THE JOURNAL OF PHYSICAL CHEMISTRY Letters

Letter

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# How to Find Out Whether a 5-Substituted Uracil Could Be a Potential DNA Radiosensitizer

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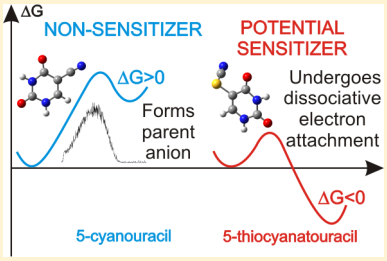
Supporting Information

**ABSTRACT:** Incorporated into genomic DNA, 5-substituted uracils could be employed in human cancer radiotherapy if they could be sensitized to dissociate upon reaction with hydrated electrons. Using the B3LYP/6-31++G(d,p) method, we calculate electron affinities and energy profiles related to the dissociation of the respective anions for a series of uracil derivatives. We demonstrate that for a uracil analogue to be an efficient electron acceptor the uracil substituent has to possess significant electron-withdrawing power. On the other hand, in order to ensure effective dissociation of the anion, the chemical bond holding together the substituent and uracil residue should be relatively weak. Our theoretical predictions are in excellent agreement with the results of our negative ion photoelectron spectroscopy experiments. We propose two new potential sensitizers that seem to possess the required properties, although they have never been tested in radiobiological experiments.




**SECTION:** Biophysical Chemistry and Biomolecules

Radiotherapy (RT) is the most common curative and palliative modality in human cancer treatments. Above fifty percent of all cancer patients receive RT at some point during their management.[1] However, it is worth emphasizing that ionizing radiation (IR) employed in RT is cytotoxic not only toward the cancer but also to normal cells, considering the target irradiated volume always includes a substantial amount of normal tissue. Hence, effective radiotherapy is unavoidably associated with a risk for early and late side-effects, including the development of a secondary cancer.[1] Furthermore, efficient repair mechanisms in cells lessen the therapeutic effects of gamma/X-ray radiation. Finally, cancer cells usually suffer from hypoxia, and it has been demonstrated that well-oxygenated cells are more radiosensitive than hypoxic ones.[2,3] The above-mentioned facts call for introducing into clinical practice substances that could specifically sensitize tumor cells to the action of $\gamma$/X-rays. This, as a consequence, should diminish the magnitude of therapeutic doses that would save normal cells as well as help to circumvent the hypoxic conditions and repair machinery of cancer cells.

As far as cell death by ionizing radiation is concerned, the DNA molecule is the most important target. Although IR deposits its energy randomly damaging all molecules within the cell, there are multiple copies of most molecules, and many of them undergo a continuous and rapid turnover that limits the destroying effects of IR. On the other hand, there are only two copies of DNA per cell, its turnover is very limited, and the molecule itself is crucial for all cellular functions. Indeed with eukaryotic cells that contain their DNA in the nucleus, little lethal damage is observed as long as IR is absorbed by the membrane or cytoplasm. However, there is a dramatic increase in cellular death in instances where the ionizing radiation reaches the nucleus.[4]

IR interacts with DNA either directly causing its ionizations/excitations or indirectly via the products of radiolysis of the molecules present in an environment. In the cell, which contains 70−80% water, the indirect action of IR far exceeds the direct effects. Namely, water radiolysis results in the hydroxyl and hydrogen radicals as well as in hydrated electrons. Studies with scavenger molecules indicate that almost all indirect DNA damage is due to attack by the highly reactive hydroxyl radicals ($OH^{\bullet}$). The reducing counterparts of $OH^{\bullet}$, i.e., hydrated electrons, although generated by the ionizing radiation in the amount similar to that of hydroxyl radicals,[5] are nevertheless relatively ineffective, especially at inducing DNA strand breaks[6] (DSBs belong to the most lethal damage, and their number generated in the DNA of X-ray irradiated cells correlates with the cell death[7]). This situation may, however, change dramatically provided that modified nucleosides of sufficient electron affinity are incorporated into cellular DNA. Additionally, in order to be effective radiosensitizers, these nucleosides must easily decompose upon electron attachment (by dissociative electron attachment), leaving behind reactive radicals in DNA that in secondary steps may produce strand breaks.

Uracil analogues, notably 5-bromouracil (5-BrU), can be used by a cell for DNA biosynthesis almost as easily as thymine

**Received:** July 1, 2013
**Accepted:** August 9, 2013
**Published:** August 9, 2013

and has long been recognized as a radiosensitizing agent with potential clinical applications.[8−10] Indeed, *in vitro* 5-BrU labeled cells are 2−3 fold more radiosensitive than the nonlabeled ones.[11] The sensitization mechanism is likely related to the rapid reaction of 5-bromo-2′-deoxyuridine (5-BrdU) with hydrated electrons, which has recently been studied by time-resolved femtosecond laser spectroscopy.[12−14] The primary anions formed as a result of electron attachment to 5-BrdU undergo bromide anion elimination with a tiny kinetic barrier,[15,16] yielding the highly reactive uridine-5-yl radical. If the latter species is produced in DNA, then a secondary hydrogen atom transfer from either the sugar of the nucleoside radical or adjacent nucleoside can ultimately lead to a single bond break.

Although 5-BrU effectively radiosensitizes cell lines *in vitro*, one of the most extensive phase III clinical trials proved no increased survival related to 5-BrdU administration in radiotherapy for various astrocytomas and malignant gliomas.[17] Moreover, the range of radiosensitizers currently employed in clinical practice is quite narrow.[18] Taking this into account, a further search for potential radiosensitizers seems to be fully justified.

In this Communication we study the propensity of 5-substituted uracils to undergo dissociation by an excess electron. Our choice of uracil derivatives is based on their usefulness as substrates for thymidine kinase[19]—a prerequisite for their incorporation into DNA under the cellular environment. We chose 5-substituted uracils since the 5 site of uracil can be easily modified chemically,[20] and this is the site not involved in the complementary hydrogen bonds responsible for the stability of double helix. For a series of 5-substituted uracil derivatives (see Figure 1) electron affinities and energy profiles

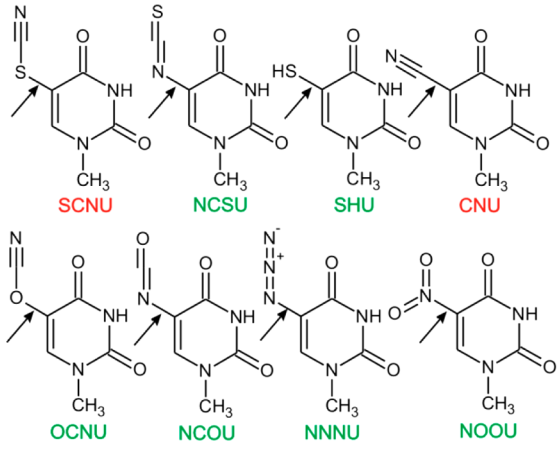



**Figure 1.** 5-substituted 1-methyl-uracil derivatives studied with corresponding name abbreviations.

related to their electron-induced degradation were calculated at the DFT level both in aqueous solution and in the gas phase (see Figure 2 and S3).

For two derivatives—one forming a stable valence anion and another one that undergoes dissociative electron attachment—the quantum chemical computational results were compared to those originating from our anion photoelectron spectroscopy (PES) experiments. The excellent accordance between the calculated and PES characteristics confirms the reliability of the quantum chemical model employed. Our studies suggest that the 5-SCNU and 5-OCNU derivatives that have never been

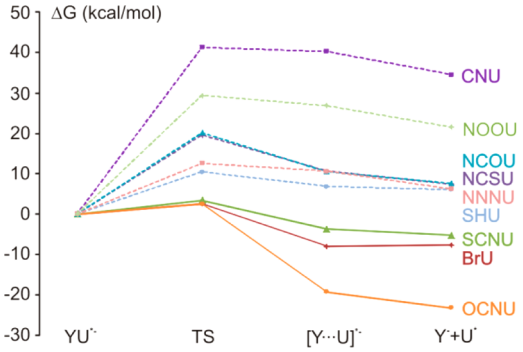



**Figure 2.** Free enthalpy profiles for electron induced degradation of 5-substituted modified uracils, in aqueous solution.

examined in radiobiological experiments so far, could be potential radiosensitizers and should be tested in *in vitro* trials with cell lines.

To model the electrophilic properties of the 5-substituted uracils and the reactivity of their anions, we applied the density functional theory method with Becke's three-parameter hybrid functional (B3LYP)[21,22] and the 6-31++G(d,p) basis set[23,24] to the gas-phase calculations and additionally the polarizable continuum model (PCM)[25−27] of the solvent for the aqueous solution. To mimic the sugar-binding sites present in a nucleoside, the uracil derivatives are methylated at site 1 (see Figure 1). The adiabatic electron affinity (AEA) is defined as the difference in the electronic free enthalpies of the neutral and the respective anion radical at their corresponding fully relaxed structures. Vertical detachment energies (VDEs) were calculated as the difference between the electronic energies of the neutral and the anion radical at the geometry of the fully relaxed anion radical.

As mentioned above, a substituted uracil having radiosensitizing properties should be (i) a substantially better electron acceptor than thymine, and (ii) its anion should easily decompose giving the uracil-5-yl radical. In order to demonstrate how the substituent at the 5 position of the uracil ring influences electrophilic properties of the studied system, we chose a series of nine substituents differing by their electron withdrawing properties (see Figure 1). As the strongest electrophile we used the nitro group, with the Hammett inductive constant, $\sigma_I$, of 0.65, considered to have nearly maximal electron-withdrawing power, while as the weakest we used the thiol function with $\sigma_I$ of 0.3.[28] Hence, the substituents studied here are characterized by a positive value of the Hammett constant, which indicates they should bind an excess electron stronger than the unsubstituted uracil. Indeed, the AEA values gathered in Table 1 confirm such a conclusion. While the electron affinity of the hydrated uracil calculated at the same level of theory amounts to only 1.94 eV,[29] the respective values for the 5-substituted uracils are substantially larger. The AEA value for the analogue substituted with the weakest electrophile, −SH, amounts to 2.26 eV, while that for the strongest, $-NO_2$, is as much as 3.55 eV (see Table 1).

The stabilities of particular anions, formed as a result of electron attachment to a given derivative, with respect to the process of vertical electron detachment, vary in a way similar to that observed for the adiabatic stabilities, i.e., VDE is the smallest for the −SH substituent and the second largest for the $-NO_2$ (see Table 1).


dx.doi.org/10.1021/jz401358w | *J. Phys. Chem. Lett.* 2013, 4, 2853−2857

**Table 1. AEA and VDE of 5-Substituted 1-Methyl-uracil Derivatives Calculated in an Aqueous Solution**

| YU | AEA[a,b] | VDE[b] |
|---|---|---|
| BrU[30] | 2.48 | 2.74 |
| CNU | 2.83 | 3.18 |
| SCNU | 2.70 | 3.07 |
| NCSU | 2.73 | 3.86 |
| NCOU | 2.40 | 2.78 |
| OCNU | 2.62 | 3.07 |
| SHU | 2.26 | 2.66 |
| NNNU | 2.38 | 2.77 |
| NOOU | 3.55 | 3.81 |

[a]In the free enthalpy scale. [b]In eV.

The electron affinity value of a modified nucleoside incorporated into the biopolymer is a crucial factor in effectively radiosensitizing DNA due to its interaction with a hydrated electron. However, a large electron affinity is not necessarily the only requirement for its radiosensitizing properties. For example, despite the largest electron adiabatic affinity and vertical stability of its anion (see Table 1), 5-nitrouracil is not a promising candidate for a DNA radiosensitizer. As indicated by Figure 2 and the thermodynamic and kinetic characteristics gathered in Table 2, dissociation of the NOOU anion leading to the reactive uracil-5-yl radical is rather unfavorable.

**Table 2. Thermodynamic and Kinetic Characteristics for Degradation of Uracil Methyl Derivatives in Aqueous Solution (kcal/mol)**

| | $YU^{\bullet-} \rightarrow [Y^{\cdots}U]^{\bullet-}$ | | $YU^{\bullet-} \rightarrow Y^- + U^*$ | $YU + e \rightarrow Y^- + U^*$ |
|---|---|---|---|---|
| YU | $\Delta G_{PC}$ | $\Delta G^*$ | $\Delta G_{SP}$ | $\Delta G_{total}$ |
| BrU[30] | −8.0 | 2.5 | −7.7 | −65.0 |
| CNU | 40.2 | 41.2 | 34.5 | −30.8 |
| SCNU | −3.7 | 3.4 | −5.2 | −67.5 |
| NCSU | 10.5 | 19.5 | 7.4 | −55.5 |
| NCOU | 10.5 | 20.1 | 7.6 | −47.8 |
| OCNU | −19.3 | 2.5 | −23.3 | −83.7 |
| SHU | 6.8 | 10.4 | 6.0 | −46.0 |
| NNNU | 10.6 | 12.5 | 6.2 | −48.8 |
| NOOU | 26.8 | 29.3 | 21.5 | −60.4 |

The reaction of NOOU is associated with the activation barrier of 29.3 kcal/mol, while the $\Delta G_{SP}$ is positive and amounts to as much as 21.5 kcal/mol (Table 2). This shows that after electron attachment to NOOU, the uracil-5-yl radical will not form at all (see Figure 2). The characteristics of $\Delta G^*$ and $\Delta G_{SP}$ are quite similar for the second most stable anion, i.e. that originating form 5-cyanouracil. The dissociation of the CNU anion is even more difficult than that of NOOU, i.e., the activation barrier is equal to 41.2 kcal/mol, while $\Delta G_{SP}$ amounts to 34.5 kcal/mol (Table 2). This again prevents the formation of the uracil-5-yl radical from the CNU anion (see Figure 2).

Thus, in order to assess the usefulness of the studied derivative, one should also take into account the chemical bond strength that connects a substituent to the C5 carbon of uracil as well as the electron affinity of the radical fragment, $Y^{\bullet}$, in addition to the stability of the substituted uracil anion. Note that the AEAs of CNU and OCNU differ by only 5 kcal/mol (0.21 eV, see Table 1) while the respective $\Delta G_{SP}$ free energies by as much as 57.8 kcal/mol (see Table 2). Consequently, despite the fact that both CNU (AEA = 2.83 eV) and OCNU (AEA = 2.62 eV) should attach an electron (cf. BrU has an AEA of only 2.48 eV that sensitizes modified DNA to hydrated electrons), only the latter compound may act as a radiosensitizer since its electron-induced dissociation is associated with a negligible activation barrier (2.5 kcal/mol; Table 2) and an exceptionally favorable $\Delta G_{SP}$ stimulus (−23.3 kcal/mol; Table 2). As the AEAs of OCNU and CNU differ by only ca. 5 kcal/mol, the advantageous dissociation thermodynamics of the $OCNU^-$ anion has to be a consequence of much weaker bond strength between the substituent and uracil moiety in the former case. Indeed, the B3LYP/6-31++G(d,p) dissociation free energies, $YU \rightarrow Y^{\bullet} + U^{\bullet}$, for OCNU and CNU are equal to 58 and 124 kcal/mol, respectively.

For strengthening our quantum modeling, we also employed the use of negative ion photoelectron spectroscopy (PES, for details see Supporting Information). With this powerful experimental technique, we confirmed the quantum chemically predicted behavior of two compounds, SCNU and CNU, differing in their potential radiosensitizing properties. As indicated by Figure 2, CNU belongs to the group of nonsensitizing species whose electron-induced dissociation is accompanied by substantial activation barriers and unfavorable thermodynamics. On the other hand, SCNU can be considered as a potential radiosensitizer (as BrU and OCNU; Figure 2) whose dissociation proceeds with a negligible activation barrier and negative thermodynamic stimulus. The PES experiment was carried out for nonmethylated CNU and SCNU since the former compound was accessible commercially. The nonmethylated form of SCNU was synthesized (for details see Supporting Information).

The PES spectrum recorded for 5-cyanouracil (CNU(-Me)) depicted in Figure 3 demonstrates that, in accordance with our

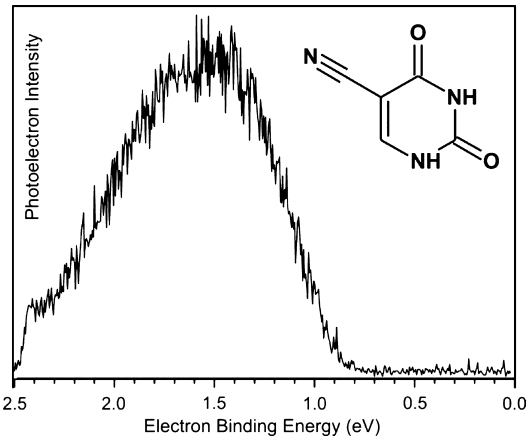



**Figure 3.** 5-Cyanouracil photoelectron spectrum recorded with 2.540 eV photons.

QM model (see Figure 2), CNU(-Me) forms a stable valence anion in the gas phase. The VDE read from the spectrum (the maximum value of photoelectron signal) is 1.55 eV. The B3LYP VDE calculated for CNU(-Me) is equal to 1.69 eV. However, it is known that the VDE values for nucleobase anions are overestimated at the B3LYP level by ca. 0.20 eV, as was determined by the difference between the VDEs of valence uracil anion calculated at the B3LYP/6-31++G and CCSD(T)/aug-cc-pVDZ levels.[31] It is worth noticing that the value of this


dx.doi.org/10.1021/jz401358w | J. Phys. Chem. Lett. 2013, 4, 2853−2857

increment is pretty close to corrections found within recent benchmark studies, where it was demonstrated that AEAs and VDEs of the isolated uracil and its complexes with water were larger than the respective CCSD(T) values by 0.2−0.3 eV.[32,33] Applying the increment of 0.2 eV,[31] one obtains 1.49 eV as a theoretical VDE, which thereafter agrees well with the experimental value. Similarly, the experimental AEA (the electron binding energy value at 10% of the maximal photoelectron intensity) is estimated to be 0.95 eV, while the theoretical value is equal to 1.02 eV. Moreover, as indicated by the mass spectrum of CNU(-Me) recorded during the PES experiment (see Figure 4B) there are no significant amounts of

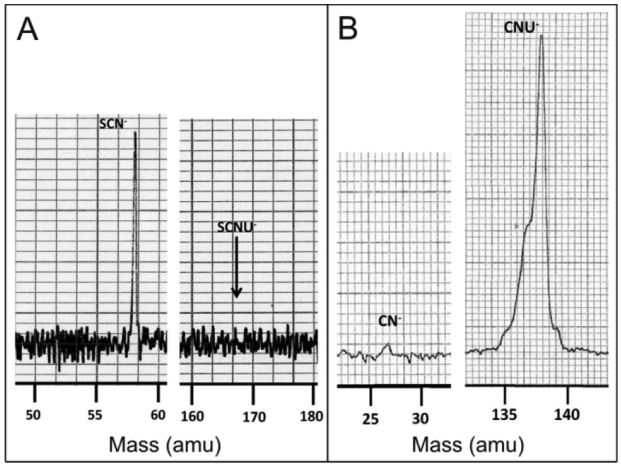



**Figure 4.** Anionic mass spectra for SCNU(-Me) (A) and CNU(-Me) (B), each pair of mass spectra having been recorded on the same signal intensity scales.

$CN^-$ present (beyond background) and only the parent CNU(-Me) anion is observed, this being in full agreement with our theoretical predictions (Figure 2 and Table 2).

The behavior of SCNU(-Me), belonging to the group of potential radiosensitizers, is completely different. We were unable to observe any of the parent anion, $[SCNU(-Me)]^-$, while the mass originating from the $SCN^-$ parent anion had a strong signal intensity (Figure 4A). This again is in complete agreement with the QM model.

In summary, we presented a protocol that should enable a potential uracil-based DNA radiosensitizer that utilizes hydrated electrons to be assessed. Efficient sensitizers should be modified with a substituent excreting a substantial electron-withdrawing effect in order to ensure uracil anion stability that will make electron transfer to modified DNA possible from hydrated electrons. What is even more important, the chemical bond connecting a substituent to the uracil residue cannot be too strong. Otherwise, the kinetic barrier and thermodynamics related to electron-induced dissociation will prevent dissociation. The results of PES experiments carried out for two derivatives, one being a sensitizer and the other resistant to the electron-induced cleavage of the Y−U bond, are in full agreement with our theoretical investigations. The limited search for new DNA radiosensitizers, comprising only eight analogues, yielded two potential candidates, 5-thiocyanato- and 5-cyanatouracil, which have never been tested in radiobiological experiments.

## ■ ASSOCIATED CONTENT

### Supporting Information

Complete experimental procedures, synthesis details, compound characterization data, computational and experimental methods, and gas phase computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the Polish National Science Center (NCN) under the Grant No. 2012/07/N/ST5/01877 (M.Z.), by the National Science Foundation under Grant No. CHE-1111693 (K.H.B.) and by the system project "InnoDoktorant − Scholarships for PhD students, Vth edition". Project is cofinanced by the European Union in the frame of the European Social Fund (L.C.). Calculations have been carried out in Wroclaw Center for Networking and Supercomputing, Grant No. 209 (L.C.).

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