

Low Energy Electron Interactions with Uracil: The Energetics Predicted by Theory

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Low energy electrons (LEEs) induce strand breaks and base damage in DNA and RNA via fragmentation of molecular bonding. This includes the formation of hydrogen atoms from N–H and C–H bond dissociations in the bases thymine, cytosine and uracil, respectively. To better understand the dissociation of uracil induced by LEEs, we theoretically characterized the potential energy surfaces (PESs) along the N–H and C–H bonds of the uracil anion, as well as the energetics involved. The PESs show that an activation barrier of less than 1 eV exists for the N₁–H dissociation with rather flat PES beyond N–H = ~1.5 Å. The PESs for C₅–H and C₆–H show larger barriers, which increase monotonically with bond stretching. All the N–H and C–H bond dissociations are endothermic; the adiabatic PESs suggest the energy threshold for formation of hydrogen from N–H and C–H bonds are in the order: 0.78 (N₁–H) < 1.3 (N₃–H) < 2.2 (C₆–H) < 2.7 eV (C₅–H). The H-deleted uracil radicals (U-yl radical family) are found to have exceptionally high adiabatic electron affinities, namely, 3.46 (N₁), 3.8 (N₃), 2.35 (C₅), and 2.67 eV (C₆). During the H bond breaking process of an uracil transient anion, these electron affinities compensate the extra energy needed to break the N–H or C–H bonds. This process may therefore explain the large hydrogen yield found experimentally from uracil upon attachment of LEEs. Potential applications of this process for the synthesis of uracil analogues using LEE irradiation are suggested.

Introduction

It is now well established that low energy electrons (LEEs) can cause DNA damage including strand breaks, via fragmentation of its basic constituents (e.g., the DNA bases, deoxyribose phosphate backbone, and structural H₂O).^{1–7} At energies below 15 eV, dissociative electron attachment (DEA)⁴ is a major mechanism leading to the dissociation of these basic constituents.^{4,5} Other cellular macromolecules such as RNA are expected to be damaged by LEEs in a similar manner. Recent experiments^{8–10} in the gas phase have confirmed that LEEs induce substantial fragmentation in uracil, thymine, and cytosine via DEA. The most efficient DEA reaction involves the attachment of a LEE to form a temporary anionic base that dissociates into a negative ion plus a hydrogen atom. It was found that for uracil, such a DEA process can occur even with electron energy well below 1 eV.⁸ In a nucleic acid several electronvolts would be required to produce the H-atom from uracil N₃–H or C–H sites because the most active N₁ site is the site of the ribose attachment.⁸ The resulting H atoms would be quite damaging, as they may form sugar radicals by hydrogen abstraction, which could lead to a strand break. It was also found that LEEs can induce ring fragmentation of DNA bases, such as thymine and halouracils.^{11,12}

The reason uracil dissociates so easily on LEE attachment has been attributed to the high electron affinities (EA) of the U-yl radicals,⁸ which are formed by detaching one of the four hydrogen atoms at the N₁, N₃, C₅, or C₆ positions. The energy released by the binding of an electron to the U-yl radical reduces the overall energy needed to fragment an N–H or C–H bond.

For example, the EAs were calculated⁸ to be 3.6, 4.0, 2.5, and 2.8 eV for U-yl radicals at site N₁, N₃, C₅, and C₆, respectively. By comparing the EAs to the binding energy of hydrogen at these sites, it was calculated⁸ with the P2MP2 method¹³ that the energy thresholds for H abstraction are 0.8, 1.4, 2.7, and 2.2 eV, respectively. These thresholds reflect the overall energy change, but it is of interest to have a detailed potential energy surface (PES) along the bond stretch to better describe the course of H abstraction.

The PES for C₅–H bond in the uracil anion has been characterized.¹⁴ This work characterizes the PES and the energetics involved in fragmentation of *each* of the C–H and N–H bonds in the uracil anion and thus provides a more detail description of the unimolecular dissociation pathways of the uracil anion after attachment of a LEE. We note that there are two type of anions of uracil observed experimentally at sub-excitation energies,^{15–19} dipole-bound and valence-bound anion. Because dipole-bound anions are formed via electron capture in the long range portion of the potential of the permanent dipole of a molecule, they are likely to be absent in the condense phase, particularly within a cellular environment. In fact no such states have so far been observed in the condense phase.^{4,20} Thus, we focus our investigation to the PESs representing the valence-bound anions, which are more biologically relevant. However, calculations for negative ion species with low EAs often find that the dipole-bound state mixes with the valence states. In this work we find that DFT calculations are confined to valence states.

Methods

All geometry optimizations, as well as the adiabatic potential energy surface (PES) searches, were performed in the gas phase using the DFT B3LYP functionals with 6-31+G(d) basis set

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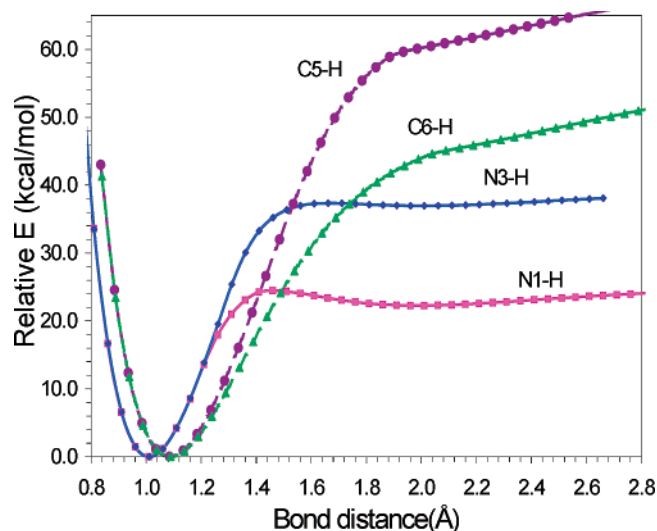


Figure 1. Adiabatic potential energy surfaces of anionic uracil along each N–H or C–H coordinate, calculated at the B3LYP/6-31+G(d) level. Energy relative to that of the optimized anion in the equilibrium state. Zero point energy is not included.

provided in the Gaussian 98 program package.²¹ The accuracy of this level of theory has been well demonstrated elsewhere.^{22,23} It should be pointed out that no dipole-bound state contribution to the uracil's equilibrium anionic state is found at this level of theory.²³ Adiabatic potential energy surfaces (PES) along the C–H or N–H bond stretch were calculated using optimization keyword `opt=ModRedundant`, with the `S` action code in the additional input, which performs geometry optimization for each point along the specified range of C–H/N–H distances, from ~ 1 up to 3.0 Å. The optimized geometries found along the coordinates were further verified by frozen distance optimizations, which also served to obtain information about the charge/spin distributions and molecular orbital symmetry. Transition states are located by specifying `opt=QST2` keyword, with the geometries of equilibrium uracil anion and the dissociative state as input.

With the optimized geometries, frequency calculations (without scaling) were performed at B3LYP with the aug-cc-pVDZ basis set to obtain zero-point corrections to energy (ZPE), the sum of electronic and thermal enthalpies (H), and the sum of electronic and thermal free energies (G). These values were used to calculate "gas phase" ΔH and ΔG for each reaction. Energy calculations at the CBS-Q²⁴ level were also performed for comparative purposes. CBS-Q calculations give excellent results for bond dissociations and electron affinities with average errors reported for bond dissociations as less than 1 kcal/mol (maximum ca. 2.3 kcal/mol) for a large range of systems.²⁴ For example, benzene C–H bond dissociation at the CBS-Q level is in excellent agreement with experiment with only a 1 kcal difference.

Results and Discussion

1. Potential Energy Surfaces (PES). Figure 1 shows the adiabatic anionic PESs along each N–H or C–H bond, calculated at the B3LYP/6-31+G(d) level, without ZPE corrections. The PESs along the two N–H coordinates lies lower than the two C–H's. Apparent transitional maxima are found along the N–H PESs near the point of crossing of the π^* and σ^* surfaces (see below) but are basis set dependent and diminish with the larger basis set aug-cc-pVDZ. However, the C–H PESs exhibit a monotonically increasing potential as the bond stretches.

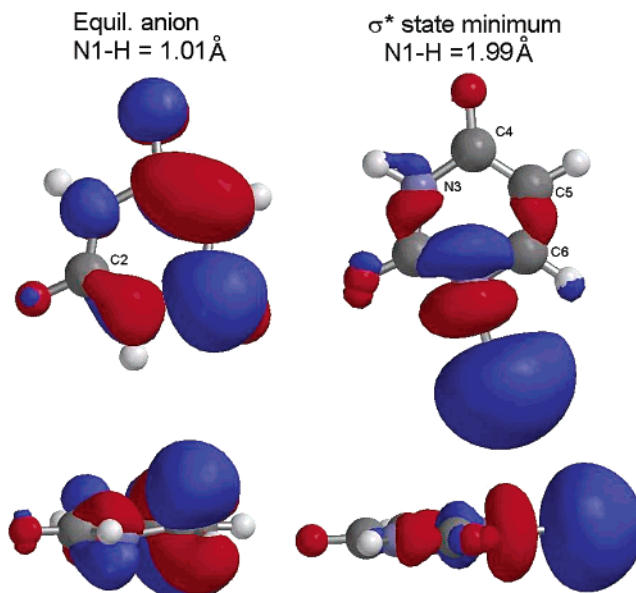


Figure 2. Calculated SOMOs at the equilibrium geometry 1.01 Å and dissociative σ^* state (1.99 Å) at B3LYP/6-31+G(d). The equilibrium anion is predominantly in the π^* state.

Multiple low lying PESs had been reported for C₅–H and C₅–X's of halouracil anions.^{14,25} Two C₅–H PESs were found¹⁴ to correspond to the uracil anion either in planar or nonplanar geometry, with that in nonplanar geometry lying slightly lower than that of the planar geometry, as expected, because the most stable uracil anion is nonplanar.²⁶ Three low lying PESs of anionic halouracils were described¹⁴ along the C₅–X coordinate: a pure π^* and a σ^* state PESs in planar geometries, and a lower lying nonplanar mixed state PES in which the nonplanar mostly π^* state becomes a mostly σ^* state at the crossing of the two pure states PESs. It is interesting to note that all the C–H and N–H PESs of uracil anion show much larger barriers to dissociation than to dehalogenation of the anionic 5-bromouracil (1.88 kcal/mol) and 5-chlorouracil (3.99 kcal/mol),¹⁴ but the anionic halouracils have transitional line shapes similar to those of anionic uracil's N–H PESs.

In the current work for the uracil N–H and C–H dissociations we find that the π^* and the σ^* states exist as well. The π^* and the σ^* states characteristics are visually shown in Figure 2, which shows the SOMO of uracil equilibrium anion radical (mostly π^* state) and the SOMO of the anion radical in its σ^* state at a local minimum (N₁–H = 1.99 Å). The pure π^* and σ^* states each have a separate potential energy surfaces (PES). For example, Figure 3 shows several PESs along the N₁–H bond: one planar π^* state at short distances, one planar localized σ^* state at long distances (H atom and U-yl[−]) that branches to a projected localized antibonding orbital, and a calculated σ^* state (based on a symmetry conserved calculation) in which a dipole-bound contribution becomes dominant at the short distance minima. The energy of this state is substantially too high and is not realistic because the basis set used is not sufficient for describing a true dipole-bound state. Nevertheless, the calculations suggest the tendency, i.e., in a reverse process in which the H atom approaches and forms the C–H bond, the electron will be ejected into a dipole-bound state if symmetry is maintained and the system is not allowed to cross over to the lower energy-bound π^* state. The lowest energy nonplanar mixed state shown in Figure 1 provides the low energy path between the initial mainly π^* state and final nonbonding σ^* state. The surface at the energy minima at short distances is

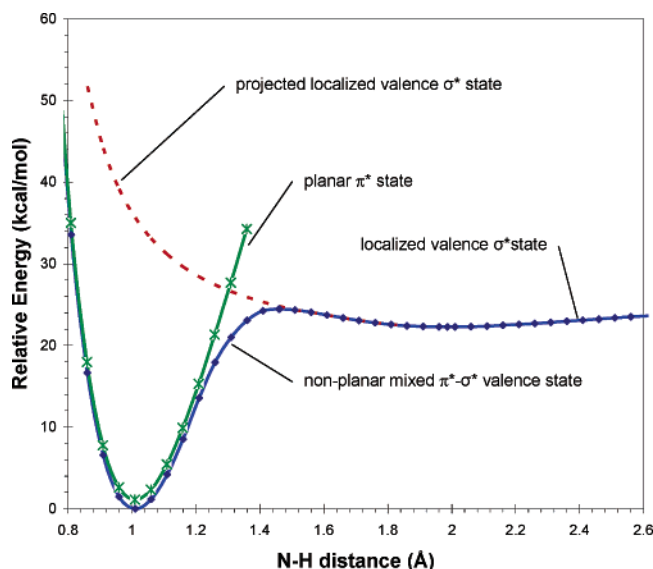


Figure 3. Uracil anion radical PESs along the N_1 -H coordinate, calculated at the B3LYP/6-31+G(d) level. The green curve represents the planar valence π^* state in which symmetry is conserved during the calculation. On allowing for molecular relaxation the lowest energy blue curve is found, which starts at short distances within a mainly π^* state and at long distances, crosses to a σ^* state. Conserving σ^* symmetry and calculating from long (2.6 Å) to short distances we find the same energies until 1.4 Å at which the calculations deviate to lower energies by mixing with a diffuse state (not shown). The red section is a projection of an expected localized σ^* state to short distances.

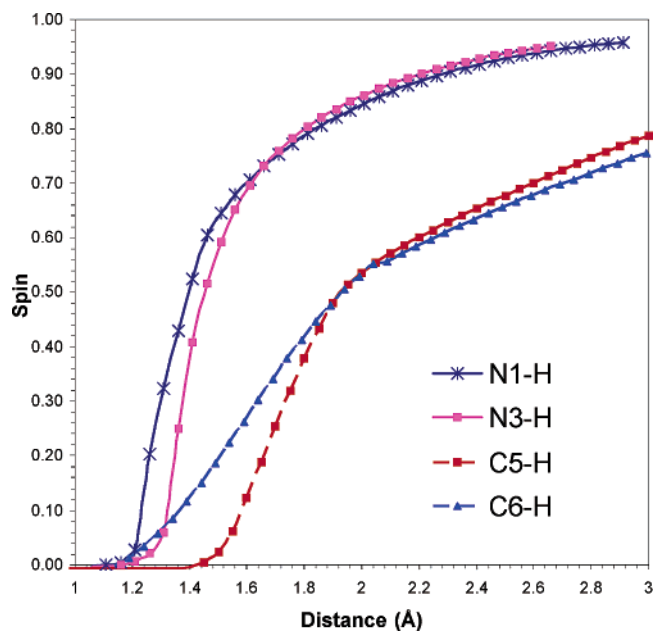


Figure 4. Spin distribution on the hydrogen as it leaves uracil anion. Method: B3LYP/6-31+G(d). See Supporting Information for the corresponding charge distribution drawing.

dominated by a delocalized π^* state that has no significant effect on the N-H or C-H bond strength. At longer distances a truly antibonding and localized σ^* state is found in which the electron is captured by the sp^2 lone orbital on the N or C atom that is bonded to the leaving H atom. The spin densities on hydrogen reported in Figure 4 are an excellent reporter of the fraction of the localized σ^* state.

The PESs shown in Figure 1 reflect the energy path for dissociation of a hydrogen atom from a valence-bound uracil anion. Clearly, these paths suggest that such processes are not thermodynamically favorable; the calculations suggest that an

TABLE 1: Energetics for Infinite Separation in the Gas Phase (kcal/mol, ZPE correction included): Uracil Anion (or Neutral) $\rightarrow$ U-yl $^-$ + H

H site	method	anion as reference			neutral as reference			ref 8
		ΔE	ΔH	ΔG	ΔE	ΔH	ΔG	
N_1	DFT ^a	21.47	22.37	15.72	16.40	17.71	9.84	18.5
	CBS-Q ^b	19.47	20.07	13.47	19.43	20.02	12.26	
N_3	DFT	33.90	34.95	27.96	28.82	30.28	22.08	32.3
	CBS-Q	31.49	32.08	25.00	31.45	32.04	23.78	
C_5	DFT	66.30	67.46	60.12	61.23	62.79	54.24	62.3
	CBS-Q	64.78	65.38	58.02	64.74	65.33	56.80	
C_6	DFT	52.33	53.31	46.53	47.26	48.64	40.65	50.7
	CBS-Q	51.36	51.95	45.16	51.31	51.91	43.95	

^a B3LYP/aug-cc-pVDZ, based on geometry optimized at B3LYP/6-31+G(d). ^b At 298.15 K. ^c P2MP2 method.

energy input of at least 0.8 eV is necessary for the dissociation to occur. At 0 eV an electron should not be able to induce DEA in uracil. In fact, the experimental observation⁸ of uracil anion fragmentation near 0 eV is now recognized as an artifact.^{9,10}

2. Energetics. More accurate energetics data are necessary besides the PES to show the general tendency. Two sets of data were calculated for the dissociation of the uracil anion: one is by DFT B3LYP/aug-cc-pVDZ//6-31+G(d); the other is by the complete basis set method (CBS-Q).²⁴ Table 1 lists the ΔE , ΔH , and ΔG calculated by both methods for dissociation of an uracil anion into infinite separation of a H atom and a fragment U-yl $^-$ ion. These values were also calculated using neutral uracil as reference.

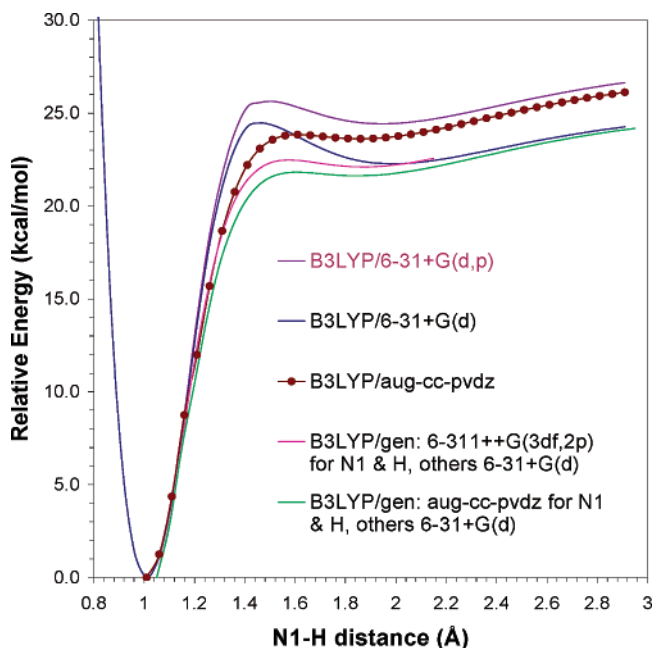
For the uracil anion as reference, the values by DFT are ca. 2.5 kcal/mol systematically higher than those by CBS-Q. However, with neutral uracil as reference, DFT is generally lower than CBS-Q by ca. 2.5 kcal/mol. This difference arises from the difference of electron affinity of uracil calculated by each method, which are 0.22 eV (5.1 kcal/mol) by B3LYP/aug-cc-pVDZ and 0.002 eV (0.04 kcal/mol) by CBS-Q. With this exception, both methods are in good agreement. These levels of theory (especially CBS-Q) are sufficient to give reasonably accurate predictions of the bond dissociation energy. However, for the CBS-Q method, which involves multiple step calculations at HF, MP2, QCISD(t), and MP4 levels,²⁴ we find that the energy difference between the neutral and the anion is negligible; this suggests no significant binding of the electron to the neutral molecule. This brings in the possibility that diffuse states such as the dipole-bound anionic state¹⁹ mix with the valence state. Support for this possibility comes from a check of the natural bond orbital analysis for the CBS-Q calculation, which shows about one-third of an electron is in diffuse Rydberg type orbitals (0.338) for the uracil anion radical at its minimum. The CBS-Q calculation suggests the valence- and dipole-bound states are quite close in energy. Experiments for uracil anion show the dipole-bound state is stable by 0.093 eV^{19a} and the valence electron affinity is near 0.070 eV.^{19b} Assuming the experiments are correct, we would conclude the DFT calculation overestimates the valence electron affinity by ca. 0.15 eV (3.5 kcal/mol).

From these results it is obvious that least energy is required to detach a hydrogen atom from N_1 of anionic uracil, with a minimum energy input of around 20 kcal/mol (~ 0.87 eV), followed by N_3 . Then C_6 and C_5 have the most difficult bonds to fragment (Table 1). Taking the electron affinity of neutral uracil into account, the threshold energies for fragmentation are ca. 18 kcal/mol (0.78 eV) for N_1 , 30 kcal/mol (1.3 eV) for N_3 , 50 kcal/mol (2.2 eV) for C_6 , and 63 kcal/mol (2.7 eV) for C_5 , estimated from both DFT and CBS-Q data sets. By comparing

TABLE 2: Energetics for N–H Separation (Å) to Plateau Minimum of the Uracil Anion Radical^a

H site	B3LYP			CBS-Q	
	N–H at plateau minimum	ΔE 6-31+G(d)	ΔE aug-cc-pVDZ ^b	N–H	ΔE
N ₁	1.99	22.27	23.74 (19.10) ^c	2.97	19.01
N ₃	2.01	36.96	37.39 (32.18) ^c		

^a $\Delta E = E(\text{N–H} = 1.02 \text{ Å}) - E(\text{N–H at plateau minimum})$ in kcal/mol. ^b Based on B3LYP/6-31+G(d) geometry. ^c Values in parentheses are ZPE corrected.

**Figure 5.** Comparison of uracil anion's N1–H potential energy surface calculated with different methods.

these to the U-yl[−] ion yield curve reported by Hanel et al.,⁸ the threshold peak at 0.7 eV is only 0.1 eV below the value found for N₁–H dissociation, whereas the highest peak located at ca. 1.1 eV is 0.2 eV below our calculated value for N₃–H dissociation. However, in the actual experiment thermal energies will lower the effective barrier; thus dissociation from vibrationally excited states, as well as possible interaction of the dissociative anion with the environment, may alter the resonance pattern.

Table 2 lists the N–H distances to the minimum in the plateau of the PES and the energy changes relative to equilibrium anion. Energetics calculated with different basis sets give slightly different values. This basis set dependence is expected and is not large.

Figure 5 shows the basis set dependence of the shape of the PES surface for the N1–H separation. Clearly, the small transition barrier is basis set dependent and is not present in the C₅–H or C₆–H surfaces although it is also present in the N₃–H surface. Thus, the small barrier for N–H may be an artifact of the calculations. However, results presented below suggest an alternative explanation; i.e., the barrier is real for N–H surfaces and nonexistent for C–H surfaces

3. Charge and Spin Distribution as the H Atom Recedes. Multiple fragments from dissociation of uracil or other bases after LEE attachment have been identified.^{8,11,12} Here we show the most likely products resulting from breaking of the N–H or C–H bonds. Figure 4 exhibits the spin density on the departing H as the N–H or C–H distance is stretched. As can be seen, as the internuclear distance increases, the spin density

TABLE 3: Adiabatic Electron Affinities of U-yl Radical Family (eV)

	H removed site			
	N ₁	N ₃	C ₅	C ₆
B3LYP/6-31+G(d)	3.46 (3.48) ^a	3.78 (3.82)	2.34 (2.30)	2.67 (2.68)
B3LYP/aug-cc-pVDZ ^b	3.44 (3.46)	3.79 (3.84)	2.34 (2.30)	2.66 (2.66)
CBS-Q ^c	3.49	4.16	2.38	2.68
ref 8 ^d	3.6	4.0	2.5	2.8

^a Values in electronvolts. Values in parentheses are without ZPE correction. ^b B3LYP/6-31+G(d) geometry. ^c 298.15 K. ^d P2MP2 method.

on H increases steadily. It increases more rapidly at shorter distances, especially for the N centers, and tends toward a saturated value of 1 beyond 1.5 Å. On the other hand, the charge distribution on H (figure available as Supporting Information) shows that at normal N–H or C–H distance, the net charge on H is positive, which decreases quickly initially as distance increases and approaches a neutral value of 0. Both spin density and charge distribution on H suggest that the H is departing as a neutral atom, the remaining fragment is, of course, a negative ion.

The unpaired spin distribution in the uracil π^* anion radical at its minimum energy is localized largely at C₆ (60%; see Supporting Information) with no substantial spin at C₅. This likely accounts for the lower barrier to dissociation for C₆–H vs that found for C₅–H as well as the delay in spin transfer to H in the C₅–H (Figure 4).

4. U-yl Radical Family. The geometry of the four radicals and their electron adducts (anions), optimized at the B3LYP/6-31+G(d) level, are provided as Supporting Information. The electron affinities of the U-yl radicals have been considered a major contributing factor in the breaking of N–H or C–H bonds after attachment of an electron to uracil.⁸ Table 3 lists the adiabatic electron affinities (AEA) of this radical family calculated by three methods: B3LYP/6-31+G(d) or aug-cc-pVDZ basis set, and CBS-Q. The three set of data are in excellent agreement, except that the results for N₃ by the CBS-Q method differ significantly from those obtained by the DFT method. Clearly, the AEA of this radical family is in the order N₃ (3.8 eV) > N₁ (3.46 eV) > C₆ (2.67 eV) > C₅ (2.35 eV).

Abdoul-Carime et al.²⁸ had estimated the vertical detachment energy for the U-yl anion at “C₅” to be 3.2–3.5 eV, on the basis of experimental observation. We have reported¹⁴ the VDE of this anion to be 2.74 eV, calculated at B3LYP/6-31+G(d) and without ZPE correction. There is a gap between the theoretical value and experimental estimate, and we were unclear on the reason. However, the data listed in Table 3 provide a likely explanation for the gap; i.e., the experimental resonance peak used to estimate the VDE is likely the result of hydrogen lost from the N₁ position.

The substantially higher electron affinities at the nitrogen radical sites vs the carbon radical sites in Table 3 suggest that on approach of the hydrogen atom to the uracil anion fragment the energetics would be substantially different for N–H and C–H systems, as is found in the potential surfaces calculated in this work (Figure 1). Further, it is possible that the small repulsive potential found for the H + Uyl(N[−]) surfaces is real and a result of the stability of the Uyl(N[−]) system. The shapes of the potential surfaces predict that an approaching hydrogen atom is more attracted to the carbanion sites than nitrogen anion sites. This is also indicated in Figure 4, which show the reluctance of the nitrogen sites to interact toward the hydrogen atom by spin transfer. This reluctance would have impact on the lifetimes of these species in the gas phase. In the aqueous phase, both types of anions would protonate quickly. Because

we have found a substantial basis set dependence for this small barrier, only improved calculations will be able to determine it's true magnitude.

The ease of production of the uracil N_1 anion fragment by LEE may find potential applications in synthesis of uracil analogues. Irradiating a mixture of uracil with potential substitute compound with LEEs, new uracil analogues may be created.

Finally we note that recently it was pointed out in other work that²⁷ "the largest contributions to the measured DEA cross sections in the gas-phase arise from the dipole-bound states. ... Furthermore, the process yielding such fragments as $(U-H)^- + H$ does so in part because of facile H atom tunneling through the barrier." Our results, which emphasize valence states, clearly show that a substantial energy input is essential for the dissociation to occur. Scheer et al.²⁷ suggest that in the gas phase a dipole-bound state is favored and may aid the initial capture of the electron, although they also report a substantial barrier of ca. 20 kcal/mol. They suggest a vibrationally excited dipole-bound state could undergo dissociation by tunneling and crossing to a valence σ^* state. As recognized by Scheer et al., tunneling is of aid only at vibrational excitation energies above bond dissociation energy. In our work we calculate potential energy surfaces for the valence anion, which will be the only stable anion state in condensed media, and find a ca. 20 kcal dissociation energy (see the minimum energy surface in Figure 3). We find for the valence states that the portion of the barrier at which tunneling would be important, i.e., the portion above the dissociation energy, is likely only a few kcal/mol, whereas Scheer et al. suggest a far larger value of ca. 0.5 eV (11.5 kcal/mol) owing to an avoided crossing of the dipole-bound and σ^* states of the same symmetry.²⁷ We note that accurate estimates of the section of the barrier where states cross, especially those of same symmetry, require multireference calculations that include more than single determinate approaches used in our work.

Summary

Our results are in good accord with earlier calculations for the electron-induced N–H and C–H bond dissociation energies of uracil.⁸ The potential energy surfaces calculated via DFT in this work show the electron may attach to the uracil initially in a near pure π^* valence state and this state intersects with an antibonding σ^* state on bond extension. The bond dissociation energies are found to be lower for N–H than C–H bonds and this is explained in part by the driving force provided by the higher electron affinities of the N radical sites over the C radical sites on uracil.

CBS-Q calculations suggest the valence electron affinity of uracil is near zero, which is in agreement with experiments that find the dipole-bound state is bound by 0.093 eV^{19a} and the valence electron affinity near 0.070 eV.^{19b} Thus in the gas phase the initial stable state is likely the dipole-bound state. Consequently, it is also likely that our DFT calculations overestimate the valence electron affinity by ca. 0.15 eV. We note, however, that it is the valence states that are applicable to the biological systems in condensed media. Thus the shapes of the PES calculated in this work for the π^* intersection with an antibonding σ^* state are pertinent to condensed media, systems in which the avoided crossing of the dipole-bound and the antibonding σ^* states predicted for the gas phase will not be found.²⁷

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Supporting Information Available: Optimized geometry of U-yl radicals and their anion, figure comparing PES. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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