

Stability and Structure of 5-Telluro-2'-deoxyuridine and 5-Telluro-2'-deoxyuridine-3',5'-biphosphate Cations

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Abstract

The stability and structure of 5-telluro-2'-deoxyuridine and 5-telluro-2'-deoxyuridine-3',5'-biphosphate cations was investigated by density functional theory calculations. With regard to a conceivable Coulomb explosion within the DNA strand after the decay of DNA-incorporated ^{125}I or ^{123}I , the phosphate groups in 5-telluro-2'-deoxyuridine-3',5'-biphosphate have a strongly stabilizing effect on the DNA component.

Keywords: Density functional calculations, Coulomb explosion, DNA-incorporated Auger electron emitter, Iodouracil, Iododeoxyuridine, Thymine, 2'-Deoxyuridine, 2'-Deoxyuridine-3',5'-biphosphate

1 Introduction

This paper is the continuation and further development of previous work [1] investigating the consequences of a sudden and high positive point charge on an atom bound to a DNA molecule. Such point charges can result from DNA bound radionuclides decaying via electron capture or internal conversion and emitting a shower of very short-range Auger electrons. Those nuclides are widely used in radiation biology to study radiation action mechanisms in biological tissue.

The most common Auger electron emitter in radiation biology is ^{125}I . Incorporated into the DNA of proliferating cells by replacing the CH_3 group in the thymine base, the decay of this nuclide has provided evidence for severe molecular and cellular damage in terms of single and double DNA strand breaks as well as cell death (for basic references see [1]). The reason for this high radiotoxic effectiveness is generally seen in the relatively great number of low-energy electrons (about 15 per decay) emitted instantaneously during the decay and depositing their energy within or strongly localized near the DNA. However, there is also another effect which deserves attention, namely the positive high point charge on the daughter atom ^{125}Te due

to the extremely fast emission of the Auger electrons. It is expected that this charge will cause an electron transfer from neighbouring atoms in a reorganization process within the affected molecule which might result in a Coulomb explosion. Such molecule destruction has been discussed earlier on the basis of experimental data [2, 3]. The possible contribution of a Coulomb explosion to the overall biological damage is not known.

The previous density functional theory calculations on the stability of tellurium-labelled bases as a function of increasing charge revealed three isomeric structures of 5-tellurouracil. These isomers differ in the position of the Te atom. Two of these structures are stable or metastable up to a total charge of +5. At charges of +6 or greater, the molecule dissociates into the 5-monodehydrouracil cation $\text{C}_4\text{H}_3\text{N}_2\text{O}_2^{3+}$ and Te^{3+} . Compared to these studies, the molecules considered here have been expanded from the uracil base to the deoxyuridine nucleoside and to deoxyuridine-biphosphate to include the influences of the sugar and phosphate groups.

2 Method

The geometries of various cations of 5-telluro-2'-deoxyuridine and 5-telluro-2'-deoxyuridine-3',5'-biphosphate and occurring fragment cations were optimized at the B3LYP level of the density func-

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tional theory using the Gaussian 03 software [4]. The basis set Lanl2DZ was applied for Te and 6-31G(d,p) for the other atoms. For Te, Lanl2DZ was also used as an effective core potential. Additionally, the vibrational frequencies and eigenvectors were calculated at the same level to discriminate between stable and transitional states. The molecular charge was changed incrementally by one, starting with the neutral molecule, i.e. the optimized structure for one charge level was used as the initial structure for the next charge level.

3 Results

3.1 5-Telluro-2'-deoxyuridine

In general, compared to 5-tellurouracil [1], the 5-telluro-2'-deoxyuridine molecule proved to be less stable at positive molecular charge. With a charge of as little as +3, 5-telluro-2'-deoxyuridine (structure *A* in Fig. 1) is no longer stable and the C(4')–C(5') bond breaks, i.e. the CH_2OH^+ group is split off. The remaining molecule is denoted as B^{2+} , see Fig. 1 and Tables 1 (row *B*, column +2) and 2. The energy barrier (transition state) for the same breaking of A^{2+} is 0.019 hartrees. The distance of the bond C(4')–C(5') varies from 1.525 to 1.522 to 1.560 Å for the charges 0 to +2 on *A* and is 3.815 Å for the transition state of A^{2+} .

If the charge on *B* is reduced to +1 or 0, the structure transforms to *B'* where the pentagonal ring is open between the atoms C(1') and O(4'). *B* is stable up to a charge of +6.

Then, with the charge +7, a CHOH^{2+} and a CHO^+ group are split off, and the remaining molecule is denoted as C^{4+} . In the structure *C*, the Te atom is bound to C(5) and to O(4) (Fig. 1). *C* exists with the charges +1 to +5. For the charges 0 to +3, there is the structure *C'* with the Te atom only bound to C(5), but *C'* is only energetically advantageous compared to *C* for the charges 0 to +2.

With the charge +6, Te^{2+} is split away from *C* and the hexagonal ring transforms into a pentagonal ring with a CO group. This molecule, denoted as *D*, exists with the charges +1 to +5. If the charge on *D* is reduced to 0, it transforms into the structure *D'* where one of the two pentagonal rings is opened. *D'* exists for charges up to +3, but *D* is energetically advantageous for the charges +2 and +3.

If the charge on *D* is raised to +6, a proton is

emitted and the molecule E^{5+} is formed. *E* exists for the charges +1 to +5. If the charge is reduced to 0, the CO group is split off. Raising the charge on *E* to +6 results in the emission of a proton and the break of both pentagonal rings, see structure *F* in Fig. 1.

3.2 5-Telluro-2'-deoxyuridine-3',5'-biphosphate

The calculations showed that the two phosphate groups in 5-telluro-2'-deoxyuridine-3',5'-biphosphate have a strongly stabilizing effect compared to 5-telluro-2'-deoxyuridine. Apart from a rearrangement of an OH group and the opening of the pentagonal cycle, 5-telluro-2'-deoxyuridine-3',5'-biphosphate remains undamaged up to a charge of +7.

Specifically, with the charge +2, the Te atom is bound to C(5), O(4) and to the oxygen atom O(6) of the one phosphate group that is bound to C(5'), see structure *B* in Fig. 2. Additionally, a hydrogen bridge from O(7) to O(11) is formed between the two phosphate groups with the bond distances 1.037 Å for O(7)–H(7) and 1.483 Å for O(11)–H(7).

With the charge +3, the bridge between Te and the phosphate group reopens, but the bond between Te and O(6) is stronger than the intraphosphate bond between P(5') and O(6), thus the affected OH group migrates from that phosphate group to the Te atom. Additionally, the Te–O(4) bond reopens, so the Te–OH group is solely bound to C(5). The hydrogen bridge from O(7) to O(11) still exists, but now the bridge hydrogen atom H(7) is bound closer to O(11) with 1.002 Å than to O(7) with 1.632 Å, see structure *C* in Fig. 2. With the charge +4, the hydrogen bridge reopens, H(7) being bound to O(7), see structure *D*. With the charge +5, the Te atom is bound to C(5) and O(4), but nothing else changes, see structure *E*.

If the charge is raised to +6, the pentagonal cycle breaks between C(3') and C(4') (see structure *F*). This structure still exists for the charge +7, i.e. up to that charge nothing is split off from the initial molecule.

Then, with the charge +8, the group beginning with the O(4') atom is split off in two parts, POOHCH_2^{2+} and CHO^+ . This break corresponds to a single strand break in DNA. The remaining molecule is denoted as G^{5+} , see Fig. 2.

If the charge on *G* is raised to +6, the structure does not change. With the charge +7, a $\text{H}_2\text{PO}_3^{2+}$ group is split off, and the remaining molecule is de-

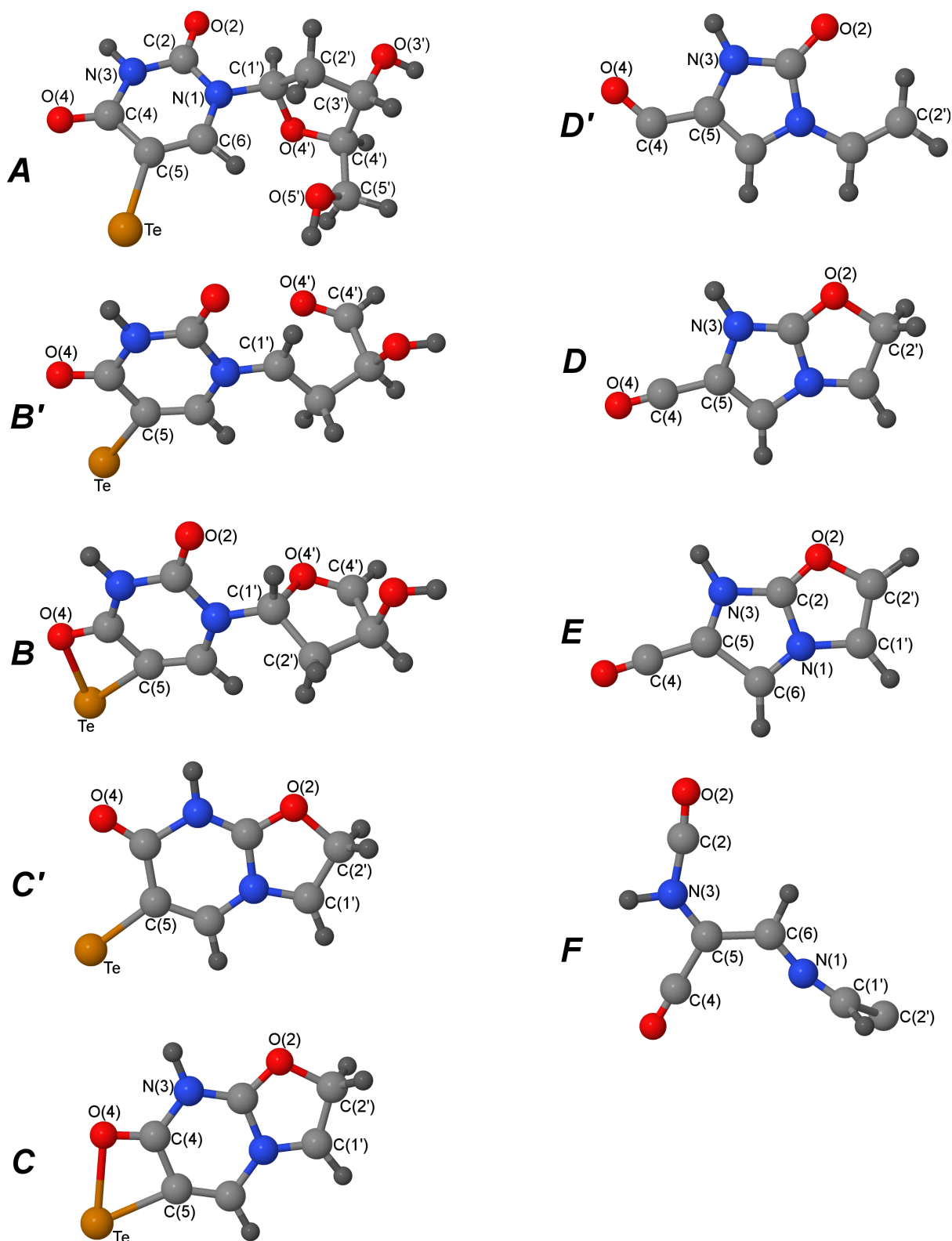


Figure 1: Gradual structural change and fragmentation of 5-telluro-2'-deoxyuridine with rising positive charge.

noted as H^{5+} . The energies for all these molecules are given in Tables 3 and 4.

Due to the considerable amount of computing time required for the geometry optimization

of the large 5-telluro-2'-deoxyuridine-3',5'-biphosphate molecule (up to about 50 CPU days per charge level on an Intel Core2 Duo CPU with 2.16 GHz), investigations of each structure by low-

Table 1: Energies [hartree] for 5-telluro-2'-deoxyuridine ($A-B$) and its fragments ($C-F$).

Charge:	0	+1	+2	+3	+4	+5	+6
A	-843.244	-842.971	-842.532 -842.513 ^{*)}	-	-	-	-
B'	-728.052	-727.819	-	-	-	-	-
B	-	-	-727.421	-726.851	-726.091	-725.203	-724.307
C'	-499.548	-499.311	-498.903	-498.287	-	-	-
C	-	-499.267	-498.899	-498.313	-497.540	-496.514	-
D'	-491.530	-491.291	-490.810	-490.122	-	-	-
D	-	-491.216	-490.819	-490.191	-489.277	-488.155	-
E	-	-490.631	-490.232	-489.542	-488.624	-487.471	-
F						-486.809	

^{*)} Energy for the transition state $A^{2+} \rightarrow B'^+ + \text{CH}_2\text{OH}^+$.

Table 2: Energies [hartree] for the fragments split off from 5-telluro-2'-deoxyuridine.

CH_2OH^+	-114.791
CHOH^{2+}	-113.444
CHO^+	-113.547
Te^{2+}	-6.927

Table 3: Energies [hartree] for 5-telluro-2'-deoxyuridine-3',5'-biphosphate ($A-F$) and its fragments ($G-H$).

A	-1978.690
A^+	-1978.415
B^{2+}	-1978.023
C^{3+}	-1977.499
D^{4+}	-1976.846
E^{5+}	-1976.087
F^{6+}	-1975.340
F^{7+}	-1974.358
G^{5+}	-1255.041
G^{6+}	-1254.049
H^{5+}	-686.403

^{*)} Energies for the transition states $F^n \rightarrow G^{n-2} + \text{POOHOC}_2\text{H}_3\text{O}^{2+}$.

Table 4: Energies [hartree] for the fragments split off from 5-telluro-2'-deoxyuridine-3',5'-biphosphate.

$\text{POOHOC}_2\text{H}_2^{2+}$	-606.059
CHO^+	-113.547
$\text{H}_2\text{PO}_3^{2+}$	-567.256

ering the charge level again, as performed for 5-telluro-2'-deoxyuridine, were dispensed with here.

Nonetheless, the first major break, the split off of $\text{POOHOC}_2\text{H}_2$ and CHO , was investigated further by determining the corresponding transition states for the charge levels +6 and +7 of structure F . In both cases, the transition state could only be determined for the break of the bond between $\text{C}(1')$ and $\text{O}(4')$, i.e. for the splitting off $\text{POOHOC}_2\text{H}_2$ and CHO together as $\text{POOHOC}_2\text{H}_3\text{O}$. Attempts

to find transition states for the break of the bond between $\text{C}(4')$ and $\text{C}(5')$, i.e. for the splitting off of $\text{POOHOC}_2\text{H}_2$ alone, failed so that the CHO group moved away from the remaining molecule and was reattached to the $\text{POOHOC}_2\text{H}_2$ fragment (total charge +7) or it formed a separate fragment (total charge +6). The partial charge of the $\text{POOHOC}_2\text{H}_3\text{O}$ fragment is +2 for both total charges +6 and +7. The energy barriers for the breaking of the bond were only 0.003 and 0.005

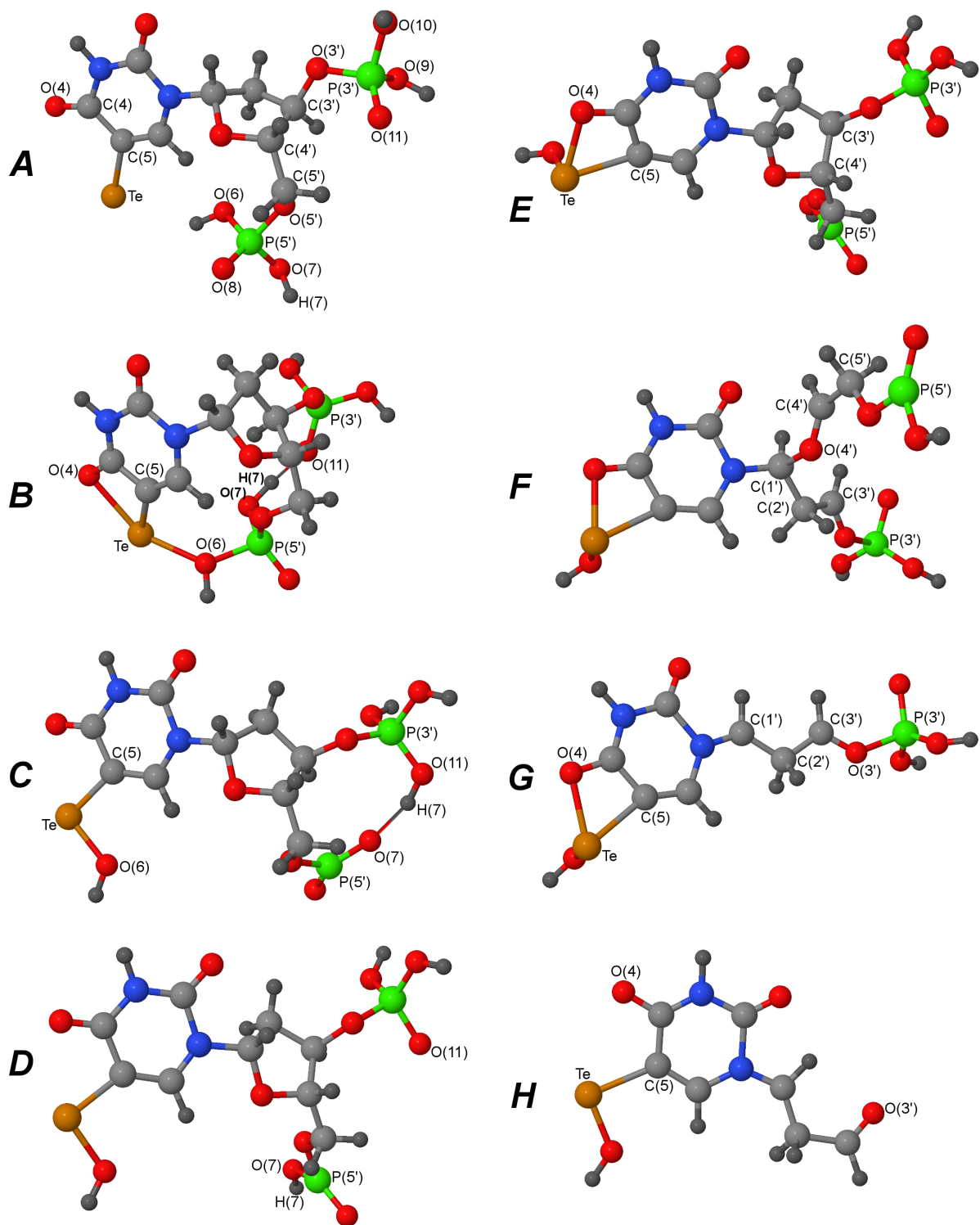


Figure 2: Gradual structural change and fragmentation of 5-telluro-2'-deoxyuridine-3',5'-biphosphate with rising positive charge.

hartrees, respectively. The distance of the C(1')–O(4') bond is 1.995 Å in the transition state compared to 1.592 Å in the energetically minimized *F* structure for the charge +6 and 1.829 Å compared to 1.5107 Å for the charge +7.

4 Conclusions

The 5-telluro-2'-deoxyuridine molecule, which is composed of 5-tellurouracil and 2-deoxyribose, proved to be less stable at positive molecular charge than 5-tellurouracil [1] due to the lower inner stability of the 2-deoxyribose molecule, i.e. the early

breaks occur within the 2-deoxyribose part of the molecule.

In DNA, the 2'-deoxyuridine molecule is flanked by phosphate groups. The calculations for positively charged 5-telluro-2'-deoxyuridine-3',5'-biphosphate molecules showed that these phosphate groups obviously have a heavily stabilizing effect on the 5-telluro-2'-deoxyuridine molecule allowing charges of up to +7. However, the energy barriers for splitting off $\text{POOHOC}_2\text{H}_3\text{O}^{2+}$ are very low for the charge levels +6 and +7. The stabilizing effect can be attributed to the fact that the charge is extended over a larger volume in the case of the 5-telluro-2'-deoxyuridine-3',5'-biphosphate molecule resulting in weaker repulsive forces between the partial charges within the cation.

Because our geometry optimizations refer to equilibrium structures, these results should be considered as a lower estimate for the damages caused by the Auger cascades after the ^{125}I decay where time-dependent perturbations could support the breaking of the structures.

One important question still remains open: How fast will the high positive excess charge initially deposited on the Te atom be spread over a large molecule? The Auger cascades after the ^{125}I decay produce an average charge of +7 within 10^{-16} to 10^{-14} s (first cascade) and the total average charge of +15 within 10^{-9} s (second cascade) on Te. Calculations of charge transfer rates between DNA bases [5], which are merely predicated on the single charge transfer theory, indicate that the time constants for these transfer processes are between the time constants of the two Auger cascades, i.e. that the charges produced by the first, fast cascade might accumulate on the primary 5-tellurouracil or 5-telluro-2'-deoxyuridine molecule whereas the charges produced by the second, slower cascade may discharge to the neighbouring bases in the course of the cascade. Considering the stabilizing effect of the phosphate groups found in this work, it is conceivable that not every decay of ^{125}I incorporated in uracil will result in a Coulomb explosion of the base molecule.

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