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Calculations of pK_a's and Redox Potentials of Nucleobases with Explicit Waters and Polarizable Continuum Solvation

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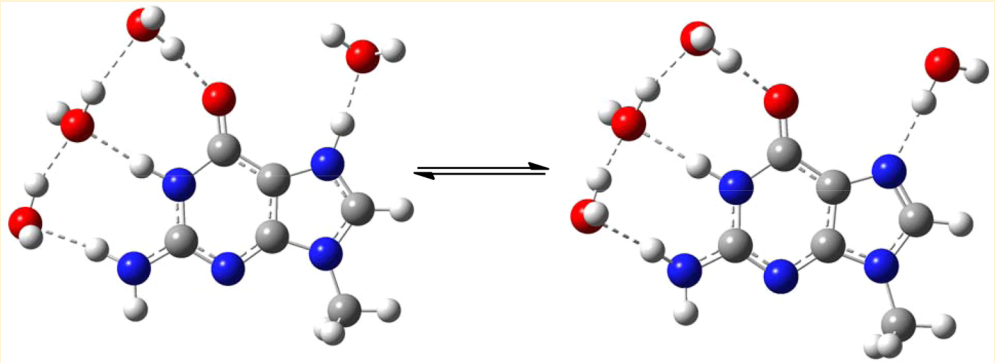
Supporting Information



ABSTRACT: The SMD implicit solvation model augmented with one and four explicit water molecules was used to calculate pK_a's and redox potentials of *N*-methyl-substituted nucleic acid bases guanine, adenine, cytosine, thymine, and uracil. Calculations were carried out with the B3LYP/6-31+G(d,p) level of theory. The same numbers of water molecules were hydrogen bonded to the neutral, protonated, and deprotonated nucleobases in their unoxidized and oxidized forms. The improvement in pK_{a1} involving neutrals and cations was modest. By contrast, the improvement in pK_{a2} involving neutrals and anions was quite significant, reducing the mean absolute error from 4.6 pK_a units with no waters, to 2.6 with one water and 1.7 with four waters. For the oxidation of nucleobases, adding explicit waters did little to improve $E(X^{\bullet},H^{+}/XH)$, possibly because both species in the redox couple are neutral molecules at pH 7.

INTRODUCTION

Oxidative damage to DNA may result from exposure to reactive species resulting from cellular metabolism, ionizing radiation or a variety of chemical oxidants.[1−8] Experimentally, the distribution of oxidation products depends on pH and the type of oxidizing agent, as well as the nature of the nucleobase and its environment (free base, nucleoside, single or double strand DNA).[5,9−13] Obtaining the reduction potential of individual nucleosides as a function of pH is important for understanding the mechanism of oxidative damage of DNA. Determination of the redox potentials in the physiologically relevant range requires the pK_a's of the parent and oxidized forms.[14] Progress in the calculation of pK_a's using continuum solvation models has been reviewed recently.[15−17] The status of computational electrochemistry is discussed in detail in a recent perspective.[18] In the present paper, we examine the effect of including a few explicit water molecules in the calculations of pK_a's and redox potentials of nucleobases with a polarizable continuum solvation model.

Numerous experimental and theoretical studies have examined the pK_a's and redox potentials of nucleobases in aqueous solution (for leading, see refs 9 and 19−46). Reliable experimental pK_a's are available for the bases and some of their oxidized products.[9,19,20,24,25,30,31,45] Several theoretical studies have computed pK_a's of nucleobases directly without resorting to linear regressions. Goddard and co-workers[34,35] calculated ensemble-averaged pK_a's of guanine using a Poisson−Boltzmann continuum solvation model. Baik et al. calculated tautomer specific pK_a's for oxidized nucleobases at the PW91 level of theory with the COSMO solvation model.[33] Verdolino et al.[40] and Psciuk et al.[45,46] calculated ensemble-averaged pK_a's for nucleobases and their oxidized forms using the CBS-QB3 and B3LYP levels of theory and the SMD continuum solvation. Sevilla and co-workers examined acid−base properties of guanine and adenine radical cations using DFT calculations and IEF-PCM solvation.[37,41] Close[44] calculated the pK_a's of DNA bases and radical ions using the same protocol developed by Verdolino et al.[40]

Guanine has long been recognized as the most easily oxidizable nucleobases. However, experimental measurements of redox potentials of nucleobases in aqueous solution are difficult because of problems with solubility and irreversibility. Of the numerous studies available for guanine, the most widely

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quoted value for the reduction potential at physiological pH comes from kinetic rate measurement by Steenken and Jovanovic.[23] They obtained 1.29 V for the half-cell potential vs SHE for guanosine at pH 7. Fukuzumi et al. reported E_7 = 1.31 V for guanosine monophosphate (GMP) from the kinetics of thermal and photoinduced electron transfer.[27] Using cyclic voltametry, Faraggi et al. obtained E_7 = 1.25 V for GMP.[22] Anderson and co-workers used pulsed radiolysis to obtain 1.22 V for guanine in the GC base pair in DNA.[32] A study by Langmaier et al. obtained the redox potential of 1.16 and 1.18 V for guanosine and 2′-deoxyguanosine respectively from equilibria with $Ru(byp)_3^{3+/2+}$.[29] Additional experimental studies by Langmaier et al.,[29] Xie et al.,[38] and Faraggi et al.[22] reported that E_7 for guanine was lower than guanosine by 0.13, 0.21, and 0.25 V, respectively. Due to higher redox potentials, other nucleobases are less likely to be oxidized under physiological pH and less likely to be involved in DNA oxidation. Consequently, their redox potentials have been studied less extensively.[21,23,27,33,45]

Several theoretical studies have examined the redox potential of DNA and RNA bases.[33,36,39,42,43,45] Baik et al.[33] calculated the standard redox potentials ($E°$) of unsubstituted DNA nucleobases using the PW91 level of theory and the COSMO solvation model. Crespo-Hernández et al.[36,39] estimated the redox potentials of various unsubstituted nucleobases using a linear correlation between $E°$ and gas phase ionization potentials and electron affinities calculatated by DFT and PMP2. Li et al.[42] calculated E_7 for unsubstituted nucleobases and their metabolites in aqueous solution using the B3LYP level of theory with the COSMO-RS solvation model. Paukku and Hill[43] obtained standard redox potentials of DNA bases using M06-2X/6-311++G(d,p) level of theory with the PCM solvation model. Psciuk at el.[45,46] calculated ensemble-averaged redox potentials for *N*-methyl-substituted nucleobases and the intermediates for guanine oxidation using the SMD solvation model with the B3LYP and CBS-QB3 levels of theory.

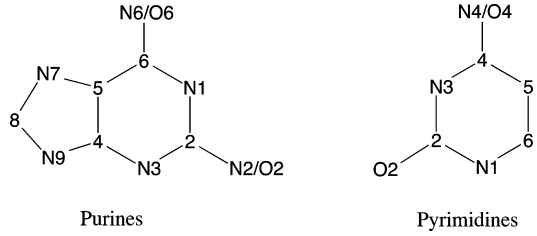
The use of continuum solvation models in the calculation of pK_a's has recently been reviewed.[15−17] Various thermodynamic cycles can be used to calculate pK_a's directly without resorting to linear fits. If suitable reference species are available, proton exchange or isodesmic reactions can provide more reliable calculations of pK_a's. In general, it is thought that including a few explicit water molecules should improve the calculation of solvation energies, especially for cations and anions, which can have strong hydrogen bonding interactions with the solvent water molecules. This has led to implicit−explicit and cluster-continuum models. Some of the earlier work is discussed in a review by Cramer and Truhlar.[47] Pliego and Riveros[48,49] determined that including two to four waters significantly improved the solvation energies of ions and predicted pK_a's. Adam[50] found that even one or two waters improved the linear fit of the calculated pK_a's. In developing the SMx and SMD implicit solvation models,[51,52] Cramer, Truhlar, and co-workers included a single explicit water for a subset of the ions with strong solute−solvent interactions. In applying the SM6 implicit solvent model to pK_a calculations, these authors also found that an explicit water molecule significantly improved the agreement with experiment[52,53] (for dicarboxylic acids up to four waters were needed[54]). Ho and Coote[15] have investigated the effect of using one to three water molecules in cluster-continuum calculations of the pK_a's for a set of 55 acids and found significantly different behavior for different solvent models. Adding an explicit water not just to the ions but also to the neutral species was shown to be beneficial for calculating the pK_a's of carboxylic acids.[55] Svendsen, da Silva, and co-workers used five explicit waters with various implicit solvation models.[56,57] Sevilla and co-workers found that seven explicit water molecules were needed to stabilize the experimentally observed tautomer of guanine radical.[37] In calculations where the number of explicit waters changes on protonation or deprotonation, care must be taken to properly account for the correct standard state of the water molecules.[58,59] Explicit water molecules beyond the first solvation shell are not bound as strongly and extensive sampling is needed to calculate the free energy. The example of molecular dynamics studies of pK_a's includes some recent QM/MM and Car−Parrinello calculations.[55,60,61] Because hundreds of water molecules and 100−200 ps simulations are typically needed, such calculations are beyond the scope of the present study.

In our previous studies[45,46] we computed the pK_a's and redox potentials for nucleobases and guanine oxidation products using B3LYP and CBS-QB3 calculations and the SMD polarizable continuum solvation model. We carefully calibrated the solvent cavity scaling parameter to account for the neglect of specific hydrogen bonding and other systematic errors. The pH specific redox potentials were calculated using standard redox potential ($E°$) and ensemble-averaged pK_a's for low energy tautomers. The objective of present work is to explore the effect of a few explicit waters on the pK_a's and reduction potentials of methylated DNA and RNA bases. We are looking for a practical protocol that extends the implicit solvation model and can be applied to the electrochemical properties of biological reaction intermediates. In the present work, we have calculated the tautomer-specific pK_a's and redox potentials at pH 0 ($E°$) and pH 7 (E_7) for 9-methylguanine, 9-methyladenine, 1-methylcytosine, 1-methylthymine, and 1-methyluracil. The calculations are carried out with the B3LYP/6-31+G(d,p) level of theory and include one and four explicit water molecules in addition to the SMD solvation model. So that the effect of the explicit waters can be judged more clearly, no cavity scaling was employed in the present study. Numerous tautomers are possible in aqueous medium, and the most stable forms have been considered for each of the degrees of protonation.

CALCULATIONAL METHODS

Electronic structure calculations were performed with the Gaussian series of programs.[62] The structures were optimized in solution using the SMD[52] implicit solvation model and the B3LYP[63,64] density functional with the 6-31+G(d,p) basis set.[65−67] Vibrational frequencies were calculated with SMD

Scheme 1. Atomic Numbering for Purine and Pyrimidine Nucleobases[a]



[a]Actual bond type, charge, multiplicity, and hydrogen atoms are not shown.

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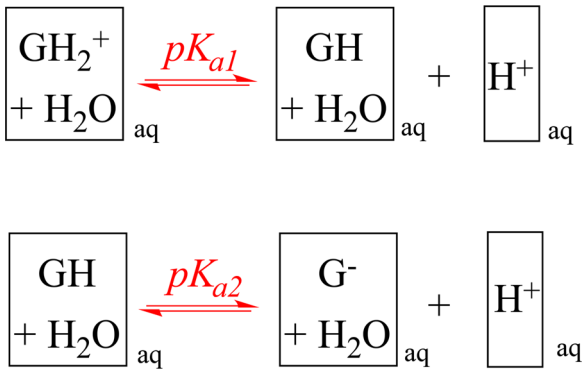

Figure 1. Cycle used to calculate pK_a.

solvation to confirm that the geometries correspond to local minima on the potential energy surface, and to obtain zero-point and thermal contributions to the energy. Our previous studies showed that pK_a's calculated with this level of theory agreed well with higher-level CBS-QB3[68,69] calculations. The labeling of atoms is shown in Scheme 1.

Solvation free energies were calculated with the SMD implicit solvation method.[52] SMD has a mean unsigned error of ~1 kcal/mol for neutral molecules and ~4 kcal/mol for charged species.[52] To improve the calculation of solvation effects and to take into account changes in specific hydrogen bonding that could be important for pK_a calculations, we included one and four strategically placed water molecules. Because some structures optimized in solution were found to have significantly different geometries than in the gas phase,

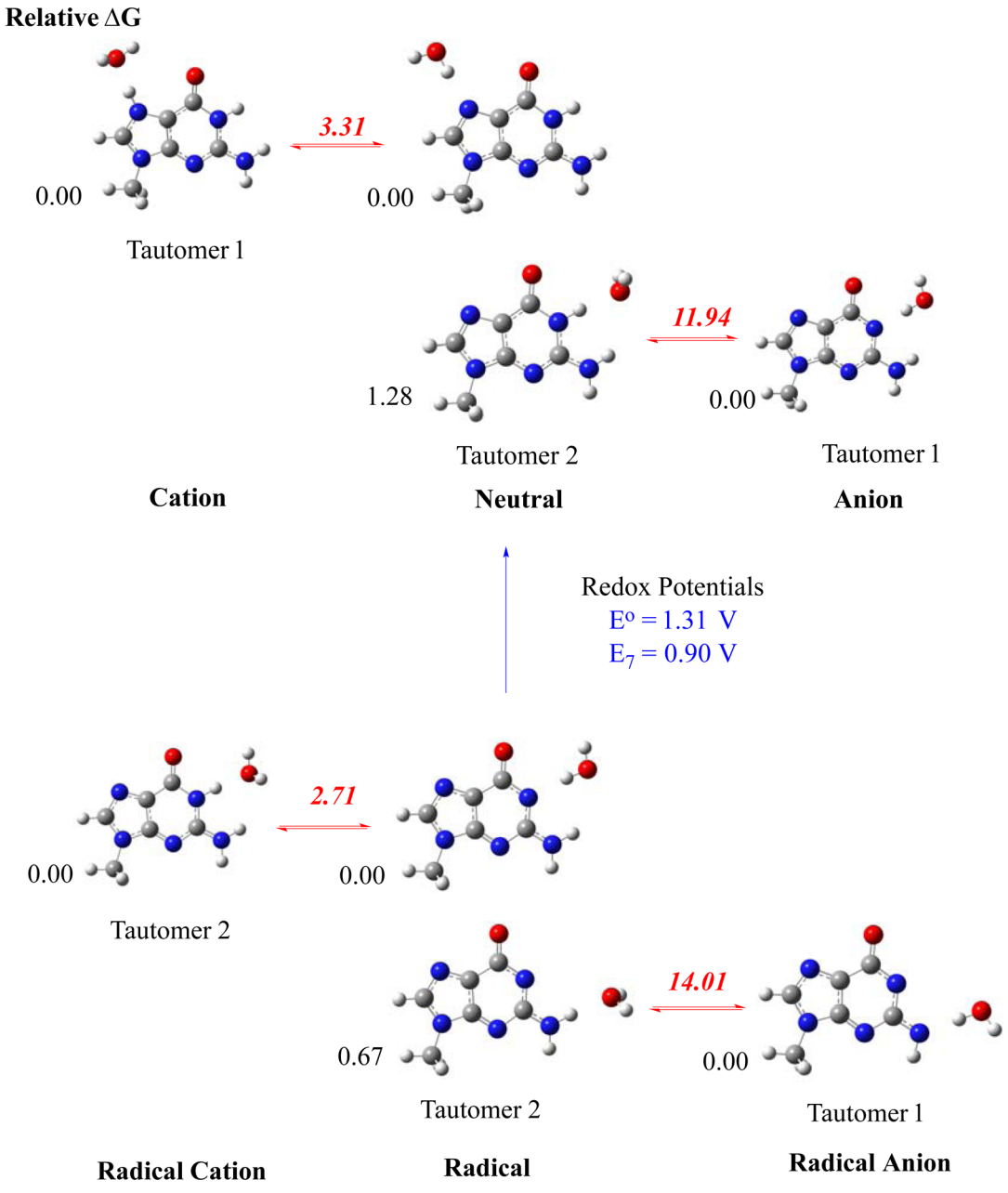

Figure 2. Structures used to calculate pK_{a1} and pK_{a2} for 9-methylguanine with one explicit water molecule. Values on the left of the structure (regular) are the free energies relative to the lowest energy tautomer. pK_a values are shown in bold *italics* (red).

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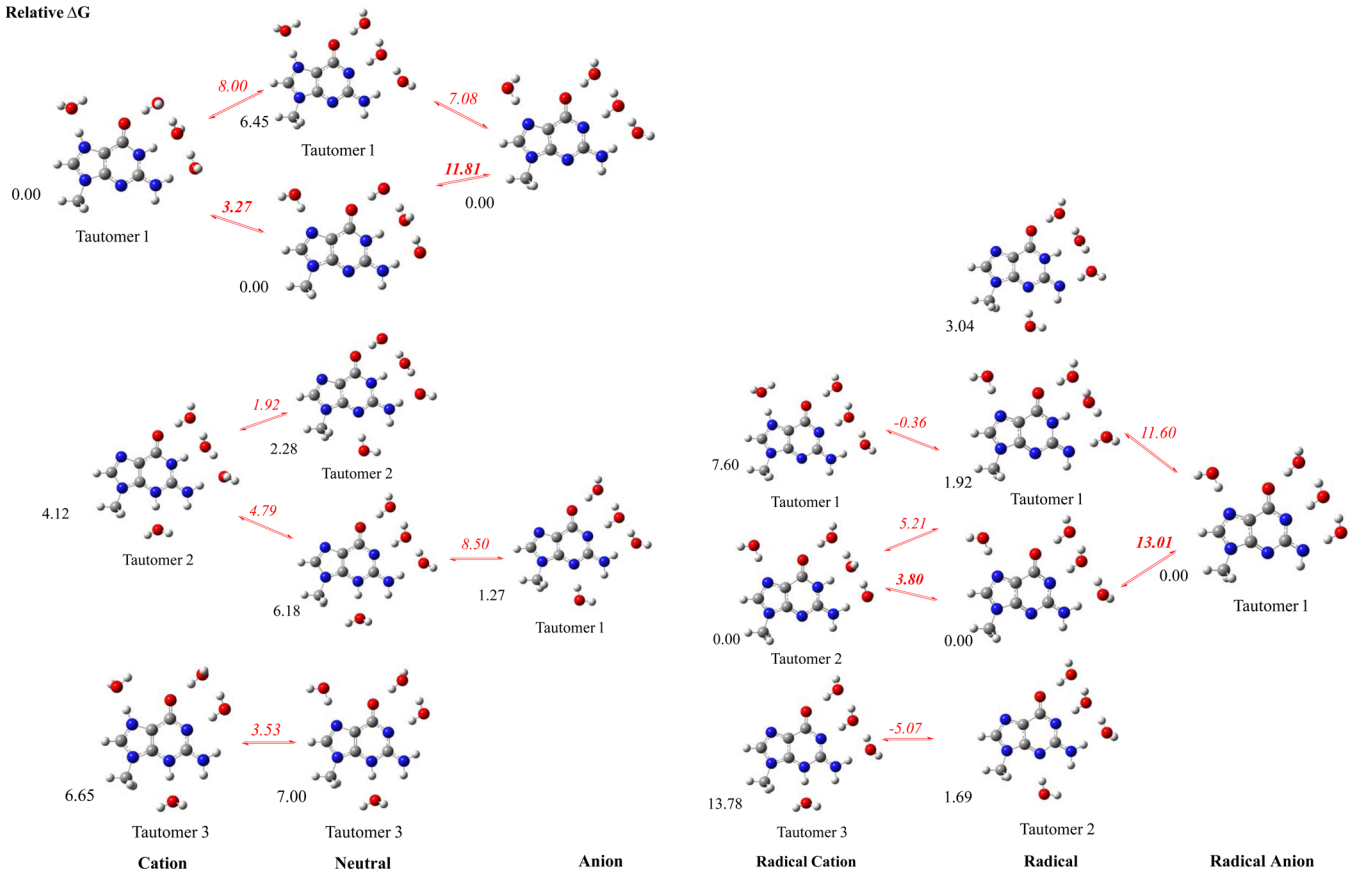

Figure 3. Calculated pK_a's and redox potentials for 9-methyl guanine. For detail, see caption of Figure 2

only solution optimized structures were used. For each nucleobase, several arrangements of explicit water molecules were considered and a number of orientations were optimized for each arrangement. The final structures were selected on the basis of relative energy and interaction with the site of protonation/deprotonation.

Methods for calculating pK_a's have been reviewed by Ho and Coote.[15,17] For an acid deprotonation reaction,

$$AH_{(aq)} = A_{(aq)}^{-} + H_{(aq)}^{+} \quad (1)$$

the pK_a, defined as negative logarithm of the dissociation constant, is given by

$$pK_a = \frac{\Delta G_{deprot(aq)}}{2.303RT} \quad (2)$$

where $\Delta G_{deprot(aq)}$ is the Gibbs energy of deprotonation in aqueous solution, R is the gas constant, and T is the temperature. The Gibbs free energy of deprotonation can be obtained by

$$\Delta G_{deprot(aq)} = G_{(aq),A^-} + G_{(aq),H^+} - G_{(aq),AH} \quad (3)$$

The aqueous phase Gibbs free energy of a proton, G_{aq,H^+}, is given by

$$G_{(aq),H^+} = G^{\circ}_{(g),H^+} + \Delta G^{1atm\rightarrow 1M} + \Delta G^{*}_{(aq),H^+} \quad (4)$$

$G^{\circ}_{(g),H^+}$ is the gas phase free energy of a proton, $\Delta G^{1atm\rightarrow 1M}$ = 1.89 kcal/mol accounts for the change in standard state from 1 atm to 1 M, and $\Delta G^{*}_{(aq),H^+}$ is solvation free energy for proton. Superscripts ° and * denote the gas phase (1 atm) and solution phase (1 mol/L) standard states, respectively.[70] The aqueous solvation free energy of a proton $\Delta G^{*}_{(aq),H^+}$ = −265.9 kcal/mol is taken from literature.[18,71−73] The gas phase standard free energy of proton is $G^{\circ}_{(g),H^+}$ = −6.287 kcal/mol at 298 K, derived from $G^{\circ}_{(g)} = G^{\circ}_{(g),H^+} - TS^{\circ}_{(g)}$ with $H^{\circ}_{(g),H^+} = {}^5/_2RT$ = 1.48 kcal/mol and $S^{\circ}_{(g)}$ = 26.05 cal/(mol K).

Methods for computational electrochemistry have been reviewed recently by Marenich, Ho, Coote, Cramer, and Truhlar.[18] For the reduction of a cation

$$A_{(aq)}^{n+} + ne_{(aq)}^{-} \xrightarrow{\Delta G^{*}_{red(aq)}} A_{(aq)} \quad (5)$$

the standard reduction potential is given by

$$E^{\circ}_{red(aq)} = \frac{-\Delta G^{*}_{red(aq)}}{nF} - SHE \quad (6)$$

where $\Delta G^{*}_{red(aq)}$ is the standard Gibbs free energy change in solution, n is the number of electrons in redox process, F is Faraday's constant (23.06 kcal/(mol V)), and SHE is the absolute potential of standard hydrogen electrode (4.281 V, obtained from the free energy of aqueous H^+).[18,71−73] Because the nucleobase redox reactions in the present study are all one electron processes, n = 1.

The free energy of reduction of cation in solution is

$$\Delta G^{*}_{red(aq)} = G^{*}_{(aq),A} - G^{*}_{A^{n+}(aq)} - G^{*}_{e^-(g)} \quad (7)$$

where $G^{*}_{e^-(g)}$ = −0.867 kcal/mol is the free energy of the electron at 298 K and is obtained using $H^{\circ}_{H^+(g)}$ = 0.752 kcal/mol and $S^{\circ}_{(g)}$ = 5.434 cal/(mol K) on the basis of Fermi−Dirac statistics.[74,75]

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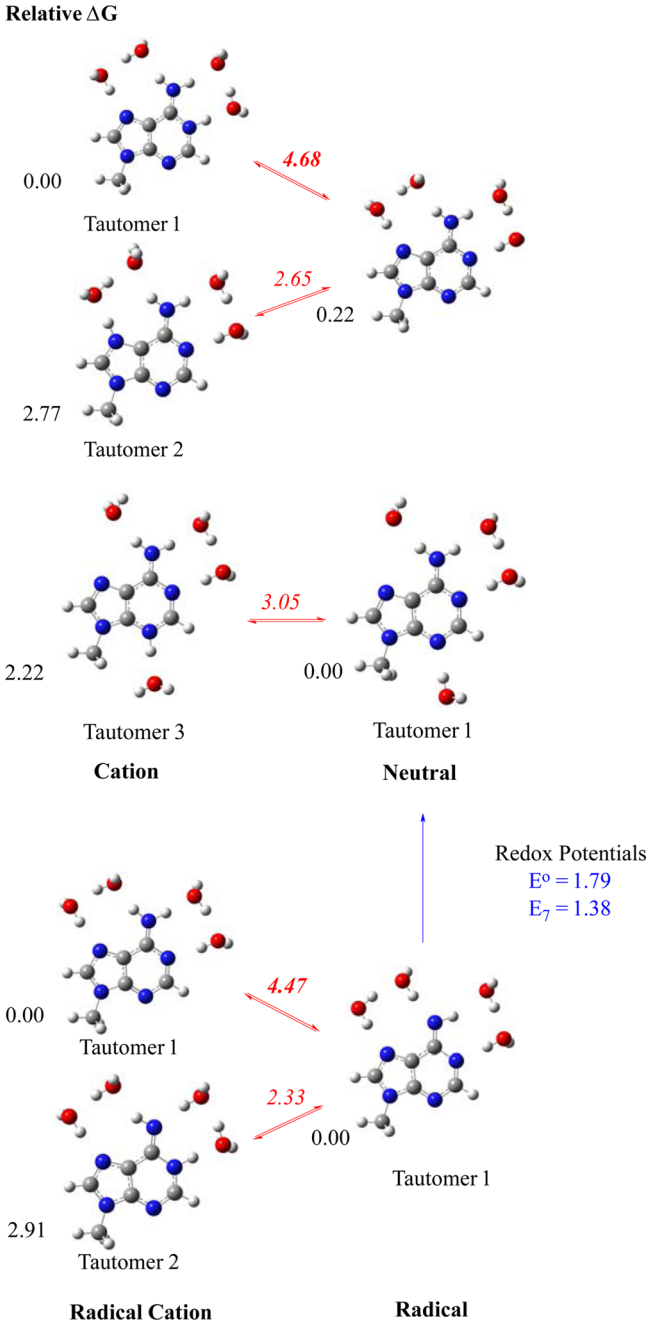

Figure 4. Calculated pK_a's and redox potentials for 9-methyl adenine. For detail, see caption of Figure 2

Our previous study[45] has shown that the *N*-methylated nucleobases (N9 for pyrimidine and N1 for purine shown in Scheme 1) could be used to compute reliable pK_a values and relative reduction potentials of the nucleobases. Because the deprotonation of hydroxyl groups of sugar moiety is very unlikely at physiological pH, *N*-methylated nucleobases should be good models for nucleosides. Note, however, that the sugars of nucleobases can also be oxidized.[76]

The reduction potential at specific pH can be obtained by using the Nernst half-cell equation

$$E_{1/2} = E^\circ - \frac{RT}{F}\ln\left(\frac{[\mathrm{Red}]}{[\mathrm{Ox}]}\right) \quad (8)$$

where E° is the standard reduction potential at pH 0. For the reduction potential at a particular pH, the equilibrium concentration of the relevant protonation states must be obtained by using acid dissociation constant (K_a). Assuming low ionic strength of the solute, an example of a pH-dependent potential for a redox system is given by[23]

$$E_{\mathrm{pH}} = E^\circ(\mathrm{A}^\bullet,\mathrm{H}^+/\mathrm{AH}) + \frac{RT}{F}\ln\left(\frac{K_{\mathrm{a1o}}}{K_{\mathrm{a1r}}}\right) + \frac{RT}{F}\ln\left(\frac{K_{\mathrm{a1r}}K_{\mathrm{a2r}}K_{\mathrm{a3r}} + K_{\mathrm{a1r}}K_{\mathrm{a2r}}10^{-\mathrm{pH}} + K_{\mathrm{a1r}}10^{-2\mathrm{pH}} + 10^{-3\mathrm{pH}}}{K_{\mathrm{a1o}}K_{\mathrm{a2o}} + K_{\mathrm{a1o}}10^{-\mathrm{pH}} + 10^{-2\mathrm{pH}}}\right) \quad (9)$$

AH represents reduced neutral form and A$^\bullet$ is the oxidized radical that has one less proton than the reduced neutral. Subscripts "o" and "r" correspond to "oxidized" and "reduced" form of the redox pair, respectively. The number on the subscript represents the dissociation constant number. For a nucleobase redox pair in aqueous solution of pH near 7, a reduction is immediately followed by a proton transfer because neutral states of reduced and oxidized nucleobases tend to dominate at that pH. Details of the pK_a and reduction potential calculation are available in a spreadsheet provided as Supporting Information.

To summarize, the basic steps that we have used to calculate the pK_a's and redox potentials in the present study are

1. The geometry of each tautomer is optimized in aqueous solution using the SMD solvation model and the B3LYP/6-31+G(d,p) level of theory with the desired explicit water molecules at the appropriate site. No cavity scaling was employed (i.e., the default cavity scaling value of α = 1.00 is used for cations, neutrals and anions).
2. The change in free energy is obtained by taking the difference between the protonated and deprotonated species in the solution as shown in Figures 1−5. pK_a's were calculated using eqs 2−4. Redox potentials were computed using eqs 6, 7, and 9 using the corresponding calculated pK_a's in Table 1.

RESULTS AND DISCUSSION

Our previous study[45] has shown that the pK_a's and reduction potentials of nucleobases can be modeled quite well by using the SMD model and solvent cavity scaling. Because our aim is to explore the effect of hydrogen bonding on the pK_a's and reduction potentials of nucleobases, cavity scaling is not included in this study. Calculations were carried out with the SMD implicit solvation model plus zero, one, and four explicit water molecules.

The structures used for calculating pK_{a1} and pK_{a2} of 9-methylguanine with one explicit water molecule are shown in Figure 2. The structures for the other nucleobases and their oxidized forms can be found in the Supporting Information. For each hydrogen bonding site, several orientations of the added water were considered and only the lowest energy structure was retained. For optimal cancelation of errors in the pK_a calculations, the water molecule was hydrogen bonded to the same site in the molecule and its deprotonated form. The most significant effect can be expected when the water is at the site of protonation/deprotonation. In this case, the donor/acceptor orientation of water changes during the process (Figure 2). Geometries optimized with an explicit water molecule at other sites were found to have slightly higher

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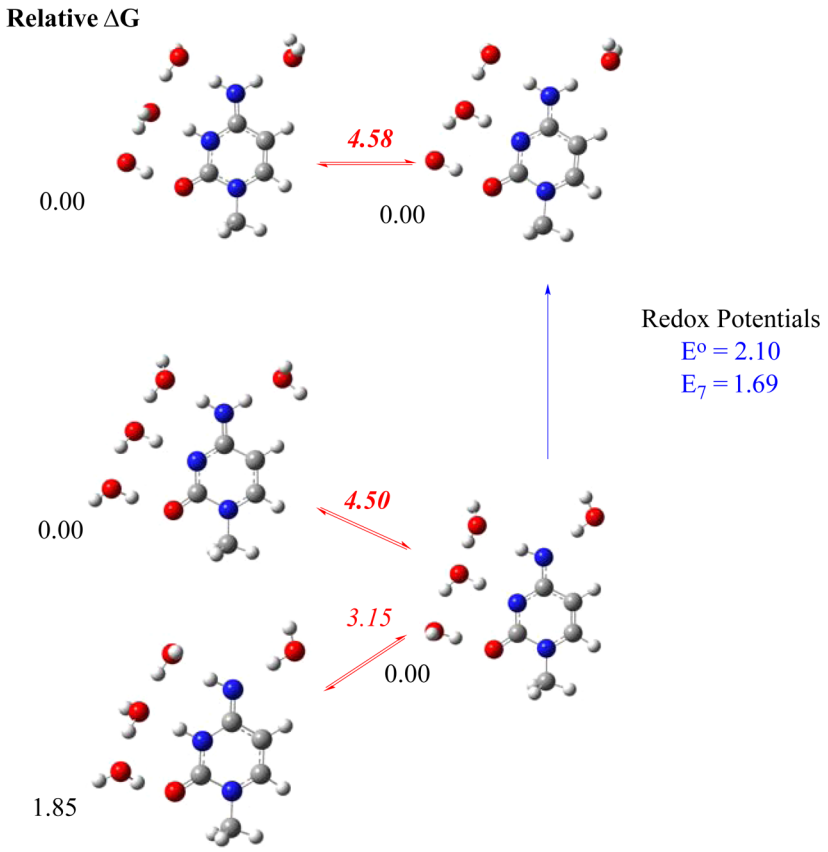

Figure 5. Calculated pK_a's and redox potentials for 1-methyl cytosine. For detail, see caption of Figure 2.

Table 1. Experimental and Calculated pK_a Values in Aqueous Solution

	experimental					current study (methyl subst)		
	NMPEt-NdMPEt[a]	NMP-dNMP nucleotides[b]	nucleotide	methyl subst nucleobase	Psciuk et al.[k] (methyl subst)	no water	one water	four waters
				Guanine				
pK_{a1}		2.5–2.7	1.9[e]	3.1[i]	3.2	2.82	3.31	3.27
pK_{a2}	9.3–9.4	9.5–9.6	9.2[e]	9.5[i]	9.36	14.4	11.94	11.81
pK_{a1ox}			3.9[f]		3.34	2.64	2.71	3.80
pK_{a2ox}			10.9[f]		10.32	16.47	14.01	13.01
				Adenine				
pK_{a1}	3.1–3.3	3.8–4.0	3.6[g]	4.1[j]	3.79	3.16	3.13	4.68
pK_{a1ox}			4.2[h]		3.9	3.91	3.35	4.47
				Cytosine				
pK_{a1}	3.8–4.1	4.3–4.5	4.2[g]	4.5[j]	4.71	4.25	5.17	4.58
pK_{a1ox}					5.69	4.05	4.75	4.50
				Thymine				
pK_{a2}	9.7–9.9	9.9[c]	9.8[g]		9.98	13.99	11.95	11.65
pK_{a1ox}					1.69	3.15	2.31	3.55
				Uracil				
pK_{a2}	9.2–9.4	9.5[d]	9.2[g]	9.7[j]	9.59	13.48	12.57	10.32
pK_{a1ox}					1.52	1.52	2.92	1.64

[a]Acharya et al.[26] measured the pK_a's of deoxy/ribonucleosides 3′-ethyl phosphates using ^{1}H NMR. [b]Mucha et al.[30] studied deoxy/ribose nucleotides using the potentiometric titration method. [c]Available only for deoxyribose nucleotide. [d]Available only for ribose nucleotide. [e]Reference 19. [f]Reference 9. [g]Reference 20. [h]Reference 31. [i]Reference 24. [j]Reference 25. [k]Psciuk et al. calculated the pK_a and redox potential of methyl-substituted nucleobases at the B3LYP level of theory and with SMD solvation model with solvent cavity scaling using the geometries optimized at the 6-31+G(d,p) level of theory and the single-point energy calculated at the aug-cc-pVTZ level of theory.[45]

energy than those with the water at the protonation/deprotonation sites. pK_a's were calculated for each of these arrangements. Because the geometries with water at the protonation/deprotonation sites were found to be more stable, only the pK_a's for those geometries are listed in Table 1. Note that protonation and deprotonation necessarily involves a different position for the water when only one explicit water is included.

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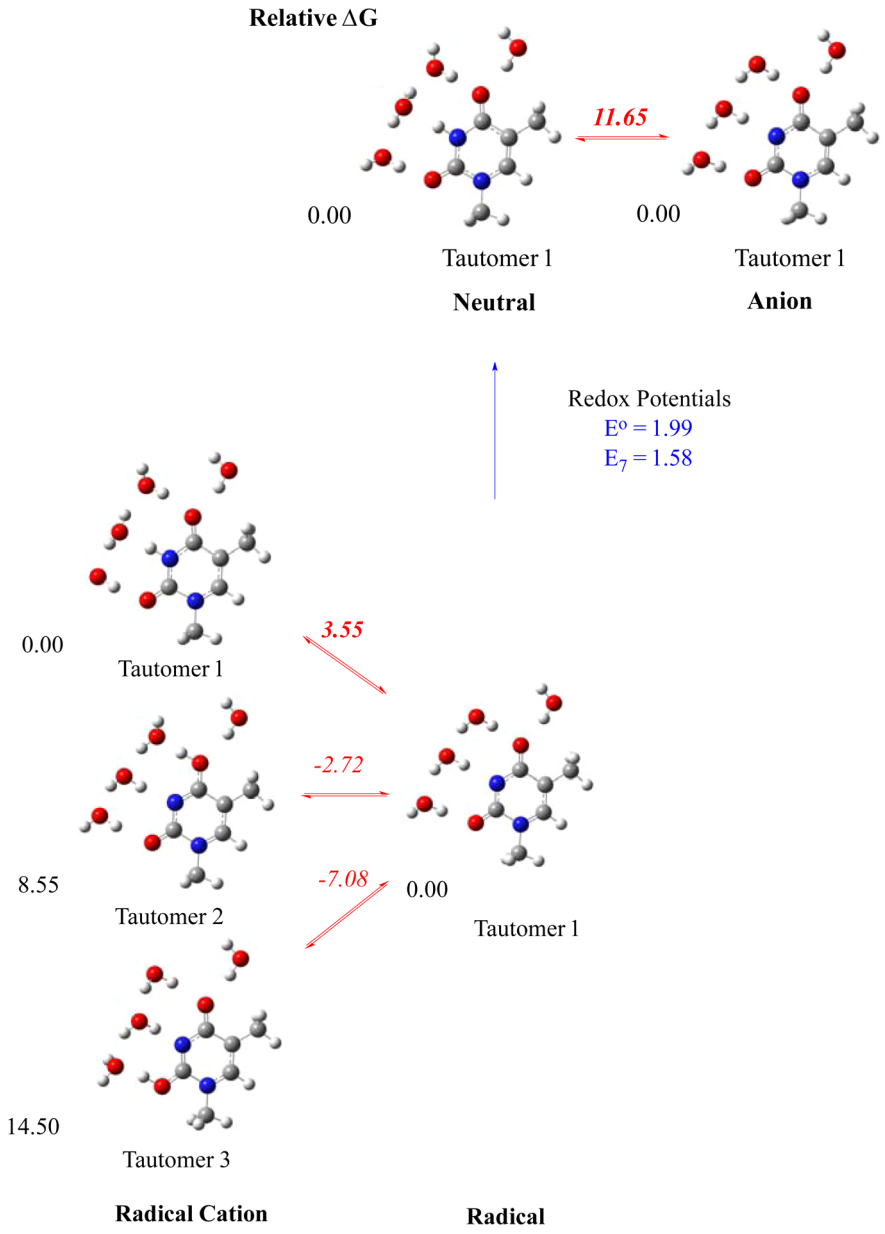

Figure 6. Calculated pK_a's and redox potentials for 1-methylthymine. For details, see the caption of Figure 2.

The calculation with one water molecule suggested that water at a hydrogen bonding site other than the protonation/deprotonation site can contribute significantly to the pK_a values. To cover the most important interactive sites, a second series of calculations was carried out. This included four explicit water molecules with four water−nucleobase hydrogen bonds and one or two water−water hydrogen bonds in addition to the SMD solvation. This allowed us to maintain the same explicit water−nucleobase environment for protonation, deprotonation, and oxidation. The lowest energy structures are shown in Figure 3−7.

The pK_a's with zero, one, and four explicit water molecules calculated at the B3LYP/6-31+G(d,p) level of theory are listed in Table 1. These values are compared with the experimental values for methyl-substituted and sugar-substituted nucleobases.[24,28] Details of the site specific pK_a's are available in the Supporting Information. Placement of one water near the protonation/deprotonation site improved the pK_a's over calculations without an explicit water molecule. The effect is moderate for the pK_{a1}'s that involve neutrals and cations. However, the effect is much larger for the pK_{a2}'s that involve anions; these are shifted ∼2 units closer to the experimental values. The influence of an explicit water on pK_a was also studied for a water hydrogen bonded to sites not involved in protonation/deprotonation. The effect was moderate for the cation−neutral equilibria but was more important for neutral−anion equilibria. Because the SMD solvation model has some difficulties in accounting for the solvation of anions, even a single water molecule can improve the pK_a calculations, and the effect is largest when the water is hydrogen bonded to the site of deprotonation.

As expected from the comparison of calculations with no water and one water, addition of more water molecules further improved the calculated pK_a's. For the cation−neutral equilibria, the effect of four explicit water molecules is still small but the values are in quite good agreement with

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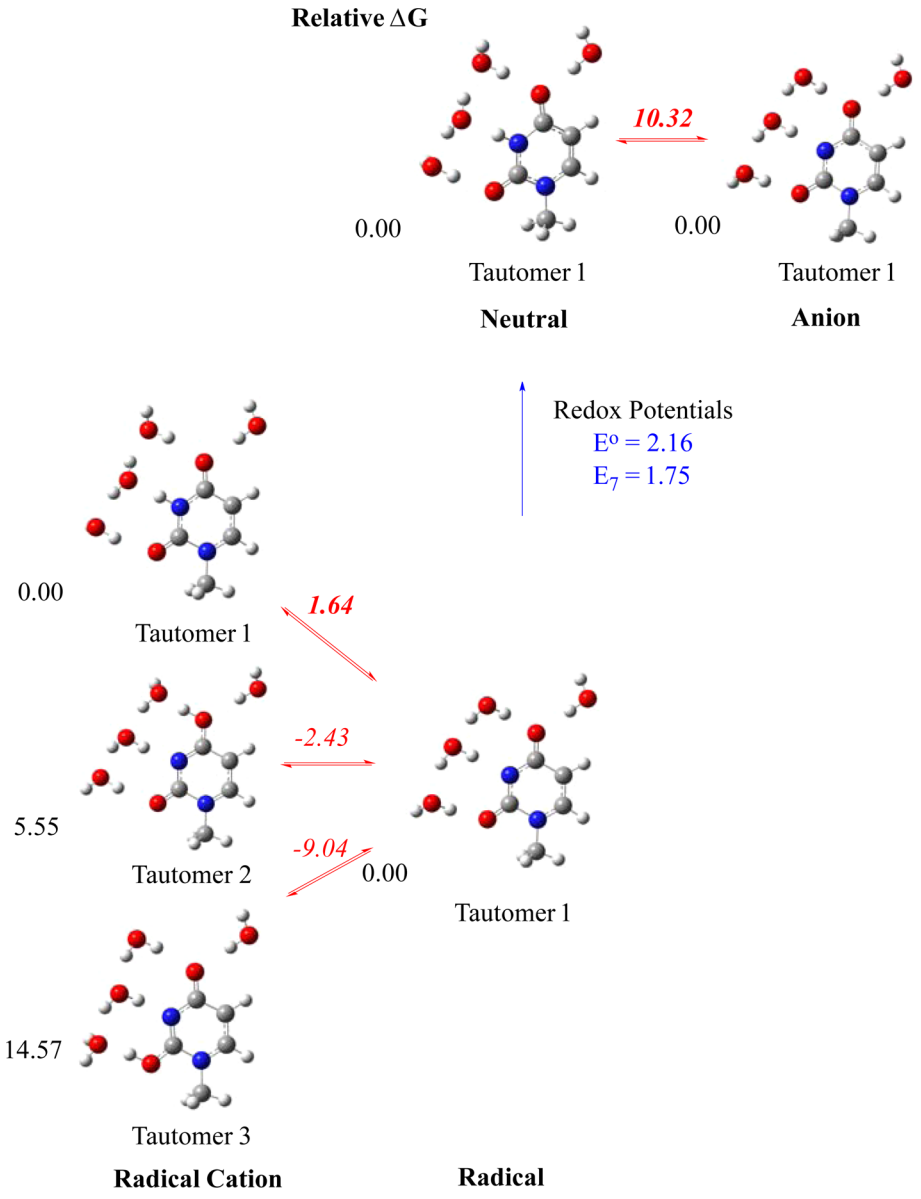

Figure 7. Calculated pK_a's and redox potentials for 1-methyluracil. For details, see the caption of Figure 2.

experiment with a mean absolute error (MAE) of 0.27 for pK_{a1}. For neutral−anion equilibria the improvement is much greater. The MAE for pK_{a2} is 4.6 with no waters, 2.6 with one water, and 1.7 with four waters. Inspection of the natural population analysis charges[77] shows that the differences in the charge distribution within the nucleobases upon protonation/deprotonation are the essentially the same with zero, one, and four explicit waters. This suggests that specific hydrogen bonding is the main reason for the improvement in pK_{a2}. Nevertheless, the calculated values are still further from experiment than desirable. Closer agreement with experiment can be achieved by introducing a cavity scaling factor for anions, as found in our previous studies.[40,45,46]

The $E°$ and E_7 reduction potentials vs standard hydrogen electrode (SHE) are summarized in Table 2 for the nucleobase in the present study. The best established experimental value in aqueous solution is E_7 = 1.29 V for guanine, obtained by Steenken and Jovanovic using kinetic rate measurements. Additional values for guanine E_7 range from 1.04 to 1.31 V, depending on the technique and whether the free base, methylated base, nucleoside, or nucleotide was measured. The other nucleobases have not been studied in as much detail, but there is also a considerable spread in their redox potentials. Some of the difficulties in getting a consistent and reliable set of experimental redox potentials for nucleobases can be attributed to solubility issues and problems of irreversibility on oxidation or reduction. The computed redox potentials are no doubt also biased by systematic errors. Because the purpose of the present investigation is to examine the effect of including a few explicit waters within an implicit solvent approach, it may be more informative to focus on the trends in the calculated numbers than to compare directly to experiment. The calculated results use eqs 6, 7, and 9 for $E(X^{\bullet},H^{+}/XH)$. The pK_a values presented in Table 1 indicate that all the unoxidized and oxidized species are in their neutral form at pH 7. The present B3LYP/6-31+G(d,p) calculations without explicit waters are in good agreement with earlier calculations with SMD solvation using larger basis sets and with higher levels of theory.[45] Compared to calculations with no explicit waters, the effect of one water is to lower the redox potential by an average of 0.07 V. Using four

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Table 2. Experimental and Calculated $E°$ and E_7 Reduction Potentials (V) in Aqueous Solution

	experimental			current study (methyl subst)[d]		
	ribose subst[a]	deoxyribose nucleotide[b]	Psciuk et al.[c] (methyl subst)	no water	one water	four waters
			Guanine			
$E°$	1.58		1.37	1.34	1.31	1.43
E_7	1.29	1.31	0.96	0.93	0.90	1.02
			Adenine			
$E°$	2.03		1.79	1.77	1.70	1.79
E_7	1.42	1.42	1.38	1.36	1.29	1.38
			Cytosine			
$E°$			2.07	2.04	2.03	2.10
E_7	~1.6	1.5	1.67	1.63	1.62	1.69
			Thymine			
$E°$			1.86	1.96	1.86	1.99
E_7	~1.7	1.45	1.45	1.55	1.45	1.58
			Uracil			
$E°$			2.13	2.18	2.17	2.16
E_7			1.72	1.77	1.76	1.75

[a]Steenken et al. measured the aqueous phase redox potentials of ribose-substituted nucleobases by kinetic rate measurements.[23,78] [b]Fukuzumi et al. reported the redox potential of DNA nucleotides obtained by cyclic voltametry measurement in aqueous medium.[27] [c]Psciuk et al. calculated the redox potential of methyl-substituted nucleobases at the B3LYP level of theory and with SMD solvation model with solvent cavity scaling using the geometries optimized at the 6-31+G(d,p) level of theory and the single-point energy calculated at the aug-cc-pVTZ level of theory.[45] [d]Reported potentials are calculated against the absolute standard hydrogen electrode (SHE) potential in aqueous solution (4.281 V).

explicit waters raises the redox potential by an average of 0.02 V. In both cases, the effect is relatively small and much less pronounced than the effect on pK_{a2}. This may be due to the fact that both species in the $E(X^{\bullet},H^{+}/XH)$ redox couple are neutral nucleobases.

CONCLUSIONS

The SMD implicit solvation model yields rather good results for nucleobase pK_{a1} calculations involving neutrals and cations. A modest improvement is obtained by including a few explicit water molecules near the site of protonation. For pK_{a2} calculations involving neutrals and anions, including explicit water molecules significantly improves the results, reducing the mean absolute error from 4.6 pK_a units with no waters, to 2.6 with one water and 1.7 with four waters. Solvent cavity scaling can be used to reduce this error further. In calculations of $E(X^{\bullet},H^{+}/XH)$ for the oxidation of nucleobases, adding explicit water molecules to the implicit solvation model does not appear to improve the results noticeably. Most likely, this is because both reactant and product in the $E(X^{\bullet},H^{+}/XH)$ redox reaction are neutral molecules.

ASSOCIATED CONTENT

Supporting Information

Details of the pK_a and reduction potential calculation are available in a spreadsheet. Structures and coordinates for the other nucleobases and their oxidized forms. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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