The Influence of Microhydration on the Ionization Energy Thresholds of Uracil and Thymine

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In the present study the ionization energy thresholds (IET's) of uracil and thymine have been calculated (with the B3LYP, PMP2, and P3 levels of theory using the standard 6-31++G(d,p) basis set) with one to three water molecules placed in the first hydration shell. Then (B3LYP) polarizable continuum model (PCM) calculations were performed with one to three waters of the hydration shell included. Calculations show there is a distinct effect of microhydration on uracil and thymine. For uracil, one added water results in a decrease in the IET of about 0.15 eV. The second and third water molecules cause a further decrease by about 0.07 eV each. For thymine, the first water molecule is seen to decrease the IET by about 0.1 eV, while the second and third water molecules cause a further decrease of less than 0.1 eV each. The changes in IET calculated here for thymine with one to three waters of hydration are smaller than the experimental values determined by Kim et al. (Kim, S. K.; Lee, W.; Herschbach, D. R. *J. Phys. Chem.* **1996**, *100*, 7933). Preliminary results presented here indicate that the experimental results may involve keto−enol tautomers of thymine. The results of placing the microhydrated structures of uracil and thymine in a PCM cavity was seen to make very little difference in the IET when compared to the IET of ordinary uracil or thymine in a PCM cavity. The implications are that accurate calculations of the IET's of uracil and thymine can be obtained by simply considering long-range solvation effects.

Introduction

This is the third article in a series aimed at calculating the ionization energy thresholds (IET's) of the DNA and RNA bases in the gas phase and in aqueous medium. Article I presented Møller−Plesset (MP2) IET calculations that were seen to deviate somewhat from the experimental results.[1] Calculations of IET's involve the difference in energy between the geometry of the optimized base and either the unoptimized base cation (vertical IET) or the geometry of the optimized base cation (adiabatic IET). Some of the results of the MP2 open shell calculations on the base cations were shown to be contaminated by higher order spin states. To significantly remove the spin contamination in the open-shell systems, projected (PMP2) calculations were performed. Calculations at the PMP2/6-31++G(d,p) level produced vertical IET's that differed from the experimental values by ca. 0.1 eV and adiabatic IET's that differed by 0.07 eV.

Article II presented similar IET calculations using density functional theory. Calculations at the B3LYP/6-31++G(d,p) level presented vertical IET calculations on the bases that differed from the experimental values by an average of 0.1 eV.[2] This article also contained a summary of more accurate electron propagator calculations (P3) on the bases that were shown to deviate from the experimental values of IET's by an average of only 0.05 eV. Both the density functional theory (DFT) calculations and the PMP2 calculations show the order of the IET's of the DNA bases as U > T > C > A > G.

In both articles I and II the level of the ionization energy calculations have approached the level of accuracy in the gas-phase experimental studies.[3] Articles I and II also presented calculations on the bases in a polarizable continuum model (PCM). In aqueous medium the ordering of the vertical and adiabatic IET's is the same as in the gas phase (U > T > C > A > G). Both previous studies neglected the influence of the first hydration shell on these IET calculations. In the present study the IET's of uracil and thymine have been calculated with one to three water molecules placed in the first hydration shell. Then PCM calculations were performed with one to three waters of the hydration shell included. The advantage of this "supermolecular" approach is the ability to account for the specific effects of hydrogen bonding of the solvated molecule and the long-range effects of the solvent.

Review of the Literature on Uracil and Thymine + $n(H_2O)$ Structures

It is not easy to calculate the positions of water molecules in the vicinity of the nucleic acid bases. Fortunately there is a great deal of information available in the literature about water clusters around the bases in the ground state. A review of the pertinent literature for uracil and thymine + nH_2O is presented here.

Much of the theoretical work on hydrated uracil was inspired by the work of Hendricks et al. which showed the transformation

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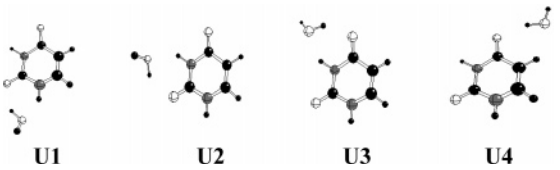

Figure 1. Structures of the four uracil monohydrates.

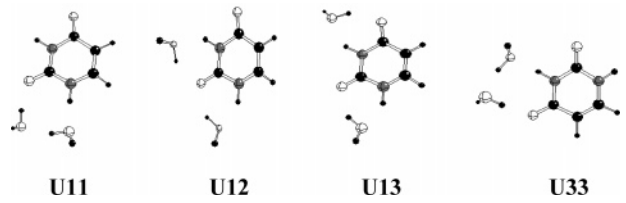

Figure 2. Structures of the four uracil dihydrates.

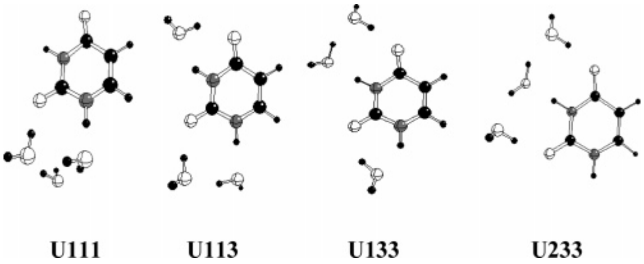

Figure 3. Structures of the uracil trihydrates.

from a dipole bound uracil anion in the gas phase to a covalently bound anion in uracil monohydrate.[4] This transformation was first modeled by Smets et al.[5] Rybak et al. studied the uracil−water interaction at two planar configurations of uracil monohydrates.[6] Nguyen et al.[7] have studied the same three uracil + $1H_2O$ complexes. Dolgounitcheva et al.[8] have found four isomeric structures of uracil + $1H_2O$, as have van Mourik et al.[9] The designations of the structures used by van Mourik are used herein (Figure 1). Dolgounitcheva et al. designations A−D are labeled herein as A = U3, B = U4, C = U1, and D = U2.

Several papers deal with uracil dihydrates (Figure 2). Ghomi et al. show a structure of uracil with one water near N1 and another near N3.[10] A paper by Gadre et al.[11] shows six uracil + $(H_2O)_2$ structures. A paper by van Mourik shows 10 different uracil + $(H_2O)_2$ structures.[12] In both of these papers some of the structures involve individual water molecules (U12, U13), while others involve water dimers (U11 and U33).

Smets et al. have shown the structure of a uracil trihydrate,[13] and Shukla and Leszczynski show the structures of a uracil trihydrate and several trihydrates involving uracil enol tautomers.[14] The paper cited above by van Mourik shows the structures of several uracil trihydrates. This paper discusses how many waters might be in the first hydration shell and concludes that a likely answer is three. A recent paper by Hu et al.[15] shows numerous uracil + $(H_2O)_n$ structures with $n = 1-4$, and a paper by Gaigeot and Ghomi discusses uracil + $(H_2O)_n$ structures with $n = 1-7$.[16]

There is an important experimental paper that makes use of heteronuclear Overhauser spectroscopy to actually measure and characterize the waters in the uracil hydration shell.[17] The authors concluded that there are three water molecules between the two amide groups of uracil. This would correspond to the uracil + $(H_2O)_3$ in the van Mourik paper labeled structure U133 (Figure 3).

A paper by Chandra et al. describes three thymine monohydrates.[18] The geometries are very similar to the uracil monohydrates discussed above. The positions of the waters in the uracil complexes were found to be satisfactory as starting geometries for the calculations presented herein on the thymine dihydrates and trihydrates. The paper cited above by van Mourik et al. shows the positions of four thymine monohydrates.[9] Their numbering schemes are the same as those for the uracil monohydrates shown in Figures 1−3 and are used herein.

The procedure followed was to begin with the effects of hydration on the IET of uracil and then to use these structures as a starting point for calculations on thymine + nH_2O. There do not appear to be any experimental data in the literature on the influence of hydration on the IET's of uracil. However there are experimental data for thymine + nH_2O, so the calculations presented herein can be compared with the experimental results. Finally, the IET's of uracil and thymine + nH_2O are calculated when these structures are placed in a PCM cavity.

Computational Methods

The procedure followed herein is to take the best geometries available in the literature for the bases with various waters of hydration as input parameters and to reoptimize the structures both at the B3LYP/6-31++G(d,p) level[19] and at the MP2/6-31++G(d,p) level. Calculations to obtain vertical ionization energies were performed at the B3LYP, PMP2, and P3[20] levels of theory using the standard 6-31++G(d,p) basis set. B3LYP frequency calculations were performed with the same basis set to verify stationary points. All calculations were performed with the Gaussian 98 suite of programs.[21]

The process for building a complex of a base with water molecules is to determine the structure of all possible monohydrated complexes. The complex with the lowest energy is chosen. A second water molecule is added, and the dihydrated complex with the lowest energy is selected. A third water molecule is added and the process repeated.

There do not seem to be good starting geometries in the literature for the radical cations of bases with waters of hydration. Attempts to compute these optimized geometries turned out to be very time-consuming. The present work therefore considers only vertical ionization energies for the uracil− and thymine−water complexes. Therefore the vertical ionization energies calculated herein involve the difference in energy between the cation radical and the neutral base in the geometry of the neutral species (optimizations of the neutral molecule using the 6-31++G(d,p) basis set followed by a single-point calculation on the cation).

Some of the MP2 calculations on the cations resulted in σ radicals with a majority of the spin density in an oxygen $2P_y$ orbital. These errant MP2 calculations have been corrected by exchanging HOMO and LUMO orbitals with the keyword guess=alter in the cation calculations.

Solvent effects were studied by performing self-consistent reaction field (SCRF) calculations using the PCM[22] with the integral equation formalism (SCRF=IEFPCM)[23] on the gas-phase optimized geometries of each base + nH_2O species. The results of the optimization on the base + nH_2O species in the PCM cavity were not reported as this was shown to have hardly any effect on the present IET calculations.

Results and Analysis

Uracil + $(H_2O)_1$. The optimized structures of four uracil monohydrates at the PMP2/6-31++G(d,p) level are presented in Table 1. The structure labeled U1, with the water in the vicinity of the N1−H and C2=O, is the most stable of the four structures. The ordering of the energies of the structures reported here is U1 > U3 > U2 > U4, in agreement with that reported by Dolgounitcheva et al.[24] and van Mourik et al.[9]

TABLE 1: PMP2 Energies for Uracil + $n\mathrm{H_2O}$ Structures

U + $n\mathrm{H_2O}$	*E*(PMP2) (hartrees)	vert IET (eV) PMP2	vert IET PCM (eV) PMP2
uracil	−413.694 8884	9.44	6.86
U1	−489.947 411	9.30	6.93
U2	−489.944 074	9.34	6.82
U3	−489.944 668	(10.37) 9.26	(8.14) 6.93
U4	−489.941 418	9.46	6.83
U11	−566.202 1602	9.22	6.85
U13	−566.197 4764	(10.32) 9.20	6.82
U33	−566.197 7884	9.24	6.76
U12	−566.196 1339	(11.09) 9.26	6.88
U111	−642.451 4274	9.21	6.79
U113	−642.452 3597	(10.27) 9.13	(8.16) 6.83
U133	−642.450 5631	(10.34) 9.11	(8.18) 6.79
U233	−642.449 6359	9.45	6.83

Uracil + $(\mathrm{H_2O})_2$. Optimization of the uracil + $(\mathrm{H_2O})_2$ complexes results in a tendency for the water molecules to dimerize. Some of these water dimers plus uracil have total energies lower than say the combination of the two lowest energy configurations of the monohydrates (for example U1+U3) as first pointed out by van Mourik.[12] The ordering of the total energies shown in Table 1 is U11 > U33 > U13 > U12. This is different from the ordering reported by van Mourik: U11 > U13 > U33 > U12. One sees, however, that U13 and U33 are very close together in total energy, so this difference most likely results from the use of slightly different bases sets (while van Mourik et al. are also performing geometry optimizations of uracil + water systems at the MP2 level, they use an interaction-optimized singly polarized double-ζ (DZPi) basis set), or possibly the fact that van Mourik et al. have included the small BSSE correction in their calculations.

Uracil + $(\mathrm{H_2O})_3$. Four structures including uracil and three waters of hydration were considered herein. The ordering in Table 1 shows U113 > U111 > U133 > U233, again using van Mourik's notation.[12] The ordering here agrees with the ordering computed by van Mourik; however, as noted, the energy of U111 is very close to the energy of U113. Our calculations on these two structures at the B3LYP level have U111 as the most stable structure.

In Table 1 (third column) one notes that for U2, U4, and U233, there is hardly any effect of microhydration on the IET. The dipole moment of the radical cations of these structures is very large, and it seems that for these particular placements of the waters of hydration there is little ability to quench this dipole moment.

Ionization Energies. Now the ionization energies of uracil with the inclusion of one to three waters of hydration can be calculated. The results are presented first in Table 1. As was discussed in Computational Methods, there are sometimes serious problems with the MP2 calculations. The results for the hydrated uracils shown in parentheses have vertical ionization energies higher than that of uracil. This is a problem with the MP2 calculations on the cations, but is not related to the problem of contamination from high-order spin states (as the table indicates, these are actually PMP2 results).[25] Rather the problem seems to be that the optimized structure determined in the calculation of the neutral molecule, and subsequently used as the geometry of the cation, sometimes ends up in structures of the wrong symmetry.[26] The corrected MP2 ionization energies are given in Table 1 on the right-hand side of each column.

TABLE 2: Ionization Energies (eV) of the Most Stable Uracil + $n\mathrm{H_2O}$ Structures

U + $n\mathrm{H_2O}$	PMP2 6-31++G(d,p)	B3LYP 6-31++G(d,p)	P3 6-311G(d,p)	P3 6-31++G(d,p)
U	9.44	9.46	9.54	9.61
U1	9.30	9.34	9.43	9.47
U11	9.22	9.25	9.36	9.40
U113	9.21	9.21	9.33	9.37

TABLE 3: PMP2 and B3LYP Energies for Thymine + $n\mathrm{H_2O}$ Structures

T + $n\mathrm{H_2O}$	*E*(PMP2) (hartrees)	vert IET (eV) PMP2	vert IET (eV) B3LYP	vert IET PCM (eV) B3LYP
thymine	−413.694 8884	9.07	9.01	6.71
T1	−529.137 8864	8.94	8.91	6.63
T2	−529.134 7937	9.05	8.98	6.63
T3	−529.135 0796	8.94	8.96	6.61
T11	−605.392 6748	8.90	8.84	6.64
T13	−605.387 8903	8.85	8.88	6.68
T33	−605.388 2756	(10.25) 8.84	8.88	6.61
T12	−605.386 8864	8.96	8.88	6.69
T111	−681.643 8357	8.83	8.76	6.61
T113	−681.642 9676	8.79	8.81	(8.16) 6.65
T133	−681.641 1750	8.77	8.81	(8.18) 6.64
T233	−681.640 5338	9.01	9.02	6.65

The vertical energies of the most stable structures from Table 1 have been included in Table 2. For all entries, three sets of calculations, projected MP2, B3LYP, and P3, are included. Starting with neutral uracil, the IET values for all three calculations are close to the experimental value of 9.50 eV. Another trend that seems evident here is that the PMP2 and B3LYP calculations all seem to give similar energies, while the P3 calculations all seem to be ca. 0.1 eV higher in energy. There are actually two sets of numbers in the P3 column. Most of the calculations that Ortiz and co-workers published are performed with the 6-311G(d,p) basis set.[8] Our P3 calculations with the 6-311G(d,p) basis set are included in Table 2. Since the other calculations performed here used diffuse basis functions, it was decided to include P3 calculations with the 6-31++G(d,p) basis set, and these are listed in the far right-hand column. These IET calculations are seen to be slightly higher than the calculations without the diffuse functions.

It would be very desirable to compare the consistent trends in Table 2 with experimental data. A paper by Kim et al.[27] on cluster beam chemistry does report ionization energies of hydrated adenine and thymine. A single water molecule is seen to reduce the IET of thymine by 0.3 eV. Additional waters decrease the IET in 0.2−0.1 eV steps.

Since uracil is so similar to thymine, one might expect the same behavior here for uracil. However the decreases in IET with additional water molecules for uracil, shown in Table 2, are considerably smaller than the experimental results observed in thymine. Several possibilities exist that might explain these differences: (1) for some reason uracil behaves differently than thymine, (2) the influence of hydration on the IET of uracil is different than for thymine, (3) the computational methods used here are faulty, or (4) the experimental results are being misinterpreted.

To address the first point, one has to admit that there are actually differences between uracil and thymine. Chemically uracil and thymine differ by a methyl group. In article II of this series it was shown that addition of a methyl group at N1 (to simulate the glycosidic bond) lowers the calculated IET of uracil by 0.4 eV. Experimentally the vertical IET of uracil is 9.50 eV, while that of thymine is ∼9.1 eV,[28] which does show the influence on a single methyl group. The second point can only be addressed by performing calculations on the hydration of thymine.

Thymine + $(\mathrm{H_2O})_n$. A complete analysis of the influence of waters of hydration on the IET of thymine has been undertaken and presented in Table 3. One notes that the calculated value of the IET of thymine is close to the experimental value of 9.1 eV for both the PMP2 and B3LYP

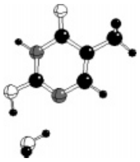

Figure 4. Monohydrated N3H−C2(enol)−C4(keto) thymine tautomer.

calculations. Addition of one water of hydration is seen to decrease the IET by 0.1 eV (for the most stable structure T1). Addition of a second water of hydration is seen to decrease the IET of thymine by only about 0.05 eV. The third water of hydration is seen to have very little effect on the IET of thymine. It is satisfying to note that these conclusions are nearly the same for the DFT and for the PMP2 calculations.

The results show that with the methods employed herein, the change in the IET of thymine with a few waters of hydration is very similar to the behavior that uracil exhibits in Table 2. Therefore at the present level of calculation, one does not see a decrease in the IET of either thymine or uracil by ca. 0.3 eV with the addition of a single water molecule. Also the addition of a second water does not decrease the IET of either thymine or uracil by ca. 0.2 eV. Kim et al.[27] report that for $T(H_2O)_3$ the drop in IET is 0.65 eV, whereas the largest decrease in Table 3 is only 0.30 eV (for T133).

Therefore the third possibility exists that the methods employed herein are not satisfactory for exploring the influence of waters of hydration on the IET's of thymine. There are two experimental results in the literature reporting the reductions of the IET found on adding a single water molecule to indole and a single ammonia molecule to phenol. For indole the decrease in IET is 0.38 eV [29] and 0.65 eV for phenol.[30] B3LYP calculations using the same basis sets as described above on a single water added to indole show a decrease in the IET of 0.37 eV. For the ammonia−phenol complex, the calculated decrease in IET is calculated to be 0.66 eV. These results indicate that the methods used herein should be capable of investigating the influence of waters of hydration on the IET's of uracil and thymine.

Finally it is necessary to look at the actual experimental results reported by Kim et al.[27] In their cluster beam experiments, the vertical ionization energy of unhydrated thymine was not actually measured.[31] The experimental values had to be scaled to match experimental IET's reported by Hush and Cheung.[28] For the changes in IET's reported for hydrated thymine one cannot rule out the possibility that those measurements involve the vertical IET of an enol tautomer of thymine plus water due to the relatively high water pressure and temperatures used in these experiments. The DNA bases have very low vapor pressures at room temperature and decompose when heated.

We have not completed the study on the influence of water on all six thymine keto−enol tautomers and rotomers. For the present study it is interesting to note that if one compares the computed IET of thymine (9.01 eV) to that of a monohydrated C2(enol)−C4(keto) thymine tautomer, Figure 4 (8.62 eV), the difference is 0.37 eV, which is more like the difference noted above for the effects of hydration on thymine by Kim et al.[27] A complete analysis of the effects of waters of hydration on the IET's of the various tautomers of thymine and uracil is in progress.

Ionization Energies in a PCM Cavity. Once the work was completed on the influence of discrete waters on the ionization energy of uracil, calculations were performed on the microhydrated uracil + nH$_2$O and the thymine + nH$_2$O molecules in a PCM cavity. The results are presented in the far right-hand columns of Tables 1 and 3. It is evident from these calculations that there is no real effect on ionization energies of placing the microhydrated uracil or thymine in a PCM cavity. The ionization energies for $n = 1-3$ discrete waters around either base molecule are essentially the same as for the ordinary base in a PCM cavity. One does note some errant PMP2 calculations shown in parentheses (Table 3), where the calculation produced a molecule in the wrong symmetry state as discussed above.

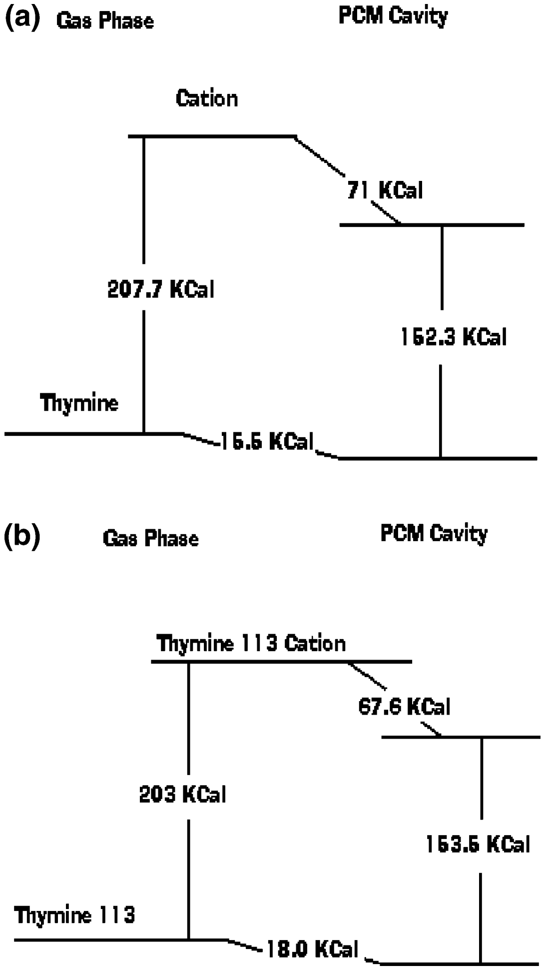

Figure 5. (a) Solvation of thymine. (b) Solvation of thymine 113.

To understand this effect, one has to compare the contribution to the solvation energy for thymine and the radical cation of thymine with the case of a microhydrated thymine and the radical cation in the PCM cavity. Figure 5 shows a plot of the energy differences for thymine and for T113 as an example.

One sees that while the solvation energies of the thymine and the radical cation are different for the two cases, the differences in energies in the PCM cavity are nearly identical, and hence the computed IET's are nearly identical.

It could be argued that this lack of an effect on the IET's in the PCM cavity might be due to the fact that optimizations were not performed on these species in the PCM cavity. A number of the structures in Table 1 were actually optimized in a PCM cavity. The energies of those that did converge were seen to hardly differ from the energies of the unoptimized structures in Table 1. For example, for U1, the IET computed on the structure optimized in the PCM cavity is 6.89 eV (vs 6.93 eV in Table 1). For U3 the IET is 6.98 eV (vs 6.93 eV in Table 1). Some of these calculations failed to converge after hundreds of iterations. The keywords SCF=QC cannot currently be applied to aid in convergence, and there are at the present time no results available on the "optimized" IET's for most of the entries in Table 1.[32]

There are other factors that may determine the effects observed here of the PCM cavity on uracil + $n\mathrm{H_2O}$ or thymine+ $n\mathrm{H_2O}$. Chandra et al.[18] have pointed out that one must consider the basicity of the oxygens and the acidity of the NH bonds in order to determine the most favorable H-bonding sites for water. For the monohydrates, the most stable uracil−water configuration, U1, is not at the site of the highest proton affinity, but the water is bonded to the oxygen with the smallest proton affinity and to the NH site with the highest acidity. So it will be necessary to extend these arguments to the dihydrates and trihydrates. Also it is important to extend these calculations to the other bases (which have fewer oxygens) in the presence of a few waters of hydration. These calculations are in progress.

Conclusions

Several important results have been presented here. First there is a distinct effect of microhydration on the vertical IET's of uracil and thymine in the gas phase. For uracil, one added water results in a decrease in the IET of about 0.15 eV. The second and third water molecules cause a further decrease of about 0.07 eV each. For thymine the first water molecule is seen to decrease the IET by about 0.1 eV, while the second and third water molecules cause a further decrease of less than 0.1 eV each.

The changes in IET calculated here for thymine are smaller than the experimental values determined by Kim et al.[27] Preliminary results present here indicate that these experimental results may involve keto−enol tautomers of thymine. A complete analysis of the effects of waters of hydration on the IET's of the various tautomers of thymine and uracil is in progress.

Finally, the results of placing various microhydrated structures of uracil and thymine in a PCM cavity was seen to make very little difference in the IET when compared to the IET of ordinary uracil or thymine in a PCM cavity. The implications are that accurate calculations of the IET's of uracil and thymine can be obtained simply by considering long-range solvation effects.[33] An analysis of the effects of hydration on the other bases is in progress.

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(25) To give one example from Table 1, for U3, the expectation value of $\langle S^2 \rangle$ is 1.01 for the cation used to calculate the IET = 10.37 and 0.84 for the IET = 9.26.

(26) This is easy to determine from an orbital population analysis. For example, in Table 1, three of the monohydrates have IET's of ca. −9.3 to −9.4 eV, while the IET of U3 is computed to be −10.37 eV. For the cation, U3 has a majority of the spin density in an oxygen 2Py orbital, while the other three monohydrate geometries are normal uracil π-cations with spin density shared between C5 and N1.

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(31) Correspondences with Professor Kim (Seoul National University) to establish that this is indeed the case are gratefully acknowledged.

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(33) It should be noted that calculations by Schuster's group indicate that vertical ionization potentials are strongly dependent on the hydration level of the bases in DNA oligomers (Barnett, R. N.; Cleveland, C. L.; Landman, U.; Boone, E.; Kanvah, S.; Schuster, G. B. *J. Phys. Chem. A* **2003**, *107*, 3525), and Schaefer's group has commented that the use of continuum models to study solvent effects "would necessarily degrade the theoretical results" (Evangelista, F. A.; Schaefer, H. F., III. *J. Phys. Chem. A* **2004**, *108*, 10258).