the quantum-mechanical level of theory MP2/6-311++G(2df,pd)// B3LYP/6-311++G(d,p), a full set of hydrogen (H)-bonded hetero associates m⁹Ade·m¹Ura in the main tautomeric forms consisting of 18 different structures was obtained. Their structural and energetical parameters were characterized and basic physical and chemical characteristics of intermolecular H-bonds that stabilize the investigated complexes were described. It was shown that global minimum of Gibbs free energy corresponds to Hoogsteen pair, after it with a small margin follow Watson–Crick pair, inverse Hoogsteen pair and inverse Watson–Crick pair. It was found that in stabilization of identified hetero associates four types of H-bonds – NH...O, NH...N, CH...O and CH...N are involved. In this case non-canonical CH...O and CH...N bonds show a linear dependence of energy on electron density in the corresponding critical point. Obtained data may be useful for experimental interpretation of the features of non-canonical base pairs association by common methods of spectroscopy, including NMR and vibrational spectroscopy. They are also important for understanding the problem of mutational variability that is caused by formation of non-complementary pairs of nucleotide bases whose role is not clear yet.

Keywords: quantum chemistry, hetero associates of nucleotide bases, hydrogen bonds, adenine, uracil.

INTRODUCTION

Nucleic acids are macromolecular components of cells that play an important role in the conservation and transmission of genetic information. Four nucleotide bases – the purine and pyrimidine derivatives are structural units of these biopolymers. In particular, a unique sequence of nucleic bases determines the DNA functionalities. The presence of two complementary pairs of nucleotide bases, namely Gua·Cyt and Ade·Thy, provides a unique ability of genetic material to replicate with high accuracy. At the same time DNA is able to form functionally important non-canonical conformations that are characterized

by presence of non-complementary pairs of nucleotide bases. In addition, problem of non-canonical nucleotide bases pairing is closely related to the emergence of spontaneous point mutations. Unfortunately, the experimental data on structural characteristics of incorrect pairs of nucleotide bases stabilized by the intermolecular H-bonds, remain rather limited. It inspirates researchers to use calculations, including quantum-chemical methods, to receive this biologically important information.

MATERIALS AND METHODS

The H-bonded hetero associates of adenine (Ade) and uracil (Ura), methylated on the 9th and 1st position of nitrogen atom respectively, which are in the main tautomeric form were studied. As a subject of study, the geometric and energy characteristics of the above mentioned complexes m^{9}Ade·m^{1}Ura and basic physicochemical parameters of H-bonds involved in their stabilization were taken.

Quantum chemical calculations of the geometric and electronic structure of the objects were carried out on the level of B3LYP/6-311++G(d,p) theory in the vacuum approximation. All optimized structures were tested for stability in the absence of imaginary frequencies in their vibrational spectra. The study was conducted using a software package "GAUSSIAN03" [5]. All possible starting structures of complexes were generated using the algorithm described in [6]. This approach allows to get a full set of complexes because it is based on up-to-date information about H-bonds and it is not limited by considerations of geometric character.

The distribution of electron density in pairs of bases was investigated by QTAIM method [1] on the basis of wave functions obtained on the levels of MP2/6-311++G(2df,pd)// B3LYP/6-311++G(d,p) theory. The identification of intermolecular H-bonds [10] was carried out in the presence of critical point of type (3,-1) between two valence-unbound atoms and positive values of Laplacian of the electron density $\Delta\rho$ at the same point. The electron density topology was analyzed by the software package AIMAll (Version 10.05.04) [8] using standard options. The energy of classic H-bonds was calculated by Iogansen method [7] and a non-canonical CH...O/N H-bonds – by Espinosa–Molins–Lecomte method [4]. In this paper generally accepted numbering of atoms is used [11].

RESULTS AND DISCUSSIONS

For the first time a complete set of H-bonded hetero associates of m^{9}Ade·m^{1}Ura which includes 18 structures was obtained. The observed complexes lie within a range of relative Gibbs energy 0–9.27 kcal/mol at normal conditions (Fig. 1, Table 1). It was found that the global minimum of Gibbs free energy corresponds to flat symmetrical pair **1** which is in Hoogsteen configuration and stabilized by three intermolecular H-bonds N6H...O4, N3H...N7, C8H...O2 (Fig. 1, Table 1). Next in the energy scale with small energy gap the plane symmetrical pairs **2** (Watson–Crick configuration), **3** (reversed Hoogsteen conformation) and **4** (reverse Watson–Crick conformation), each of which is stabilized by three intermolecular H-bonds (Fig. 1) are located. These data are consistent with the crystallographic data available in literature [9]. The total population of 1–4 pairs under normal conditions is 41.7 % (1) + 29.2 % (2) + 24.5 % (3) + 4.4 % (4) = 99.8 %: namely they determine the complexation equilibrium in a free state under normal conditions.

(0.00)   (0.21)

(0.32)   (1.33)
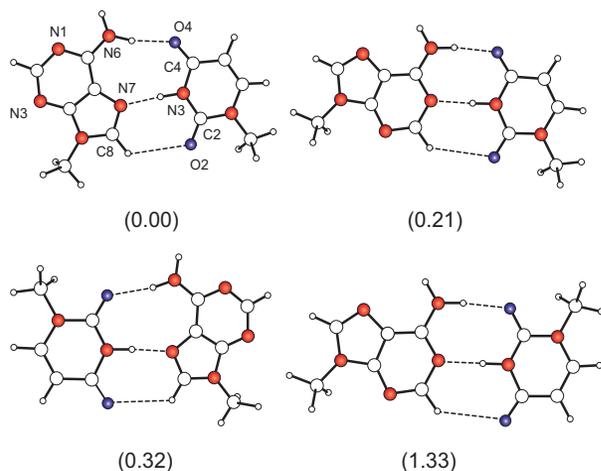
Fig. 1. The most stable hetero associates of m^{9}Ade·m^{1}Ura (see also Table 1 and Table 2). Intermolecular H-bonds are shown as dotted lines. Numbering of atoms is generally accepted

Рис. 1. Найстабільніші гетероасоціати m^{9}Ade·m^{1}Ura (див. також табл. 1 і табл. 2). Міжмолекулярні Н-зв'язки зображено пунктиром. Нумерація атомів загальноприйнята

Table 1. **Energetic characteristics of all possible H-bonded complexes of m^{9}Ade·m^{1}Ura in which bases are in main tautomeric form. Calculation was performed on the level of theory MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) in free state**

Таблиця 1. **Енергетичні характеристики всіх можливих Н-зв'язаних комплексів m^{9}Ade·m^{1}Ura, у яких основи перебувають в основній таутомерній формі. Розрахунок на рівні теорії MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) у вільному стані**

Complex	ΔG, kcal/mol	μ, D	Intermolecular H-bonds which stabilize complexes
1	0.00	6.88	N6H…O4, N3H…N7, C8H…O2
2	0.21	2.07	N6H…O4, N3H…N3, C2H…O2
3	0.32	5.15	N6H…O2, N3H…N7, C8H…O4
4	1.33	2.83	N6H…O2, N3H…N1, C2H…O4
5	4.73	3.31	C9H…O4, N3H…N3, C2H…O2
6	4.98	5.17	C9H…O2, N3H…N3, C2H…O4
7	6.30	4.06	N6H…O4, C5H…N1
8	6.40	7.46	N6H…O4, C5H…N7
9	6.92	4.79	N6H…O2, C1H…N1
10	7.13	2.46	C9H…O4, C5H…N3
11	7.59	6.30	N6H…O2, C1H…N7
12	7.72	3.95	C8H…O4, C5H…N7
13	8.12	3.63	C9H…O2, C1H…N3
14	8.36	4.03	C8H…O2, C1H…N7
15	8.78	5.55	C1H…N1, C2H…O2
16	8.85	4.96	C5H…N1, C2H…O4
17	9.16	7.10	C1H…N3, C2H…O2
18	9.27	7.07	C5H…N3, C2H…O4

Comments: ΔG – relative Gibbs energy under standard conditions, μ – dipole moment
Примітки: ΔG – відносна енергія Гіббса за нормальних умов, μ – дипольний момент

All fixed hetero associates of m^{9}Ade·m^{1}Ura are polar complexes, whose dipole moment is within a range from 2.07 to 7.46 D. Among them, seven structures – flat symmetrical, another 11 pairs have a non planar structure.

Also, the basic physical and chemical characteristics of intermolecular H-bonds that stabilize hetero associates (Table 2) were studied in detail. The total number of studied intermolecular H-bonds is 42, namely: 8 – NH…O, 6 – NH…N, 16 – CH…O та 12 – CH…N contacts. Thus, their energy is within the range from 1.40 (CH...N) to 7.84 (NH...N) kcal/mol. Three intermolecular H-bonds for 6 from studied pairs of nucleotide bases and two for the remaining 12 pairs are observed.

The strongest H-bond of NH...N type (hetero associate **2**) has energy equal 7.84 kcal/mol and the following geometric parameters: d_{AB} = 2.883 Å, d_{HB} = 1.838 Å, $\angle AHB$ = 178.4°. The weakest H-bond of the same type has energy 6.31 kcal/mol (complex **6**) and the following geometric characteristics: d_{AB} = 2.996 Å, d_{HB} = 1.970 Å, $\angle AHB$ = 170.8°.

In its turn, the H-bond NH...O with energy of 3.96 kcal/mol in complex 2 is the strongest and it has the following geometric parameters: d_{AB} = 2.939 Å, d_{HB} = 1.923 Å, $\angle AHB$ = 173.5°. The weakest H-bond of the same type in pair **11** has energy E_{HB} equal 1.07 kcal/mol and the following geometric characteristics: d_{AB} = 2.980 Å, d_{HB} = 1.997 Å, $\angle AHB$ = 162.9°.

The strongest H-bond of CH...N type is the bond with the energy of 1.94 kcal/mol observed in hetero associate **7** and characterized by geometric parameters: d_{AB} = 3.446 Å, d_{HB} = 2.393 Å, $\angle AHB$ = 163.5°. The weakest H-bond of the same type has energy 1.40 kcal/mol and the following geometric characteristics: d_{AB} = 3.586 Å, d_{HB} = 2.536 Å, $\angle AHB$ = 161.2° (complex **14**).

The strongest H-bond of type CH...O in a complex **5** has energy 2.68 kcal/mol and is characterized by geometric parameters: d_{AB} = 3.288 Å, d_{HB} = 2.239 Å, $\angle AHB$ = 160.9°. The weakest H-bond of the same type has energy 0.77 kcal/mol and the following geometric characteristics: d_{AB} = 3.688 Å, d_{HB} = 2.868 Å, $\angle AHB$ = 132.3° (complex **2**).

The dependence of the energy of non-canonical H-bonds CH...N and CH...O on the electron density in the corresponding critical point shows a linear dependence (Fig. 2): $E_{CH...O}$ = 187.4·ρ and $E_{CH...N}$ = 135.1·ρ. On the one hand, it means that the parameter ρ is a convenient descriptor of non-canonical H-binding [2, 3]. On the other hand, these dependencies allow to assess the values of electron density which correspond to H-bonds with the lowest possible energy ~ 0.2 kcal/mol [10]: $\rho_{CH...O}$ = 0.0011 a.u., $\rho_{CH...N}$ = 0.0015 a.u.
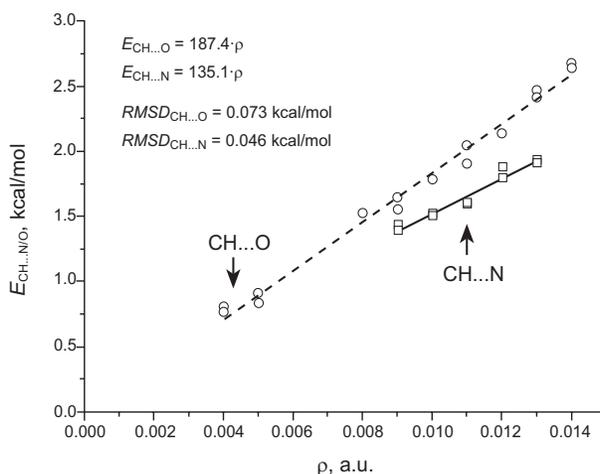
Fig. 2. Dependence of the energy of hydrogen bonds CH…O/N on electron density in critical point ρ

Рис. 2. Залежність енергії водневих зв'язків СН…O/N від електронної густини у критичній точці ρ

Table 2. **Electron-topological, geometrical and energetic characteristics of intermolecular hydrogen bonds in all possible hetero associates of m⁹Ade·m¹Ura. Calculation on the level of theory DFT B3LYP/6-31++G(d,p) in free state**

Таблиця 2. **Електронно-топологічні, геометричні та енергетичні характеристики міжмолекулярних водневих зв'язків у всіх можливих гетероасоціатах m⁹Ade·m¹Ura. Розрахунок на рівні теорії DFT B3LYP/6-31++G(d,p) у вільному стані**

Hetero associate	H-bond AH…B	ρ, a.u.	$\Delta\rho$, a.u.	$d_{A…B}$, Å	$d_{H…B}$, Å	$\angle AH…B$, deg	Δd_{AH}, Å	E_{HB}, kcal/mol
1	N6H…O4	0.024	0.089	2.958	1.949	170.9	0.0120	3.27
	N3H…N7	0.041	0.099	2.853	1.810	176.8	0.0313	7.66
	C8H…O2	0.004	0.016	3.535	2.852	121.2	0.0001	0.81
2	N6H…O4	0.026	0.093	2.939	1.923	173.5	0.0142	3.96
	N3H…N3	0.040	0.093	2.883	1.838	178.4	0.0329	7.84
	C2H…O2	0.004	0.014	3.688	2.868	132.3	0.0002	0.77
3	N6H…O2	0.021	0.081	3.001	1.993	171.2	0.0101	2.62
	N3H…N7	0.042	0.099	2.847	1.805	176.2	0.0311	7.65
	C8H…O4	0.005	0.017	3.496	2.797	122.3	0.0003	0.91
4	N6H…O2	0.024	0.086	2.975	1.962	172.8	0.0119	3.31
	N3H…N1	0.040	0.093	2.883	1.838	178.8	0.0324	7.78
	C2H…O4	0.005	0.015	3.658	2.828	133.2	0.0002	0.84
5	C9H…O4	0.014	0.048	3.288	2.239	160.9	-0.0016	2.68
	N3H…N3	0.028	0.080	2.997	1.969	171.1	0.0226	6.32
	C2H…O2	0.010	0.031	3.366	2.452	141.0	-0.0006	1.79
6	C9H…O2	0.013	0.045	3.318	2.273	160.2	-0.0015	2.47
	N3H…N3	0.028	0.080	2.996	1.970	170.8	0.0224	6.31
	C2H…O4	0.011	0.033	3.346	2.421	142.2	-0.0004	1.91
7	N6H…O4	0.024	0,089	2.963	1.948	174.7	0.0120	3.36
	C5H…N1	0.013	0.037	3.446	2.393	163.5	0.0048	1.94
8	N6H…O4	0.023	0.086	2.944	1.972	159.4	0.0095	2.39
	C5H…N7	0.013	0.038	3.447	2.378	168.5	0.0044	1.92
9	N6H…O2	0.021	0.085	2.986	1.976	173.6	0.0082	1.84
	C1H…N1	0.012	0.035	3.503	2.420	171.3	0.0013	1.89
10	C9H…O4	0.012	0.038	3.390	2.339	161.3	-0.0001	2.14
	C5H…N3	0.011	0.031	3.534	2.457	173.0	0.0038	1.60
11	N6H…O2	0.020	0.082	2.980	1.997	162.9	0.0075	1.07
	C1H…N7	0.012	0.034	3.509	2.426	171.0	0.0011	1.80
12	C8H…O4	0.014	0.047	3.270	2.242	157.6	0.0026	2.64
	C5H…N7	0.009	0.028	3.532	2.499	159.3	0.0031	1.44
13	C9H…O2	0.011	0.038	3.412	2.322	179.4	-0.0015	2.05
	C1H…N3	0.011	0.030	3.559	2.486	167.1	0.0015	1.61
14	C8H…O2	0.013	0.046	3.277	2.250	157.8	0.0013	2.42
	C1H…N7	0.009	0.026	3.586	2.536	161.2	0.0011	1.40
15	C1H…N1	0.010	0.028	3.586	2.507	169.2	0.0016	1.53
	C2H…O2	0.009	0.028	3.486	2.460	157.0	-0.0002	1.56
16	C5H…N1	0.011	0.031	3.509	2.460	162.8	0.0035	1.61
	C2H…O4	0.009	0.027	3.519	2.488	158.2	0.0003	1.56
17	C1H…N3	0.010	0.028	3.586	2.504	170.6	0.0017	1.51
	C2H…O2	0.008	0.027	3.493	2.471	156.3	-0.0001	1.53
18	C5H…N3	0.010	0.029	3.529	2.482	162.5	0.0035	1.51
	C2H…O4	0.009	0.028	3.496	2.462	158.8	0.0003	1.65

Comments: ρ and $\Delta\rho$ – value of the electron density and Laplacian of the electron density at the critical point, respectively; $d_{A…B}$, $d_{H…B}$ – distance between atoms A and B and H and B respectively, that participating in H-bond AH...B; $\angle AH...B$ – angle of H-binding; Δd_{AH} – extension of AH bond in the formation of AH…B H-bond; E_{HB} – energy of H-bond

Примітки: ρ i $\Delta\rho$ – значення електронної густини і лапласіану електронної густини у критичній точці відповідно; $d_{A…B}$, $d_{H…B}$ – відстань між атомами А і В та Н і В відповідно, які беруть участь у Н-зв'язку АН…В; $\angle AH…B$ – кут Н-зв'язування; Δd_{AH} – подовження зв'язку АН у разі утворенні Н-зв'язку АН…В; E_{HB} – енергія Н-зв'язку

CONCLUSIONS

For the first time, on the quantum-mechanical level of theory MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) a full set of hydrogen (H)-bonded hetero associates $m^9Ade·m^1Ura$ in the main tautomeric forms consisting of 18 different structures, was obtained. The basic physical and energy characteristics of intermolecular H-bonds that stabilize them were also analyzed. These data may be useful for experimental study of features of hetero association of nucleotide bases by spectroscopy techniques, including vibrational and NMR.

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КВАНТОВО-ХІМІЧНИЙ АНАЛІЗ ГЕОМЕТРИЧНИХ ТА ЕНЕРГЕТИЧНИХ ХАРАКТЕРИСТИК ГЕТЕРОАСОЦІАТІВ m⁹Ade·m¹Ura У ОСНОВНІЙ ТАУТОМЕРНІЙ ФОРМІ

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Уперше на квантово-механічному рівні теорії MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) отримано повну множину воднево (Н)-зв'язаних гетероасоціатів m⁹Ade·m¹Ura у основній таутомерній формі, яка складається із 18 різних структур. Охарактеризовано їхні структурно-енергетичні параметри й описано основні фізико-хімічні характеристики міжмолекулярних Н-зв'язків, що стабілізують досліджені комплекси. Уперше встановлено, що глобальному мінімуму вільної енергії Гіббса відповідає Хугстинівська пара, за нею з невеликим відривом розташовуються Вотсон-Криківська, обернена Хугстинівська й обернена Вотсон-Криківська пара. Встановлено, що у стабілізації виявлених гетероасоціатів беруть участь чотири типи Н-зв'язків – NH…O, NH…N, CH...O та CH...N. У цьому разі неканонічні CH...O та CH...N зв'язки демонструють лінійну залежність енергії від електронної густини у відповідній критичній точці. Отримані результати можуть бути корисними для експериментальної інтерпретації особливостей асоціації неканонічних пар основ поширеними методами спектроскопії, зокрема коливальної та ЯМР. Також вони є важливими для розуміння проблеми мутаційної мінливості, що зумовлена утворенням некомплементарних пар нуклеотидних основ, роль яких до кінця не зрозуміла.

Ключові слова: квантова хімія, гетероасоціати нуклеотидних основ, водневий зв'язок, аденін, урацил.

КВАНТОВО-ХИМИЧЕСКИЙ АНАЛИЗ ГЕОМЕТРИЧЕСКИХ И ЭНЕРГЕТИЧЕСКИХ ХАРАКТЕРИСТИК ГЕТЕРОАССОЦИАТОВ m⁹Ade·m¹Ura В ОСНОВНОЙ ТАУТОМЕРНОЙ ФОРМЕ

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Впервые на квантово-механическом уровне теории MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) получено полное множество водородно (Н)-связанных

гетероассоциатов m⁹Ade·m¹Ura в основной таутомерной форме, состоящей из 18 различных структур. Охарактеризованы их структурно-энергетические параметры и основные физико-химические характеристики межмолекулярных Н-связей, стабилизирующие исследованные комплексы. Впервые показано, что глобальному минимуму свободной энергии Гиббса соответствует Хугстиновская пара, за ней с небольшим отрывом располагаются Вотсон-Криковская, обратная Хугстиновская и обратная Вотсон-Криковская пары. Установлено, что в стабилизации выявленных гетероассоциатов участвуют четыре типа Н-связей – NH...O, NH...N, CH...O и CH...N. При этом неканонические CH...O и CH...N связи демонстрируют линейную зависимость энергии от электронной плотности в соответствующей критической точке. Полученные результаты могут быть полезными для экспериментальной интерпретации особенностей ассоциации неканонических пар оснований распространенными методами спектроскопии, в частности колебательной и ЯМР. Также они важны для понимания проблемы мутационной изменчивости, обусловленной образованием некомплементарных пар нуклеотидных оснований, роль которых до конца не ясна.