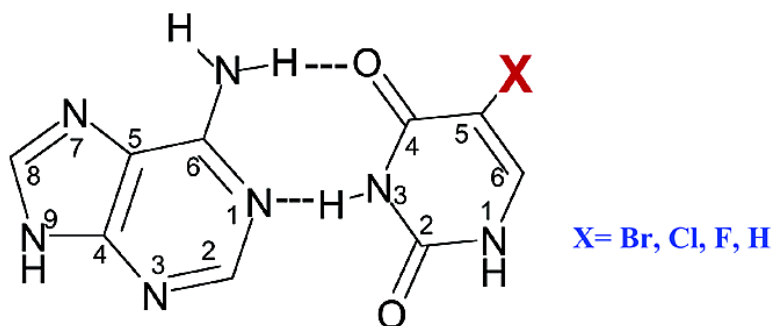


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DFT Investigation of Dehalogenation of Adenine–Halouracil Base Pairs upon Low-Energy Electron Attachment

Xifeng Li,[†] Michael D. Sevilla,^{*,‡} and Léon Sanche^{†,§}

Contribution from the Group of the Canadian Institutes of Health Research in the Radiation Sciences, Faculty of Medicine, Université de Sherbrooke, Quebec, J1H 5N4, Canada, and Department of Chemistry, Oakland University, Rochester, Michigan 48309

Received January 22, 2003; E-mail: sevilla@oakland.edu

Abstract: The energetics of the dehalogenation of adenine–halouracil base pairs (A5XU), upon attachment of low-energy electrons, was investigated by use of density functional theory. These results are compared to those of single halouracils reported previously [*J. Phys. Chem. A* **2002**, *106*, 11248–11253]. Using the B3LYP functionals it was found that the gas phase adiabatic electron affinities (EA) of halogenated base pairs (A5BrU 0.59, A5CIU 0.56, A5FU 0.47 eV) are higher than that of AU (0.32 eV) and are slightly higher or comparable to the other DNA abundant base pair, guanine–cytosine (0.49 eV). Base pairing with adenine slightly decreases the EA of the halouracils, in contrast to the substantial increase in EA on base pairing of natural bases; as a result, the probability of electron capture by halouracils when in double-stranded DNA is suggested to be substantially reduced relative to that in single-stranded DNA. Even though the activation barriers for dehalogenation are small for both BrU–A and CIU–A, only the former has negative values of both ΔH (–0.95 kcal/mol) and ΔG (–1.52), while the latter has negative ΔG (–0.28) but positive ΔH (1.27). Infinite separations into halogen anions plus the remaining A–U-5-yl neutral radical are energetically unfavorable owing to sizable halide ion, radical interactions as reported earlier for non base paired halouracils. It is found that base pairing does not change the reactive nature of the uracil-5-yl radical. The results suggest that the radiosensitization properties of halouracils should be less effective in double-stranded DNA than in single-stranded DNA.

Introduction

Attachment of a low-energy electron to a neutral stable molecule may turn that molecule into an unstable, dissociative anion. This process, known as dissociative electron attachment (DEA),¹ usually occurs at electron energies lower than about 20 eV. Low-energy secondary electrons of such energies are generated in large quantity by the interaction of ionization radiation with any type of gaseous or condensed matter. However, the role of these electrons and DEA in radiation damages to DNA has been somewhat neglected until the recent experimental observation that low-energy electrons can cause single- and double-strand breaks to DNA.^{2,3}

Low-energy electron interaction with halouracils is of particular interest since, when incorporated in cellular DNA, the molecules are known to have radiosensitization properties, which can find applications in radiation therapy.^{4–6} These properties

have been recently found to be related to low-energy electrons via DEA; that is, upon attachment of a low-energy electron to a halouracil, the resulting anion is unstable and dissociates into a stable anion (such as a halogen anion) plus a very reactive neutral radical.^{7,8} Such processes have been experimentally observed and studied in the gas phase,⁷ as well as in aqueous solution, where lifetimes ($\tau_{1/2}$) of the radical anions, resulting from attachment of e_{aq}^- , were found⁹ to increase in the order iodouracil (1.7 ns) < bromouracil (7.0 ns) < chlorouracil (4.9 μ s) < fluorouracil (> 15 μ s). Recently, these radiosensitization properties were investigated theoretically by us⁸ and Wetmore et al.¹⁰ for single (unpaired) halouracils in the gas phase. We note that Sommerfeld has also reported the existence of multiple π^* - and σ^* -states of 5-chlorouracil anion and calculated their lifetimes.¹¹ Several important points from our previous work⁸ were as follows: (1) All single 5-halouracils (BrU, CIU, FU) have higher electron affinities than any natural DNA/RNA base; in other words, the halouracils provide a deeper potential energy well than ordinary bases in DNA for either direct electron trapping or electron transfer from neighboring bases. (2)

[†] Université de Sherbrooke.

[‡] Oakland University.

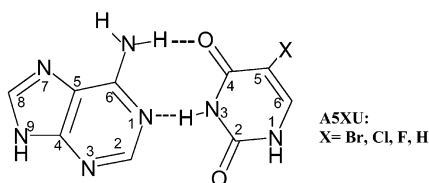
[§] Canada Research Chair in the Radiation Sciences.

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5-Halouracil anion radicals were found to have multiple thermally accessible electronic states: a metastable planar pure π^* -state, a locally stable nonplanar π^* -type mixed state, and a planar dissociative pure σ^* -state. (3) Formation of the dissociative σ^* -states requires only small activation energies for the anion radicals of BrU (1.88) and ClU (3.99 kcal/mol) and are exothermic for both. (4) Dehalogenations from the halouracil anions lead to Br^- or Cl^- plus the reactive U-5-yl radical. (5) For 5-F uracil anion, dehalogenation reaction is energetically unfavorable and more likely leads to formation of the hydrogen fluoride molecule. It was concluded that the sensitivity of the halouracils to low-energy electrons is in the order $\text{BrU} \approx \text{ClU} \gg \text{FU}$. These findings are in agreement with experimental observations.^{7,12–18}

Since most experimental and theoretical studies focus on single halouracils, rather than on their pairs with adenine, one may wonder about the impact of the base pair configuration, which better mimics the environment in double-stranded DNA, on the radiosensitization properties. In the present work, we extend our previous density functional theory (DFT) investigations⁸ to include the base pair partner adenine. Our goal is to observe the energetics of dehalogenation after attachment of a low-energy electron to a halouracil paired with adenine (abbreviated as A5XU: A5BrU, A5ClU, and A5FU) as shown below:



Calculation Methods

Unless stated otherwise, all calculations were performed using the DFT B3LYP functionals with the 6-31+G(d) basis set provided in the Gaussian 98 program package.¹⁹

The DFT B3LYP method is employed in this work for electron affinities, as it is the best affordable method for modeling molecular systems as large as base pairs. A detailed review by Schaefer's group on the theoretical computations of electron affinities is available.²⁰ A more recent paper from the same group²¹ points out that, "In general,

Table 1. Electron Affinities (eV) of Halouracils (5XU)^a and Base Pairs with Adenine

		X				5-yl ^b	B3LYP/6-31+G(d) ZPE correction ^c
		Br	Cl	F	H		
AEA	5XU	0.63	0.60	0.48	0.18	2.34	yes
	A5XU	0.51	0.49	0.37	0.066	2.30	no
VEA	5XU	0.59	0.56	0.47	0.32	2.36	yes
	A5XU	0.57	0.55	0.45	0.18	2.32	no
AEA ^d	5XU	0.11	0.06	-0.15	-0.35	1.89	no
	A5XU	0.18	0.15	-0.10	-0.13	1.79	no
(solvated)	5XU	2.44	2.26	2.21	2.02	4.47	no
	A5XU	2.20	2.36	2.30	1.92	3.95	no
VDE	5XU	1.21	1.20	1.14	0.76	2.74	no
	A5XU	1.33	1.33	1.27	0.93	2.87	no

^a Values for unpaired halouracils were taken from ref 8. Note that the VEA for 5FU and uracil reported in ref 8 should be negative and are correct as shown in this table. ^b A5ylU = AUracil-5-yl radical. ^c Zero-point energy corrections. ^d H₂O, $\epsilon = 78$.

BHLYP underestimates AEAs, while B3P86 always overestimates AEAs⁷. The B3LYP functionals on the other hand usually give values between these two functions. We employ the medium size 6-31+G(d) basis set with the B3LYP functionals since this basis set gives acceptable accuracy and lessens the mixing of dipole-bound with valence-bound anionic states found with very large basis sets.²²

Methods for optimization and calculation of electron affinities (adiabatic, vertical, solvated, etc.) as well as the search for adiabatic potential energy surfaces (PES) have been described in our previous report.⁸ Briefly, all geometries of the 5-X-uracil adenine base pairs, where X = H, F, Cl, or Br, and dehalogenated-5yl radical (A5ylU) were optimized in the gas phase. Frequency calculations (without scaling) were performed to obtain zero-point corrections to energy (ZPE). The isodensity PCM model (SCRFP=IPCM)²³ was used in calculations of the energies in solvated environment with water as solvent, based on optimized gas phase geometries. Adiabatic potential energy surfaces (PES) along the C–X bond stretch were calculated using optimization keyword opt=ModRedundant and included the S action code in the additional input. The optimized geometries found along the C–X coordinates were further verified by frozen C–X distance optimizations, which also served to obtain information about the charge/spin distributions and molecular orbital symmetry.

Results and Discussion

1. Electron Affinities of Single 5-Halouracils and their Pairs with Adenine. Electron affinities of single 5-halouracils have been reported previously.^{8,10} For easy comparison, we list the values of electron affinities for single halouracils we reported previously⁸ together with those of their pairs with adenine in Table 1, all calculated at the B3LYP/6-31+G(d) level. Single halouracils were found to have adiabatic electron affinities (AEA) substantially higher than that of uracil. However, once base paired, these differences are reduced: the AEAs of A5XUs are only slightly higher than the natural adenine–uracil pair (AU: 0.32 eV) or adenine–thymine pair (AT: 0.30 eV).²⁴ That of the FU–A pair (0.47 eV) is comparable to the other DNA abundant base pair, guanine–cytosine, which has an AEA of 0.49 eV.²⁴ The considerably reduced advantage in electron capture suggested from the smaller affinities of the base-paired halouracils versus isolated halouracils is remarkable. On considering the effectiveness of radiosensitization, these results clearly indicate that halouracils in double-stranded (ds) DNA

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Table 2. C–X Distance (Å) of Halouracils (5XU) in Different States

		X			
		Br	Cl	F	H
neutral	5XU	1.878	1.733	1.344	1.082
	A5XU	1.880	1.735	1.346	1.082
anion (minimum)	5XU	1.918	1.771	1.383	1.085
	A5XU	1.910	1.767	1.379	1.085
transition state anion	5XU	2.147	2.041	2.093	
	A5XU	2.184	2.065		
dissociative state anion	5XU	2.614	2.607	2.131	
	A5XU	2.606	2.592		

would be less effective competitive electron scavengers/acceptors than in single-stranded (ss) DNA. Furthermore, previous results¹² have shown that in well-stacked ds DNA electron scavenging by halopyrimidines is greatly reduced, likely because electron transfer through the DNA occurs before dehalogenation reactions. However, unstacked DNA bases provide for longer residence times so that the lifetime of the anionic state increases substantially to allow the dehalogenation to take place. Thus, halouracils are likely to be more effective in ss-DNA versus ds-DNA for two reasons: higher electron affinities and longer residence times.

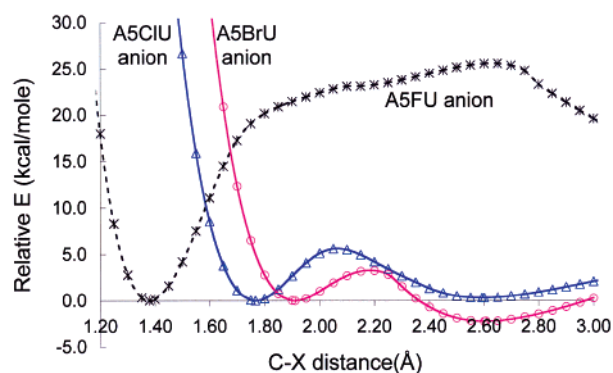
The differences in AEAs with/without ZPE corrections are about 0.12 eV for all isolated 5XU and uracil. In base pairs, these differences reduce to ca. 0.02 eV for A5XU, but that for AU remains similar to the uracil's. These changes indicate base pairing affects the electronic structures of halouracils so as to reduce ZPE corrections to near negligible amounts. This suggests the non-ZPE-corrected values reported for the other EAs of A5XUs in Table 1 are likely very near those after correction.

The solvated AEA values (H_2O , $\epsilon = 78$) are estimated based on gas phase geometries and do not include ZPE corrections. The expected substantial stabilization of the anion radical on solvation leads to a ca. 2 eV increase in the AEA on solvation. Further investigations of the effect of solvent on the energetics of dehalogenation or structural geometrical changes may yield interesting new information.

Removal of X leaves the A5ylU radical (where X = 5-yl, the uracil C₅ is a radical site). This radical still has a very high electron affinity comparable to the reactive U-5-yl radical,⁸ indicating that base pairing does not reduce the reactive nature of the radical.⁹

2. Geometries and C–X Bond Potential Energy Surface (PES) of Base Pair Anion Radicals. All the optimized neutral pairs with adenine are found to exist in planar geometries: not only are the two bases (adenine and halouracils/uracil) planar but the planes of the bases are also coplanar. Upon attachment of an electron, each optimized geometry is distorted from planarity at C₆ of halouracils; however, the overall geometry remains close to a planar geometry. This is consistent with the radical nature of halouracil C₆ in the anion radical base pairs and very similar to the structure found in the anion radical of the AT base pair.²¹ Table 2 lists the C–X distances in optimized neutral, radical anions, as well as the transition state and dissociative state anions found for A5BrU and A5CIU. These optimized geometries are available in the Supporting Information.

As mentioned in the Introduction, the radical anions of halouracils have been found to have several thermally accessible

**Figure 1.** Potential energy surfaces (PES) along the C₅–X bond of the radical anions formed by adding an electron to the adenine–halouracil base pairs. All energies are relative to equilibrium position of the corresponding anions.**Table 3.** Energetics of Dehalogenation from Halouracil Radical Anions: Effect of Base Pairing with Adenine (kcal/mol)

		X			ZPE correction
		Br	Cl	F	
activation energy	5XU	1.88	3.99	20.80	no
	A5XU	3.29	5.62	25.6	no
ΔH	5XU	-2.98	-0.98	20.82	yes
	A5XU	-0.95	1.27		yes
ΔG	5XU	-3.80	-2.32	19.01	yes
	A5XU	-1.52	-0.28		yes
$\Delta E(\text{infinite}) (A5ylU + X^-)$	5XU	21.0	18.0	49.6	yes
	A5XU	23.2	19.6	51.8	yes

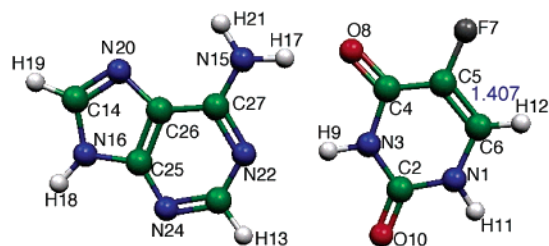
low-lying electronic states: a planar π^* -state, a dissociative planar σ^* -state, and a nonplanar π^* -type mixed state that connects the two planar states.^{8,11} Adiabatic dehalogenation of halouracil radical anions follow the nonplanar mixed state potential energy surface (PES). For the A5XU base pair radical anions, we have calculated only the nonplanar mixed state PES along the C–X bond. Figure 1 compares the potential energy surfaces found on extension of the C–X (X = Br, Cl, or F) bond of A5XU anions. For convenience, the energies of optimized anions are used as references for each PES.

Structures of transition state and dissociative state were successfully found for A5BrU and A5CIU radical anions. For A5FU anion, however, the F anion is attracted to the neighboring hydrogen on C₆, then migrates to that on N₁ of uracil. There is no local minimum before the F atom localizes next to the hydrogen on N₁.

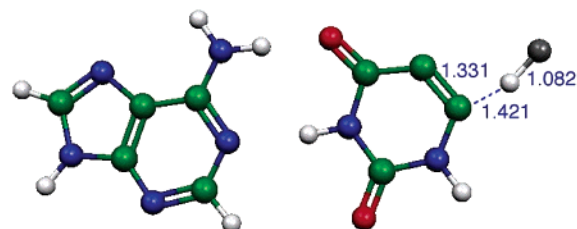
3. Thermodynamics of Dehalogenation Reactions from the Anion Radicals. From the PES of A5XU anions (Figure 1), it can be seen that only the dehalogenation of the A5BrU radical anion is energetically favored. Dehalogenation of the A5CIU anion is slightly unfavorable; however, hydration of the resulting Cl anion should provide sufficient additional driving force to make the dehalogenation process favorable. For A5FU anion, dehalogenation is highly unfavorable energetically.

Table 3 compares the activation energy, ΔH , ΔG , and $\Delta E(\text{infinite})$ for dehalogenation from anions of unpaired halouracils and their pairs with adenine. From the paired anions, the activation energies for dehalogenation are about 1.5 kcal/mol higher than from unpaired BrU or CIU anions and the ΔH , ΔG are less negative for both A5BrU and A5CIU. In fact, only the A5BrU has small but negative values of ΔH , ΔG , while A5CIU has positive ΔH and a ΔG near zero. These values

Initial Structure



Transition State



Final Structure

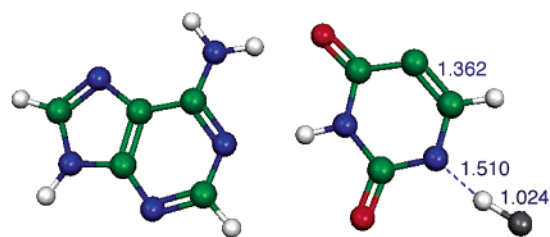


Figure 2. Migration of fluorine from uracil C₅ to H(C₆) and then to H(N₁) in the adenine–uracil(5-F) base pair anion. The result is molecular HF associated with the uracil-yl radical anion. Bond distances shown are in Å.

suggest that dehalogenation is less favorable once the Br-uracil or Cl-uracil is paired with adenine as in DNA. Thus the energetics of dehalogenation, as well as the electron affinities discussed previously, suggest that radiosensitization by halouracils is less effective in double-stranded DNA than in single-stranded DNA or in analogue nucleotides.

The dehalogenation from A5FU anion is an interesting case to follow as the dissociation proceeds to hydrogen abstraction. The activation energy of 25.6 kcal/mol is estimated from the C₅–F bond PES (Figure 1), where the C₅–F distance is around 2.65 Å. Beyond this point, the F atom first approaches H(C₆) and the PES is downhill all the way until it finally migrates to H(N₁) with a H–F bond distance of 1.024 Å and a H–N bond distance of 1.51 Å. Thus it effectively abstracts this hydrogen to form HF. Figure 2 shows the migration of the F atom. This was discovered in an effort of searching for the dissociative state of A5FU anion. Interestingly, after migration, the energy of the base pair is lowered by –3.86 kcal/mol (without ZPE correction). It is likely that such migration will also occur with a non-base-paired 5-F uracil anion, but in that case the migration was only followed up to the C₆–H in our previous report.⁸ In a nucleotide or in DNA, the N₁ hydrogen is not available, as the nitrogen is the site of the deoxyribose. The migration of the F atom must therefore change destination. Since the fluorine atom dehalogenates as an anion, in a water solution it will quickly protonate to form HF. The lower energy after migration suggests that dissociation of fluorine in the form of a HF molecule may be favorable energetically, even though it must

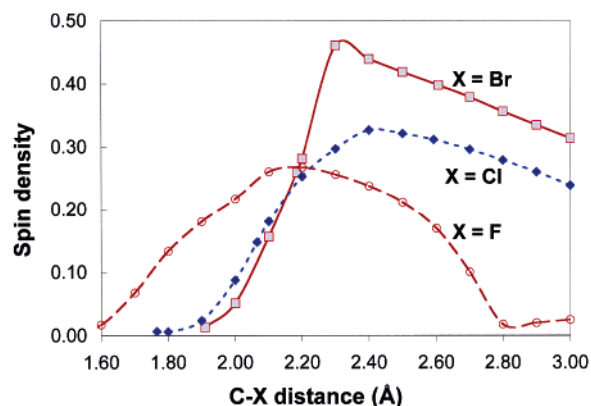


Figure 3. Spin density on X (X = Br, Cl, F, or H) along the C–X bond PES of adenine–halouracil radical anion.

overcome a large activation barrier of ~25 kcal/mol. This is in agreement with the experimental observation¹³ that an electron must have an energy of >2 eV to induce the dissociation of fluorine.

The ΔE values (Table 3) were calculated for complete separation of halogens as halide ion (X[–]) from the A5XU anions. These values show that complete separation of X[–] in the gas phase is energetically unfavorable for anions of halouracils when alone or in a base pair with adenine. These reflect the sizable ion–dipole interaction energies between the leaving halogen and the remaining uracil radical. A comparison of Tables 1 and 3 shows that the production of X[–] via DEA correlates quite well with the vertical electron affinity.

4. Charge Spin Distributions and the Possible Products of Dehalogenation Reactions. In the A5XU radical anions, over 90% of negative charge and 100% spin density fall on the halouracils rather than on adenine.

The spin densities on the departing halogens (X) along the PES surfaces are shown in Figure 3. As can be seen, the spin density on X experiences a maximum and then decreases as the C₅–X distance increases. At the same time, the negative charge on X increases steadily (not shown). These dependencies of the spin density and the negative charge on X indicate that the X[–]s are departing as anions, leaving behind the A5ylU radical. For A5XU with X = Br or Cl, formation of the halide anion is expected and is as we found previously for non-base-paired 5-bromouracil and 5-chlorouracil. However for F, since it interacts with the hydrogen at N₁, the final product of dehalogenation is HF and the AU-5yl anion.

Conclusions

The most remarkable result found in this work is that base pairing with adenine slightly decreases the electron affinities of the halouracils (Table 1), while in previous work we have found²⁴ that base pairing for DNA bases substantially increases their EAs. For example, base pairing increases the EAs from 0.18 eV for U to 0.32 eV for AU, from 0.20 eV for T to 0.30 eV for AT, and most surprisingly from –0.06 eV for C to 0.49 eV for GC. The substantial increase in GC is associated with the fact G has one net donor hydrogen involved in the hydrogen bonding to C. Each net donor hydrogen has been suggested in earlier work to increase the electron affinity by ca. 0.5 eV.²⁵

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Note that in every case the captured electron resides on the pyrimidine base.

Our calculated EAs for bases and base pairs can be used to estimate the driving force for electron capture at the halouracils in ss-DNA and ds-DNA, respectively. In double-stranded DNA the electron is initially trapped at the GC base pair; thus our simplified model for the driving force for electron capture at the halouracil in ds-DNA is the difference in EA between GC (0.49 eV) and A5BrU (0.59 eV). This amounts to only 0.1 eV for ds-DNA. However, in single-stranded DNA the most likely electron capture site is T (EA = 0.20 eV) or less likely C (EA = -0.06 eV).²² Thus the difference in the EAs between T and 5BrU is 0.43 eV, and that between C and BrU is 0.69 eV.^{8,22} The reduction in driving force of electron trapping at the halouracil on base pairing is then at least from 0.43 to 0.1 eV. Similarly we find the driving forces for electron capture to be substantially reduced on base pairing for all halouracils. While base stacking and solvation will tend to alter these numbers, the differences in driving forces are large and are not likely to alter the large reduction in driving force found here.

As a result, the competitiveness of halouracils in base pairs for excess electrons is significantly reduced relative to non-base-paired halouracils. We project that the probability of capture of a low-energy electron by A5XU is decreased, and thus the radiosensitivity of halouracils is likely to be reduced in double-stranded DNA in which the halouracils are paired with adenine. The potential energy surfaces along the C₅-X bond (Figure 1) suggest an additional reduction in the effectiveness of sensitization of halouracils to low-energy electrons once paired with adenine; that is, slightly higher activation barriers and smaller ΔH and ΔG are found for dehalogenation reactions of Br- and Cl-uracil anions in the pairs than those unpaired.

In the case of 5FU the strongly basic character of the departing fluoride ion results in an additional step. The F atom on uracil C₅ is found to migrate first to H(C₆), then forms HF with the hydrogen at N₁ in the A5FU anion. The products, HF and uracilyl(-H) anion radical, are actually a few kilocalories lower in energy than the A5FU anion. However, the formation of the HF and uracilyl(-H) anion radical needs to overcome a substantial activation barrier of around 25.6 kcal/mol.

While we find that the dehalogenation step is hindered by base pairing, the high electron affinity predicted for AU5yl radical suggests that once formed base pairing will have little effect on the well-known high reactivity of this species.

Finally, we note that the considerably higher electron reactivity with non-base-paired halouracils compared to those within ds-DNA indicates that during cell division and replication, when DNA must be at times in the single-strand form, DNA containing halouracils may be much more vulnerable to excess electron attack. Such information may be of significance to the development of new clinical modalities in radiotherapy.

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Supporting Information Available: Optimized geometries of adenine-halouracil pairs and the dehalogenated radical (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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