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Hydration of the Lowest Triplet States of the DNA/RNA Pyrimidines

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Abstract: The effects of hydration on the lowest triplet states of the DNA/RNA pyrimidines have been studied by including one and two water molecules explicitly. Three configurations for the singly hydrated cytosine moiety were located, and six for the doubly hydrated system. For thymine and uracil, four singly and eight doubly hydrated structures were found. The singlet−triplet energy gaps of all three pyrimidines (cytosine, thymine, and uracil) fall in the low-energy range of ultraviolet radiation (UVA). Energetic excited states can be a step leading to lesions in DNA, such as a mismatched base pairs. Although the adiabatic and vertical electronic excitation energies for all three pyrimidines slightly increase upon inclusion of additional water molecules, this effect upon the excitation energies is much smaller than hydration effects upon the electron affinities and ionization energies of the three nucleobases. Because both the ground state and the triplet state are neutral, the hydration energy difference between the two states is not significant (compared to those between the neutral and charged species), making the excitation energy less sensitive to hydration.

Introduction

Growing concern for the effects of radiation damage on living cells has motivated the study of various mechanisms of such damage on the molecular scale. Radiative damage to DNA can occur both through direct ultraviolet (UV) exposure, or indirectly, as a result of interaction with reactive products (often reactive oxygen-containing radicals) created by radiation damage to other nearby molecules. Helpful reviews describing the effects of UV light on DNA have recently appeared.[1,2]

An example of a directly UV-induced photoproduct, the cyclobutane pyrimidine dimer (CPD) has been known and studied for nearly half a century.[3] CPDs are the primary photoproducts of DNA UV damage,[1,4,5] and can result from exposure to UVA and UVB light.[6,7] A majority of UV-induced mutations occur due to the formation of CPDs;[5,8] they are mutagenically effective due to their slow rate of repair and high rate of bypass by nucleic acid polymerases[9,10] (the cell's mechanism for repair to damaged DNA), thus allowing their persistence in the genome. Although many vertebrates such as fish, reptiles, and marsupials have an alternative repair mechanism involving photolyases,[11−16] which reverse the CPD lesion to two pyrimidine monomer units using visible light, it is believed that placental mammals including humans do not have this enzyme.[16−19] Formation of CPDs is sequence-specific,[6,20,21] and various combinations of pyrimidines [usually thymine (T) and cytosine (C)] can arise, including T-T, C-T, and C-C dimers. Especially after exposure to UVA radiation, the most common CPD produced is the T-T dimer.[5,6] Various experimental and theoretical studies have shown that it is formed through an ultrafast triplet-energy exchange,[5,22,23] for which a mechanism has recently been proposed.[24] Hence it is important to understand the configurational changes within the pyrimidines that result from excitation, leading to the formation of CPDs and other photoproducts.

The singlet−triplet energy separations (gaps) of the pyrimidines fall well within the UVA absorption range (cytosine: 3.50 eV,[25] uracil: 3.65−3.68 eV,[26,27] thymine: 3.6 eV[28]). For all of the pyrimidines, the lowest-lying excited states are triplets; the excited singlets lie higher energetically (at ∼4 eV).[29,30] Using electron energy loss spectroscopy

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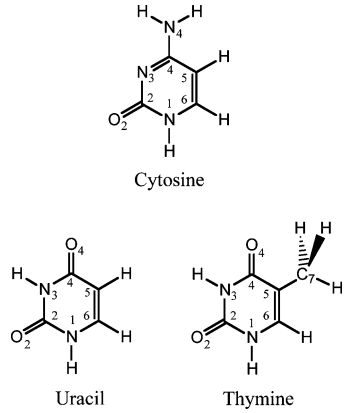

Figure 1. Canonical structures of uracil, thymine, and cytosine with atom numbering schemes.

(EELS), Abouaf, Pommier, and Dunet determined the singlet−triplet energy gap of thymine to be 3.6 (±0.08) eV.[28] The same group later measured the singlet−triplet energy gap of cytosine at 3.50 eV[25] and uracil at 3.65 (±0.05) eV.[31] A recent study by Bosca et al.[32] has also delivered an estimate of the adiabatic triplet excitation energy of thymine in DNA of ∼2.8 eV. Recent DFT computations by Nguyen and co-workers are in good agreement with experimental results.[31] Although hydration plays an important role in biological systems, few studies have explored the hydration effects on the triplet excited states of the DNA/RNA nucleobases.[33]

Much work has been done on the hydration of nucleobases in their ground states. Over the years, many studies have detailed the effects of discrete and continuous hydration of the DNA/RNA nucleobases[34−44] as well as studies focusing specifically on cytosine,[45−58] uracil,[59−73] and thymine.[74−76] In the present work, hydration effects on the lowest triplet states of the three pyrimidine nucleobases have been studied using density functional theory. In particular, structural changes, changes in the triplet excitation energies upon hydration, sites favoring hydration, and hydration energies are reported.

Computational Methods

All computations were performed using the Gaussian 94 computational chemistry software package.[77] Only complexes of the canonical forms of the pyrimidines (Figure 1) were considered, with the water molecules hydrogen bonded in the plane of the molecule. A search was carried out for new monohydration sites for the triplet state of the three bases including nonplanar complexes, in which a water molecule may interact with the aromatic π-system of the pyrimidine ring, but none were encountered.

For all computations, a specially calibrated double-ζ quality basis set with polarization and diffuse Gaussian functions (DZP++) was used. This basis set is constructed with the Huzinaga−Dunning *sp* contractions, adding one set of five *d*-type polarization functions for each C, N, and O atom, and one set of *p*-type polarization functions for each H atom.[78,79] Lee's prescription,[80]

$$\alpha_{\text{diffuse}} = \frac{1}{2}\left(\frac{\alpha_1}{\alpha_2} + \frac{\alpha_2}{\alpha_3}\right)\alpha_1$$

determined the even-tempered orbital exponents ($\alpha_1 < \alpha_2 < \alpha_3$), with the final DZP++ basis set containing six functions per H atom and 19 functions per C, N, and O atom. When tested, the use of a similar triple-ζ quality (TZ2P++) basis set afforded no significant change in results for several times the computational cost, so it was not further employed. Structural optimizations and harmonic frequency analyses for each base and its corresponding mono- and dihydrates were obtained using the B3LYP density functional, a combination of Becke's three-parameter functional (B3),[81] with the correlation functional of Lee, Yang, and Parr (LYP).[82] The self-consistent isodensity polarized continuum model (SCIPCM)[83] was employed to take into account the effect of macrosolvation upon the energetics of the pyrimidine hydrates. The SCIPCM single point energies at their optimized gas-phase geometries were computed at the B3LYP/DZP++ level of theory, with the dielectric constant of water ($\varepsilon = 78.39$) and the isodensity value of 0.0001.

In the present work, we estimated physical properties of interest as follows: the vertical excitation (VEx) energy is

Table 1. Relative Energies (E_{rel}) in kcal mol^{-1} for Singly and Doubly Hydrated Uracil, Thymine, and Cytosine Ground State and Triplet Excited State (Denoted by *)[a]

	E_{rel}				E_{rel}		
structure	gas		SCIPCM	Gas structure	gas		SCIPCM
			uracil hydrate				
U1A	0.00	(0.00)	0.00	U1A*	0.00	(0.00)	0.00
U1B	1.61	(1.52)	0.23	U1B*	1.41	(1.42)	0.36
U1C	2.30	(2.13)	0.68	U1C*	1.91	(1.79)	0.65
U1D	3.38	(3.05)	2.03	U1D*	2.80	(2.49)	1.97
U2A	0.00	(0.00)	0.00	U2A*	0.00	(0.00)	0.00
U2B	2.59	(2.37)	1.14	U2B*	2.11	(2.03)	1.68
U2C	3.40	(2.94)	3.57	U2C*	3.73	(3.23)	3.87
U2D	4.01	(3.55)	2.01	U2D*	3.25	(2.90)	1.71
U2E	4.71	(4.09)	4.14	U2E*	4.61	(3.96)	4.14
U2F	5.44	(4.69)	5.46	U2F*	5.21	(4.50)	5.49
U2G	7.43	(6.47)	6.03	U2G*	6.89	(6.06)	6.04
U2H	7.36	(6.50)	5.77	U2H*	6.81	(6.11)	5.81
			thymine hydrate				
T1A	0.00	(0.00)	0.00	T1A*	0.00	(0.00)	0.00
T1B	1.73	(1.60)	0.28	T1B*	1.42	(1.39)	0.24
T1C	2.12	(1.93)	0.59	T1C*	1.95	(1.81)	0.68
T1D	4.25	(3.80)	2.24	T1D*	3.62	(3.24)	2.07
T2A	0.00	(0.00)	0.00	T2A*	0.00	(0.00)	0.00
T2B	2.80	(2.60)	1.28	T2B*	2.22	(2.19)	1.10
T2C	3.51	(3.03)	3.55	T2C*	3.61	(3.15)	3.63
T2D	3.82	(3.36)	1.92	T2D*	3.38	(3.06)	1.83
T2E	4.52	(3.95)	4.02	T2E*	4.57	(3.98)	4.10
T2F	6.23	(5.42)	5.64	T2F*	5.91	(5.08)	5.53
T2G	8.11	(7.11)	6.11	T2G*	7.70	(6.69)	6.15
T2H	8.51	(7.57)	6.15	T2H*	7.75	(6.96)	5.82
			cytosine hydrate				
C1A	0.00	(0.00)	0.00	C1A*	1.38	(1.27)	1.61
C1B	0.61	(0.54)	0.09	C1B*	0.00	(0.00)	0.00
C1C	6.08	(5.14)	2.94	C1C*	4.96	(4.03)	2.80
C2A	0.00	(0.00)	0.00	C2A*	1.84	(1.68)	2.08
C2B	1.36	(1.24)	0.80	C2B*	0.38	(0.23)	0.23
C2C	1.47	(1.24)	2.09	C2C*	2.54	(2.18)	3.17
C2D	2.78	(2.37)	2.70	C2D*	0.00	(0.00)	0.00
C2E	6.65	(5.68)	4.66	C2E*	7.52	(6.26)	5.84
C2F	7.30	(6.30)	4.86	C2F*	5.96	(4.97)	4.14

[a] Zero-point vibrational energy (ZPVE)−corrected values are in parentheses.

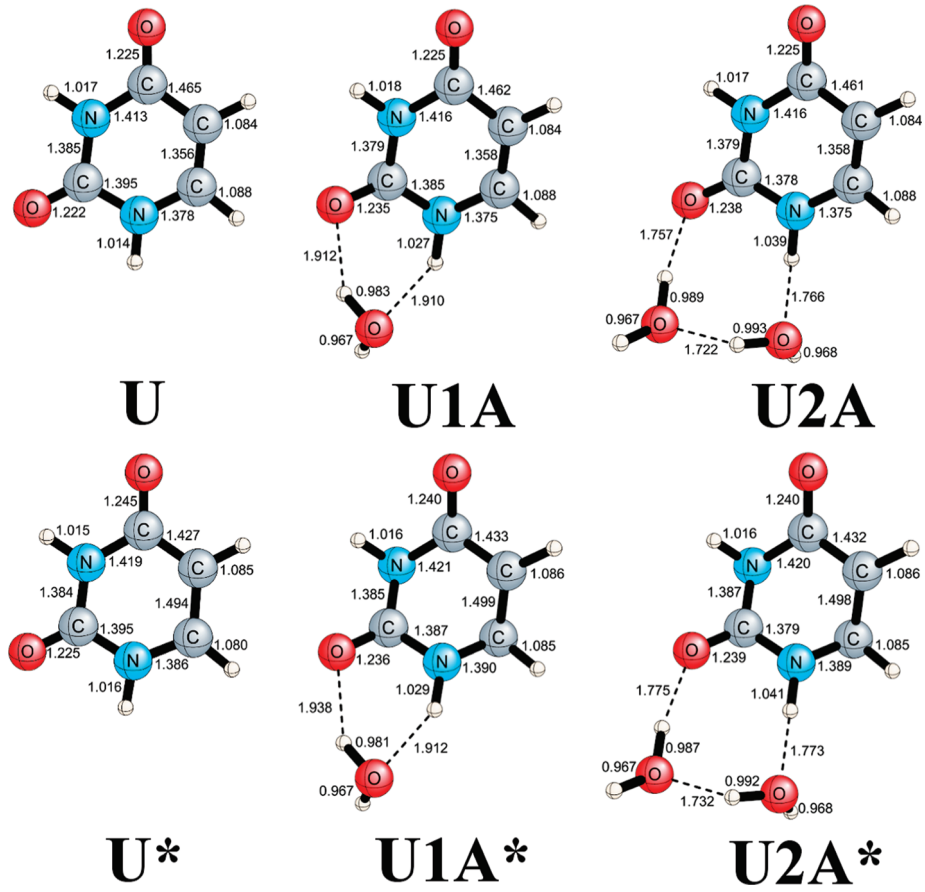

Figure 2. Structures of uracil and its lowest-energy mono- and dihydrates in the ground and lowest triplet states, optimized at the B3LYP/DZP++ level of theory.

defined as the change in absolute energy for a ground state equilibrium geometry upon photonic excitation. The singlet−triplet gap is the difference between the energies of the optimized ground state geometry and the optimized triplet state geometry.

$$\text{VEx} = E(\text{triplet energy at optimized singlet geometry}) - E(\text{optimized singlet})$$

$$\text{singlet−triplet gap} = E(\text{optimized triplet}) - E(\text{optimized singlet})$$

Results

Predicted relative energies of the pyrimidine mono- and dihydrates are listed in Table 1. Figures 2, 3, and 4 display the lowest-energy structures for the free bases and their hydrates in both the ground and the lowest triplet states. All optimized structures have been included as Supporting Information and their intermolecular hydrogen bond lengths are summarized in Tables 2 and 3. The numbering formalism used is as follows: C, T, or U denoting cytosine, thymine or uracil structure, respectively, followed by a 1 or 2 indicating the number of water molecules included, and a capital letter for the relative energetic ordering within each set of either singly or doubly hydrated pyrimidines (i.e., C2A < C2B < C2C). The corresponding triplet structure is indicated by an asterisk (*) and the letter may not indicate the relative energetic ordering of the triplet structures (i.e., in the case of cytosine, C1B* is the lowest-energy triplet structure, not C1A*).

Molecular Structures and Relative Energies. The lowest-energy monohydrate structure of the ground-state uracil (U1A) is characterized by a $N_1-H\cdots O_w-H_w\cdots O_2=C_2$ cyclic hydrogen bond between the uracil base and the water molecule. The $N_1-H\cdots O_w$ and $C_2=O_2\cdots H_w$ hydrogen bond lengths are computed to be 1.910 and 1.912 Å, respectively. The lowest-energy structure of uracil dihydrate in the ground state (U2A) also has a cyclic hydrogen bond that connects the uracil moiety and two water molecules. However, its intermolecular distances are shorter than those of monohydrate U1A, with the $N_1-H\cdots O_w$, $C_2=O_2\cdots H_w$, and $O_w-H_w\cdots O_w$ hydrogen bond lengths being 1.766, 1.757, and 1.722 Å, respectively. The excitation of U1A and U2A to their lowest-triplet states (U1A* and U2A*) increases the intermolecular hydrogen bond distances, implying that stabilization through hydration is reduced in the triplet state, compared to the ground state. Other uracil mono- and dihydrate structures also show a similar weakening of the intermolecular hydrogen bond upon excitation to their lowest-triplet states.

Structural differences between the ground state and the lowest-triplet state of thymine hydrates are similar to those of uracil hydrates in general. In addition, the different hydrated ground state and triplet state thymine and uracil structures display the same energetic ordering. However, in the case of cytosine, neither the singly nor doubly hydrated isomers have the same energetic ordering for the ground state and the triplet state. While the lowest-energy structures of

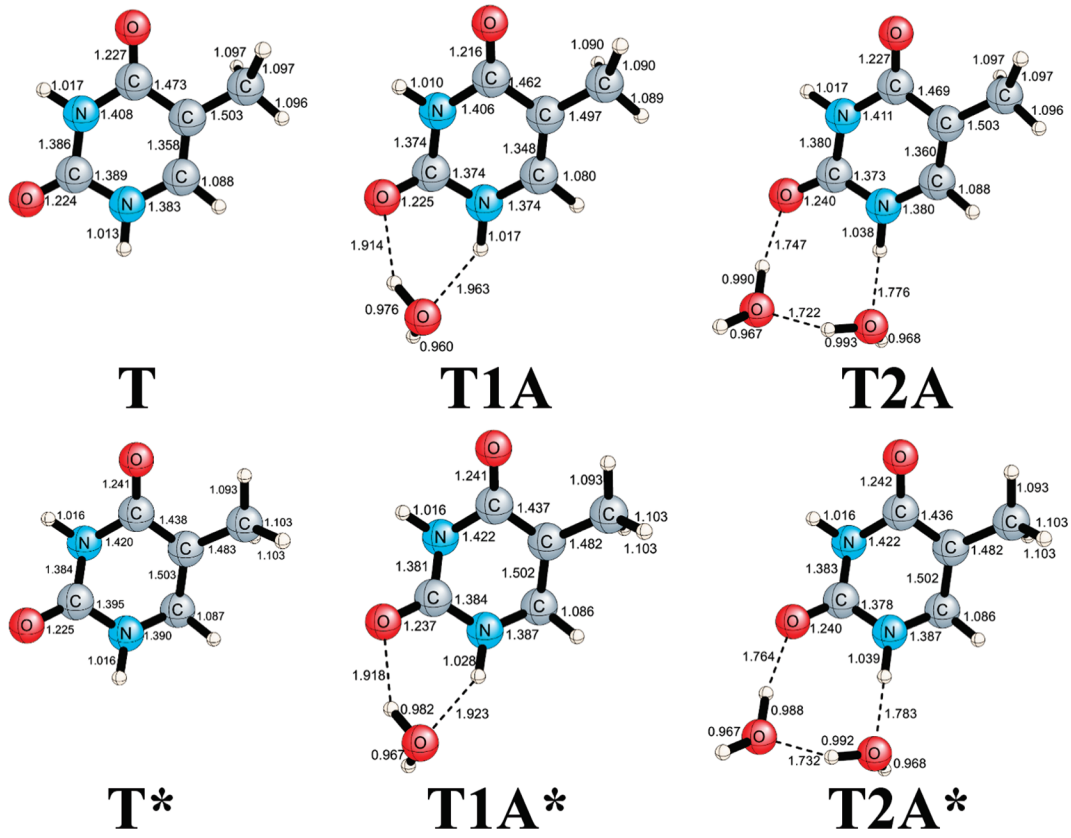

Figure 3. Structures of thymine and its lowest-energy mono- and dihydrates in the ground and lowest triplet states, optimized at the B3LYP/DZP++ level of theory.

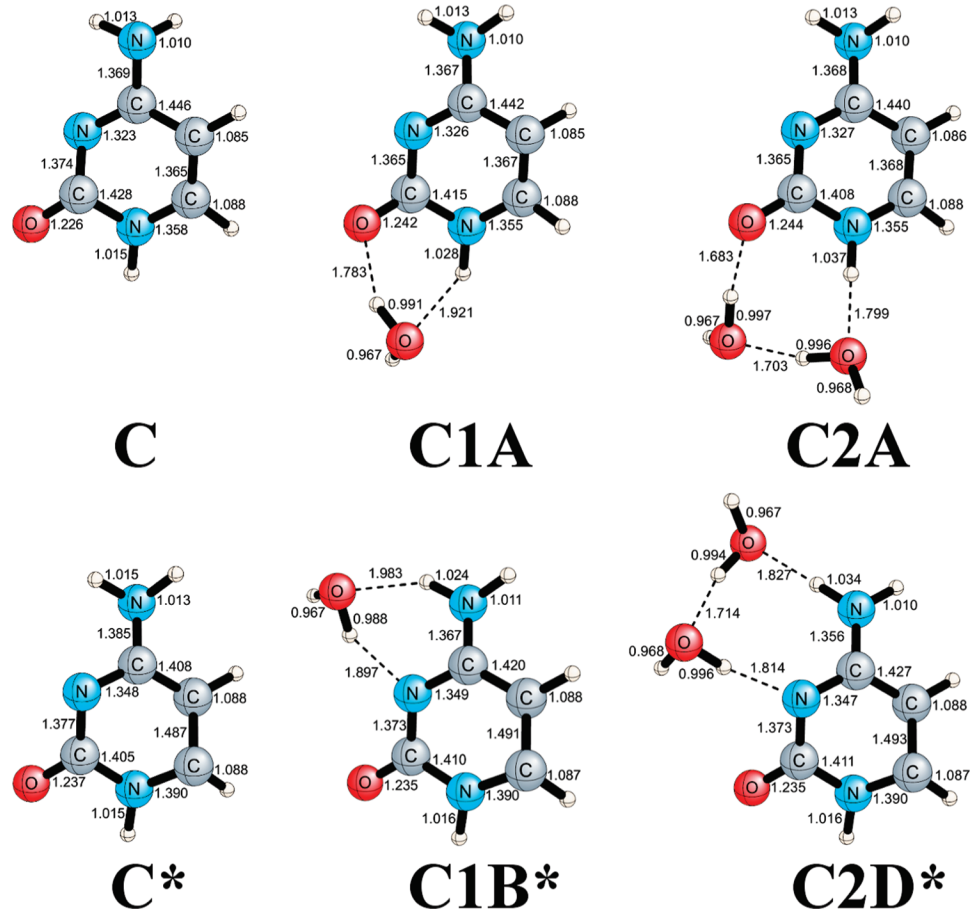

Figure 4. Structures of cytosine and its lowest-energy mono- and dihydrates in the ground and lowest triplet states, optimized at the B3LYP/DZP++ level of theory.

Table 2. Intermolecular Hydrogen Bond Distances in Å for Singly and Doubly Hydrated Uracil and Thymine in the Ground States and the Lowest Triplet Excited States

structure	parameter[a]	singlet	triplet	structure	parameter[a]	singlet	triplet
	uracil monohydrates				thymine monohydrates		
U1A	$N_1-H\cdots O_w$	1.910	1.912	T1A	$N_1-H\cdots O_w$	1.923	1.923
	$C_2=O_2\cdots H_w$	1.912	1.938		$C_2=O_2\cdots H_w$	1.894	1.918
U1B	$N_3-H\cdots O_w$	1.952	1.968	T1B	$N_3-H\cdots O_w$	1.963	1.981
	$C_4=O_4\cdots H_w$	1.891	1.925		$C_4=O_4\cdots H_w$	1.886	1.898
U1C	$C_2=O_2\cdots H_w$	1.937	1.960	T1C	$C_2=O_2\cdots H_w$	1.917	1.939
	$N_3-H\cdots O_w$	1.977	1.989		$N_3-H\cdots O_w$	1.986	2.006
U1D	$C_4=O\cdots H_w$	1.882	1.905	T1D	$C_4=O_4\cdots H_w$	1.878	1.867
	uracil dihydrates				thymine dihydrates		
U2A	$N_1-H\cdots O_{w1}$	1.766	1.773	T2A	$N_1-H\cdots O_{w1}$	1.776	1.783
	$O_{w1}-H_{w1}\cdots O_{w2}$	1.722	1.732		$O_{w1}-H_{w1}\cdots O_{w2}$	1.722	1.732
	$C_2=O_2\cdots H_{w2}$	1.757	1.775		$C_2=O_2\cdots H_{w2}$	1.747	1.764
U2B	$N_3-H\cdots O_{w1}$	1.765	1.777	T2B	$N_3-H\cdots O_{w1}$	1.771	1.786
	$O_{w1}-H_{w1}\cdots O_{w2}$	1.754	1.762		$O_{w1}-H_{w1}\cdots O_{w2}$	1.757	1.764
	$C_4=O_4\cdots H_{w2}$	1.759	1.780		$C_4=O_4\cdots H_{w2}$	1.754	1.764
U2C	$N_1-H\cdots O_{w1}$	1.905	1.912	T2C	$N_1-H\cdots O_{w1}$	1.919	1.923
	$C_2=O_2\cdots H_{w1}$	1.900	1.934		$C_2=O_2\cdots H_{w1}$	1.883	1.914
	$N_3-H\cdots O_{w2}$	1.949	1.975		$N_3-H\ldots O_{w2}$	1.956	1.984
	$C_4=O_4\cdots H_{w2}$	1.884	1.922		$C_4=O_4\cdots H_{w2}$	1.881	1.895
U2D	$C_2=O_2\cdots H_{w1}$	1.785	1.799	T2D	$C_2=O_2\cdots H_{w1}$	1.773	1.788
	$O_{w1}\cdots H_{w2}-O_{w2}$	1.786	1.790		$O_{w1}\cdots H_{w2}-O_{w2}$	1.783	1.791
	$N_3-H\cdots O_{w2}$	1.767	1.779		$N_3-H\cdots O_{w2}$	1.773	1.788
U2E	$N_1-H\cdots O_{w1}$	1.907	1.909	T2E	$N_1-H\cdots O_{w1}$	1.919	1.919
	$C_2=O_2\cdots H_{w1}$	1.920	1.944		$C_2=O_2\cdots H_{w1}$	1.905	1.926
	$C_2=O_2\cdots H_{w2}$	1.950	1.963		$C_2=O_2\cdots H_{w2}$	1.930	1.945
	$N_3-H\cdots O_{w2}$	1.973	1.988		$N_3-H\cdots O_{w2}$	1.980	2.002
U2F	$N_1-H\cdots O_{w1}$	1.901	1.906	T2F	$N_1-H\cdots O_{w1}$	1.909	1.913
	$C_2=O_2\cdots H_{w1}$	1.929	1.957		$C_2=O_2\cdots H_{w1}$	1.917	1.941
	$C_4=O_4\cdots H_{w2}$	1.879	1.906		$C_4=O_4\cdots H_{w2}$	1.878	1.868
U2G	$C_2=O_2\cdots H_{w1}$	1.952	1.978	T2G	$C_2=O_2\cdots H_{w1}$	1.940	1.960
	$N_3-H\cdots O_{w1}$	1.957	1.973		$N_3-H\cdots O_{w1}$	1.957	1.984
	$C_4=O_4\cdots H_{w2}$	1.870	1.898		$C_4=O_4\cdots H_{w2}$	1.871	1.864
U2H	$N_3-H\cdots O_{w1}$	1.935	1.954	T2H	$N_3-H\cdots O_{w1}$	1.939	1.956
	$C_4=O_4\cdots H_{w1}$	1.928	1.954		$C_4=O_4\cdots H_{w1}$	1.927	1.939
	$C_4=O_4\cdots H_{w2}$	1.886	1.905		$C_4=O_4\cdots H_{w2}$	1.891	1.868

[a] Oxygen and hydrogen atoms of a water molecule are denoted with O_w and H_w, respectively. Subscripts w1 and w2 are used to distinguish two different water molecules in the dihydrate structures.

the ground-state cytosine mono- and dihydrates (C1A and C2A) have a $N_1-H\cdots(O_w-H_w)_n\cdots O_2=C_2$ cyclic hydrogen bond, the water molecules in the lowest-energy structures of the triplet-state cytosine hydrates (C1B* and C2D*) bind to the cytosine unit through the N_3 and N_4-H atoms of cytosine, implying that the intermolecular hydrogen bonding in C1B* and C2D* stabilizes the system more strongly than C1A* and C2A*, respectively.

In general, the spread in relative energies for the triplet state structures is approximately 0.5 kcal mol^{-1} smaller than that of their ground state analogs. The SCIPCM method predicted that the effects of macrosolvation narrow the energy differences among the different hydrate structures for the three pyrimidines, but do not significantly change the relative orderings for all three pyrimidine hydrates both in the ground and in the lowest triplet states. Especially for all the nucleobases, the lowest-energy mono- and dihydrate structures in the gas phase were also predicted to be energetically favorable in the condensed media.

Excitation Energies. Estimated vertical and adiabatic excitation energies of the bases and their hydrates are reported in Table 4. In general, cytosine and its hydrates show the largest vertical and adiabatic excitation energies, while thymine and its hydrates have the smallest excitation energies. The methyl group of the unhydrated thymine lowers the vertical and adiabatic excitation energies by 0.13 and 0.18 eV, respectively, compared to those of free uracil. In the thymine hydrates, the methyl group also lowers the excitation energies by similar magnitudes (0.11−0.16 eV for and 0.17−0.20 eV for the vertical and adiabatic excitation energies, respectively). A consequence of this methyl group effect is that the excitation energies of uracil and its hydrates become closer to those of cytosine and its hydrates, compared to the thymine hydrates.

The singlet−triplet gaps of the gas phase uracil, thymine, and cytosine are estimated to be 2.92, 2.74, and 2.97 eV, respectively. The addition of one and two water molecules to thymine and uracil causes a negligible increase in the vertical excitation energies and singlet−triplet gap, as shown in Figure 5. For the cytosine molecule, the effect is slightly more pronounced, with the addition of each water molecule adding ∼0.05 to 0.1 eV to the vertical excitation energies and singlet−triplet gap. In addition, the macrohydration effects estimated using the SCIPCM method were not predicted to cause a significant change in both the vertical and adiabatic excitation energies for the three nucleobases and their hydrates. These results are encouraging in suggesting that the hydrated species are well approximated by the isolated pyrimidines.

Table 3. Intermolecular Hydrogen Bond Distances in Å for Singly and Doubly Hydrated Cytosine in the Ground States and the Lowest Triplet Excited States

structure	parameter[a]	singlet	triplet
	cytosine monohydrates		
C1A	$N_1-H\cdots O_w$	1.921	1.965
	$C_2{=}O_2\cdots H_w$	1.783	1.889
C1B	$N_3\cdots H_w-O_w$	1.894	1.897
	$N_4-H\cdots O_w$	1.981	1.983
C1C	$N_4-H\cdots O_w$	2.023	2.051
	cytosine dihydrates		
C2A	$N_1-H\cdots O_{w1}$	1.799	1.828
	$O_{w1}-H_{w1}\cdots O_{w2}$	1.703	1.743
	$C_2{=}O_2\cdots H_{w2}$	1.683	1.762
C2B	$N_3\cdots H_{w1}-O_{w1}$	1.819	1.811
	$O_{w1}\cdots H_{w2}-O_{w2}$	1.731	1.729
	$N_4-H\cdots O_{w2}$	1.841	1.826
C2C	$N_1-H\cdots O_{w1}$	1.917	1.953
	$C_2{=}O_2\cdots H_{w1}$	1.796	1.881
	$N_3\cdots H_{w2}-O_{w2}$	1.901	1.892
	$N_4-H\cdots O_{w2}$	1.980	1.970
C2D[b]	$C_2{=}O_2\cdots H_{w1}$	1.904	
	$N_3\cdots H_{w1}-O_{w1}$		1.814
	$O_{w1}\cdots H_{w2}-O_{w2}$	1.857	1.714
	$N_4-H\cdots O_{w2}$	1.892	1.827
C2E	$N_1-H\cdots O_{w1}$	1.945	1.989
	$C_2{=}O_2\cdots H_{w1}$	1.758	1.846
	$N_4-H\cdots O_{w2}$	2.018	2.031
C2F	$N_3\cdots H_w-O_{w1}$	1.873	1.868
	$N_4-H\cdots O_{w1}$	2.037	2.025
	$N_4-H\cdots O_{w2}$	2.027	2.029

[a] Oxygen and hydrogen atoms of a water molecule are denoted with O_w and H_w, respectively. Subscripts w1 and w2 are used to distinguish two different water molecules in the dihydrate structures. [b] Upon excitation of C2D to its lowest triplet excited states, the $C_2{=}O_2\cdots H_{w1}$ bond breaks and the $N_3\cdots H_{w1}-O_{w1}$ forms.

Hydration Energies and Dipole Moments. Table 5 reports hydration energies of the different hydrate structures of the three bases in the ground and lowest triplet states. For comparison purposes, those of the anionic hydrates, computed at the same level of theory, are also included. In all singly and doubly hydrated structures of cytosine, thymine, and uracil considered, with the exception of C2D*, the hydration energy of the triplet state is less (~0.5 to 3.5 kcal mol^{-1}) than that of the corresponding singlet structure. The difference is more pronounced for the cytosine structures than for thymine and uracil. The decrease in the hydration energy upon the excitation from the ground state to the lowest-triplet state for all three bases is attributed to the smaller dipole moment in the lowest triplet states, as shown in Table 6, which compares the dipole moments of the three bases and their hydrates in the ground and lowest triplet states. In a recent study on 4-thiouracil by Shukla and Leszczynski,[84] a similar decrease in dipole moment was predicted upon the excitation from the ground to the lowest singlet excited state.

For the cytosine hydrates, the hydration energy change upon the excitation of the hydrated structures may alter their relative energy ordering compared to that of the corresponding neutrals. For example, the excitation from C2A to C2A* is accompanied by a large decrease in the hydration energy by 3.6 kcal mol^{-1} (from 19.9 to 16.3 kcal mol^{-1}). On the contrary, the excitation from C2D to C2D* increases the hydration energy by 0.4 kcal mol^{-1} (from 17.5 kcal mol^{-1} to 17.9 kcal mol^{-1}). As a consequence, the energy ordering between C2A* and C2D* is swapped, compared to that between the corresponding neutrals, C2A and C2D. Therefore, it is the change in hydration energy upon excitation that alters the relative energetic ordering of the lowest-triplet hydrate structures of cytosine. For the uracil and thymine hydrates, the changes in hydration energy upon excitation do not vary enough to affect their energetic orderings.

Table 4. Vertical and Adiabatic Excitation Energies in eV for Singly and Doubly Hydrated Uracil, Thymine, And Cytosine[a]

	VE_x		singlet−triplet gap		
structure	gas	SCIPCM	gas		SCIPCM
	uracil and its hydrates				
U	3.56	3.59	3.04	(2.92)	3.09
U1A	3.57	3.60	3.07	(2.95)	3.11
U1B	3.56	3.59	3.06	(2.95)	3.11
U1C	3.59	3.62	3.06	(2.94)	3.11
U1D	3.54	3.58	3.05	(2.93)	3.11
U2A	3.58	3.61	3.09	(2.97)	3.12
U2B	3.56	3.60	3.07	(2.96)	3.15
U2C	3.57	3.60	3.11	(2.99)	3.14
U2D	3.60	3.63	3.06	(2.94)	3.11
U2E	3.60	3.63	3.09	(2.97)	3.12
U2F	3.55	3.58	3.08	(2.96)	3.12
U2G	3.58	3.61	3.07	(2.95)	3.12
U2H	3.53	3.57	3.07	(2.96)	3.13
	thymine and its hydrates				
T	3.43	3.45	2.85	(2.74)	2.89
T1A	3.44	3.46	2.88	(2.76)	2.90
T1B	3.42	3.44	2.87	(2.75)	2.90
T1C	3.47	3.49	2.87	(2.76)	2.91
T1D	3.39	3.42	2.85	(2.74)	2.90
T2A	3.45	3.47	2.90	(2.78)	2.92
T2B	3.42	3.45	2.88	(2.77)	2.91
T2C	3.43	3.45	2.91	(2.79)	2.92
T2D	3.49	3.50	2.88	(2.77)	2.92
T2E	3.48	3.49	2.90	(2.78)	2.92
T2F	3.40	3.43	2.89	(2.77)	2.92
T2G	3.44	3.46	2.88	(2.76)	2.92
T2H	3.37	3.40	2.87	(2.76)	2.91
	cytosine and its hydrates				
C	3.54	3.62	3.10	(2.97)	3.19
C1A	3.63	3.68	3.21	(3.08)	3.27
C1B	3.56	3.62	3.13	(3.00)	3.19
C1C	3.56	3.64	3.11	(2.98)	3.19
C2A	3.67	3.71	3.26	(3.13)	3.30
C2B	3.58	3.62	3.14	(3.01)	3.18
C2C	3.64	3.66	3.22	(3.10)	3.26
C2D	3.65	3.69	3.06	(2.95)	3.09
C2E	3.64	3.69	3.22	(3.08)	3.26
C2F	3.56	3.62	3.12	(3.00)	3.18

[a] Zero-point vibrational energy (ZPVE)—corrected values are in parentheses.

Discussion

In order to better understand hydration effects upon excitation of the three pyrimidine bases from the ground state to the lowest triplet state, it would be helpful to consider two pathways through which the ground-state unhydrated base changes into the hydrate of the triplet state. As displayed in Figure 6(a), one involves the excitation from the ground state to the triplet state of the unhydrated base, followed by

Table 5. Comparison of Hydration Energies (kcal mol^{-1}) of the Neutral Hydrates of Uracil, Thymine, And Cytosine in the Ground and the Triplet Excited States with the Corresponding Anionic Hydrates Computed at the B3LYP/DZP++ Level of Theory[a]

	neutral					
structure	ground state		triplet state		anion[b]	
			uracil hydrates			
U1A	10.7	(8.5)	9.9	(7.8)	13.1	(10.9)
U1B	9.1	(6.9)	8.5	(6.4)	14.8	(12.9)
U1C	8.4	(6.3)	8.0	(6.0)	12.0	(10.2)
U1D	7.3	(5.4)	7.1	(5.3)	15.0	(13.2)
U2A	23.4	(18.5)	22.1	(17.3)	24.4	(19.9)
U2B	20.8	(16.1)	20.0	(15.3)	27.3	(22.6)
U2C	20.0	(15.6)	18.4	(14.1)	27.6	(23.4)
U2D	19.4	(15.0)	18.9	(14.4)	27.2	(22.6)
U2E	18.6	(14.4)	17.5	(13.4)	23.9	(19.8)
U2F	17.9	(13.8)	16.9	(12.8)	27.6	(23.6)
U2G	15.9	(12.0)	15.2	(11.3)	26.3	(22.6)
U2H	16.0	(12.0)	15.3	(11.2)	28.6	(24.7)
			thymine hydrates			
T1A	10.7	(8.4)	10.0	(7.8)	13.0	(10.9)
T1B	9.0	(6.8)	8.5	(6.4)	14.7	(12.7)
T1C	8.6	(6.5)	8.0	(6.0)	11.9	(10.1)
T1D	6.4	(4.6)	6.3	(4.6)	14.2	(12.4)
T2A	23.3	(18.5)	22.1	(17.4)	24.4	(19.8)
T2B	20.5	(15.9)	19.9	(15.2)	27.1	(22.3)
T2C	19.8	(15.5)	18.5	(14.3)	27.4	(23.2)
T2D	19.5	(15.1)	18.8	(14.4)	27.1	(22.3)
T2E	18.8	(14.5)	17.6	(13.4)	23.8	(19.6)
T2F	17.1	(13.1)	16.2	(12.4)	26.8	(22.8)
T2G	15.2	(11.4)	14.4	(10.7)	25.5	(21.8)
T2H	14.8	(10.9)	14.4	(10.5)	27.5	(23.7)
			cytosine hydrates			
C1A	12.1	(9.7)	9.4	(7.1)	15.7	(13.7)
C1B	11.5	(9.1)	10.7	(8.4)	17.7	(15.3)
C1C	6.0	(4.5)	5.8	(4.3)	9.7	(6.6)
C2A	24.8	(19.9)	21.1	(16.3)	27.6	(23.7)
C2B	23.5	(18.6)	22.6	(17.7)	31.4	(26.8)
C2C	23.3	(18.6)	20.4	(15.8)	32.3	(27.9)
C2D	22.0	(17.5)	22.9	(17.9)	33.6	(28.7)
C2E	18.2	(14.2)	15.4	(11.7)	22.7	(18.4)
C2F	17.5	(13.6)	17.0	(13.0)	22.2	(18.0)

[a] Zero-point vibrational energy (ZPVE)—corrected results are in parentheses. [b] Refs., 73, 76 and 58 for uracil, thymine, and cytosine, respectively.

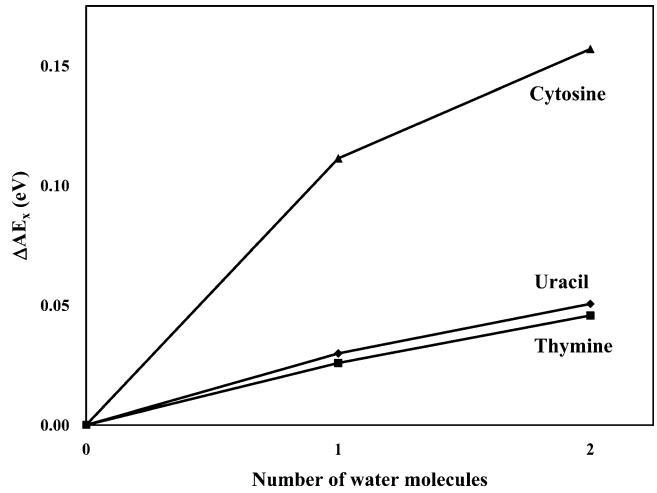

Figure 5. Changes in adiabatic excitation energies (eV) for the lowest energy structure upon addition of one and two water molecules for the three pyrimidines.

Table 6. Dipole Moments (μ, Debye) of the Neutral Hydrates of Uracil, Thymine, And Cytosine in the Ground and the Triplet Excited States, Computed at the B3LYP/DZP++ Level of Theory

structure	μ	structure	μ
	uracil hydrate		
U	4.63	U*	3.91
U1A	4.00	U1A*	3.31
U1B	4.57	U1B*	3.95
U1C	5.16	U1C*	4.31
U1D	2.95	U1D*	2.25
U2A	3.72	U2A*	2.98
U2B	4.14	U2B*	3.49
U2C	3.90	U2C*	3.05
U2D	5.12	U2D*	4.57
U2E	5.16	U2E*	4.40
U2F	2.97	U2F*	2.25
U2G	3.78	U2G*	2.98
U2H	2.57	U2H*	2.12
	thymine hydrate		
T	4.59	T*	4.28
T1A	3.69	T1A*	3.29
T1B	4.79	T1B*	4.69
T1C	5.01	T1C*	4.44
T1D	3.68	T1D*	3.28
T2A	3.36	T2A*	2.97
T2B	4.34	T2B*	4.18
T2C	3.93	T2C*	3.57
T2D	4.96	T2D*	4.77
T2E	4.74	T2E*	4.14
T2F	3.74	T2F*	3.37
T2G	4.64	T2G*	4.09
T2H	3.31	T2H*	3.17
	cytosine hydrate		
C	6.79	C*	5.28
C1A	5.71	C1A*	4.49
C1B	6.23	C1B*	5.10
C1C	9.64	C1C*	8.41
C2A	5.23	C2A*	3.98
C2B	5.99	C2B*	5.19
C2C	4.84	C2C*	3.84
C2D	5.42	C2D*	4.97
C2E	9.01	C2E*	8.12
C2F	8.73	C2F*	8.05

subsequent hydration. In the other process, formation of the hydrate of the ground-state base occurs first, and then the hydrate is excited to the triplet state. Because the energy difference between the initial state (the unhydrated base at its ground state equilibrium geometry) and the final state (the hydrate of the triplet-state base) should be independent of the two pathways, an equation for hydration effects on the excitation energy of a DNA/RNA base can be derived:

$$E_{ex}(B) - E_{hyd}(B^*) = E_{ex}(B \cdot H_2O) - E_{hyd}(B)$$

$$E_{ex}(B \cdot H_2O) - E_{ex}(B) = -[E_{hyd}(B^*) - E_{hyd}(B)]$$

$$\Delta E_{ex}(B \cdot H_2O, B) = -\Delta E_{hyd}(B^*, B)$$

where B and B* denote a nucleobase in its ground and triplet-excited states, respectively. The equation above shows that the change in the excitation energy upon hydration, $\Delta E_{ex}(B \cdot H_2O, B)$, is equivalent to the negative value of the difference in hydration energy between the ground and triplet states of the unhydrated base, $\Delta E_{hyd}(B^*,B)$. As shown in Table 5, the hydration energy of the triplet state is smaller

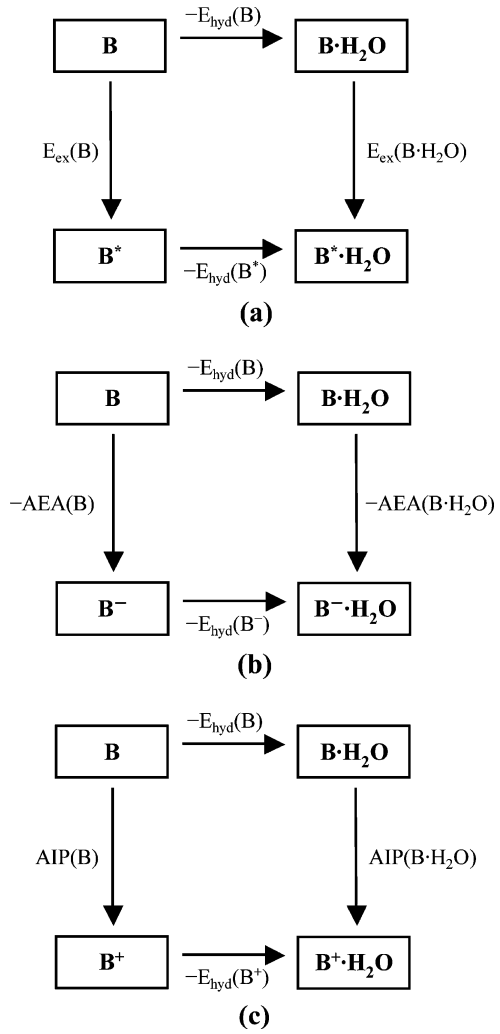

Figure 6. Two potential pathways in which the unhydrated neutral nucleobase in the ground state (B) is converted into (a) the hydrate of the neutral base in the lowest triplet state (B*); (b) the anionic hydrate of the base (B^-); and (c) the cationic hydrate of the base (B^+). E_{ex}, AEA, and AIP represent the excitation energy, adiabatic electron affinity, and adiabatic ionization potential, respectively.

than that of the ground state, making the $\Delta E_{hyd}(B^*,B)$ term negative and hence, the $\Delta E_{ex}(B\cdot H_2O, B)$ term positive. However, note that the magnitude of the $\Delta E_{hyd}(B^*,B)$ term for monohydrates of uracil and thymine, which is only 0.4 kcal mol^{-1} on average, indicates that the change in excitation energy upon hydration, $\Delta E_{ex}(B\cdot H_2O, B)$, is less than 0.02 eV. The corresponding value for the cytosine monohydrates is 1.1 kcal mol^{-1} (~0.05 eV).

Many experimental and theoretical studies have shown that, in spite of the near-zero electron affinities of the gas-phase DNA/RNA bases, hydration with even a single water molecule causes an increase in the adiabatic electron affinities of the three pyrimidine bases (by as much as 0.3 eV) and successive addition of more water molecule increases the AEA values even more.[58,73,76] These effects enable negative charge formation on the DNA bases in aqueous solution, leading to lethal DNA lesions through subsequent single- or double-strand breaks. On the contrary, the excitation energies of the three nucleobases computed in the present study are insensitive to the hydration effects, compared to their electron

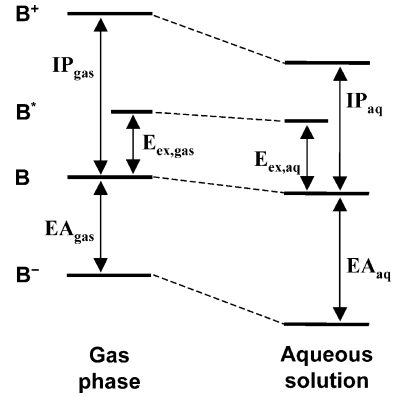

Figure 7. Schematic energy diagram showing the hydration effects upon the excitation energy, electron affinity and ionization potential of the DNA/RNA bases.

affinities. Therefore, it may be helpful to compare anion hydration with the triplet state hydration in the present study. As shown in Figure 6(b), there are also two possible pathways for forming the anionic hydrates of the bases from the unhydrated bases. Similar to the triplet state cases, the changes in electron affinities of the bases upon hydration can be correlated with the changes in the hydration energy between anion (B^-) and neutral bases (B).

$$\Delta AEA(B\cdot H_2O,B) = \Delta E_{hyd}(B^-, B)$$

That is, the change in adiabatic electron affinity, $\Delta AEA(B\cdot H_2O,B)$, is equivalent to the difference between the base and its anion, $\Delta E_{hyd}(B^-, B)$. As shown in Table 5, the hydration energies of the anions, essentially greater than those of neutrals, are responsible for the increase in the AEA upon hydration. In a similar manner, Figure 6(c) can be used to show that the hydration effect on the ionization potential is equivalent to the difference in the hydration energy between the cation (B^+) and the neutral (B).

$$\Delta AIP(B\cdot H_2O,B) = -\Delta E_{hyd}(B^+, B)$$

Although no studies have been reported on the hydration energies of the cations that are computed at the same level of theory employed in the present study, many experimental evidence[85] as well as other theoretical studies[86,87] using different levels of theory showed a significant increase in hydration energy for the cation, compared to the corresponding neutrals, leading to a significant decrease in the ionization potentials of the DNA/RNA bases. For example, while monohydration of thymine is predicted in the present study to increase its excitation energy by only 0.02 eV, its ionization potential upon monohydration was computed to decrease by 0.1 eV (at the B3LYP/6-31+G** level of study)[86,87] and the experimentally determined decrease (by 0.3 eV) is even more significant.[85] Figure 7 displays a schematic energy diagram that compares hydration effects upon the electron affinities, ionization potentials, and excitation energies of the nucleobases. Stabilization due to hydration is more significant in charged species than in neutral species, causing the increase in the electron affinity and the decrease in the ionization potential. On the other hand,

because both the ground state and the excited state of the nucleobases are neutral, the hydration energy difference between the two states is relatively small, compared to that between the neutral and charged bases, making the excitation energies of the nucleobases less sensitive to hydration than their electron affinities and ionization potentials.

Conclusions

The singlet ground states and lowest triplet states of mono- and dihydrates of the three DNA/RNA pyrimidine bases, cytosine, uracil, and thymine, have been investigated at the B3LYP/DZP++ level of theory. For uracil and thymine, the energetic ordering of hydrate structures of the triplet states is the same as that of the corresponding singlet ground states. For all three bases, it was found that hydration does not have a significant effect upon the energy difference between the singlet and triplet states, compared to hydration effects on electron affinities and ionization potentials, which involve charged species. A water molecule is likely to interact with a charged species more strongly than with a neutral species, resulting in the increase in electron affinity and the decrease in ionization potential. On the contrary, if a molecule is neutral in the ground state, its triplet state is necessarily also neutral, and as shown in the present study, the differential stabilization due to hydration of the triplet state is quite modest, making the excitation energy relatively insensitive to hydration.

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Supporting Information Available: Cartesian coordinates, absolute energies, and vibrational frequencies for the optimized structures of the ground and the lowest triplet state of the mono- and dihydrates of the three pyrimidine hydrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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