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Ab initio molecular treatment of charge-transfer processes induced by collision of carbon ions with 5-halouracil molecules

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The charge transfer in the collision of C^{4+} ions on 5-halouracil molecules has been studied theoretically by means of *ab initio* quantum chemistry molecular methods followed by a semiclassical dynamical treatment. The process appears markedly less efficient than the corresponding charge transfer with a uracil target which induces an enhancement of the complementary fragmentation process in agreement with the radio sensitivity of 5-halouracil molecules widely recognized. The mechanism seems to be driven by both electronic and steric effects which induce a lowering of the charge transfer cross sections and favor various orientations of the projectile with respect to the 5-halouracil target considered.

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I. INTRODUCTION

Severe damage to DNA may be induced by interaction of ionizing radiation with biological tissue [1]. Early studies have shown that the replacement of thymine by 5-bromouracil in cellular DNA induces strong enhancement of DNA damage through ionizing radiation and results in significant increase of cell death [2]. Such sensitivity to ionizing radiation is also recognized for other 5-halouracil molecules and radiosensitization properties have been widely employed in radiation therapy [2–4]. In such processes, important damage is due to the secondary particles generated along the track after interaction of the ionizing radiation with the biological medium [5]. In that sense, experimental and theoretical studies have been performed in order to investigate the mechanism involved in attachment of secondary low-energy electrons on such molecules [6–10].

However, singly and multiply charged ions can also be possible secondary particles and a number of experiments have been developed recently involving the action of such ions on biological systems [11–14]. These collisions, generally at relatively low energies, may induce different processes: excitation and fragmentation of the biomolecule, ionization of the gaseous target, and also possible charge transfer from the multicharged ion towards the biomolecule. Experimentally, the relative cross sections for the different ionization and fragmentation channels may be determined from the mass spectra. But theoretically it is possible to investigate the charge transfer process in the framework of the molecular representation of the collision. We have studied in particular the charge transfer induced by collision of C^{q+} ions with uracil [15,16], in relation with the experiments of de Vries *et al.* [11]. Fragmentation and charge transfer have been shown to be complementary processes and a strong influence of the electronic structure and charge q ($q=2-4$) of the C^{q+} ion has been pointed out [15]. At low velocities, the charge transfer cross sections are very small for the C^{2+} projectile ion and almost complete fragmentation is observed experimentally. On the contrary, charge transfer is much more efficient for the C^{4+} projectile and weakly dependent on collision energy, in correspondence with lower experimental fragmentation yield. The process has been shown to be highly anisotropic: for the C^{4+}+uracil system, it is enhanced by up to a factor 100 for collisions in a solid angle about 20° in the perpendicular direction compared to reactions occurring in the planar or near-planar geometry [16]. As 5-halouracil molecules are supposed to enhance sensitivity to ionizing radiation, the collision with ions, here carbon ions, would favor fragmentation of the biomolecule in the collision involving a halouracil, compared to the same reaction with uracil. That means that, on the contrary, the charge transfer process would be less efficient. In order to check this point, we have thus undertaken a detailed study of these processes involving a comparison of the different halouracils and their influence on the collision cross-section values, and also a consideration, in each case, of the preferred geometry for the collision process. In order to investigate in detail all these points, we have calculated the charge transfer cross sections for the collision of the C^{4+} projectile ion on, respectively, 5-fluorouracil, 5-chlorouracil, and 5-bromouracil targets for a series of geometries, from perpendicular to near-planar orientation. We chose the C^{4+} projectile carbon ion as the collision cross sections have been shown to be significantly higher in the C^{4+}+uracil system compared, for example, to the C^{2+}+uracil collision [16]. As in previous work [15,16], *ab initio* molecular calculations of the potential energies and couplings followed by a semiclassical dynamics in the $[3-150]$ keV collision energy range have been performed.

II. MOLECULAR CALCULATIONS

As developed previously [15,16], the collision has been represented as the evolution of a polyatomic C^{4+}-halouracil complex treated in the framework of the simple one-dimensional reaction coordinate approximation model [17]. The evolution of such a pseudo-diatomic-molecule system is thus driven by the reaction coordinate corresponding to the

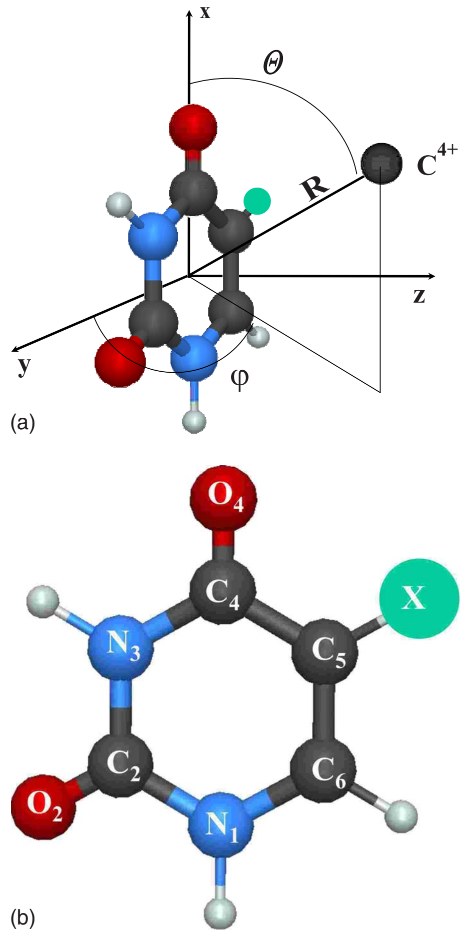

FIG. 1. (Color online) (a) Internal coordinates for the C^{4+} +halouracil system. (b) Geometry of the halouracil molecules 5-FU (X=F); 5-ClU (X=Cl); 5-BrU (X=Br).

TABLE I. Vertical ionization potentials of the 5-halouracil molecules (in eV).

	VIP our calculation	VIP Wetmore *et al.* [18]	VIP Experiment [19]
U	9.56 [15]	9.47	9.50
5-FU[a]	9.55	9.46	
5-ClU[b]	9.35	9.21	
5-BrU[c]	9.12	9.07	

[a] Fluorouracil.
[b] Chlorouracil.
[c] Bromouracil.

distance between the center-of-mass of the halouracil molecule and the colliding carbon ion. Such an approach does not, of course, take into account the internal motions of the molecule but may be reasonable for very fast collision processes where nuclear vibration and rotation periods are assumed to be much longer than the collision time.

The geometry of the process is represented in Figs. 1(a) and 1(b) for the three halouracils. The different molecular states of the collision system are calculated along the reaction coordinate R for different approaches θ from the perpendicular ($\theta=90°$) to a near-planar geometry in order to take into account the anisotropy of the process. The potentials have been determined for a large number of R distances in the 0.5–9 Å range for a number of specific values of the angle $\theta=[90°,70°,45°,20°]$; the angle φ has been kept fixed at $\varphi=60°$ which corresponds to a direction opposite to the halogen atom. An all-electron calculation has been performed, with no symmetries and using Cartesian coordinates with origin of coordinates at the center-of-mass of the halouracil molecule. The geometry of the ground state of each halouracil molecule has been optimized by means of the density functional theory (DFT) method with the Becke three-parameter Lee-Yang-Parr hybrid functional using the 6-311G^{**} basis sets. The vertical ionization potentials are presented in Table I and compare favorably to previous results [18,19], in particular, the recent calculations of Wetmore *et al.* [18]. Such an optimized geometry has been taken frozen during the collision process. The molecular calculations have been carried out by means of the MOLPRO suite of *ab initio* programs [20]. The molecular orbitals were optimized in state-averaged complete active space self-consistent field (CASSCF) calculations. Dynamical correlation effects are not taken into account at this level of theory, but we can expect a correct description of the relative energies of the different excited states. Taking into account our previous work [15,16], the active space includes the six highest valence orbitals constructed mainly on the $2p_z$, $3p_z$, $4p_z$ orbitals centered, respectively, on fluor, chlorine, and bromine, the $2p_z$ orbitals centered on the oxygen atoms, the $2p_{z(\mathrm{C5})}$ and $2p_{z(\mathrm{C6})}$ orbitals [see Fig. 1(b)], and the $2p_x$, $2p_y$, and $2p_z$ orbitals of the colliding carbon ion. The $1s$ orbitals are treated as frozen core as well as the s and p doubly occupied orbitals on the halogen atoms.

The radial coupling matrix elements between all pairs of states have been calculated by means of the finite difference technique

$$g_{KL}(R)=\langle\psi_K|\partial/\partial R|\psi_L\rangle=\lim_{\Delta\to 0}\frac{1}{\Delta}\langle\psi_K(R)|\psi_L(R+\Delta)\rangle,$$

with the parameter $\Delta=0.0012$ a.u. as previously tested and using the three-point numerical differentiation method for reasons of numerical accuracy. The center-of-mass of the halouracil molecule has been chosen as origin of electronic coordinates.

The potential energy curves for the different C^{4+} on 5-halouracil molecules collision systems are presented in Figs. 2(a)–2(c) for the perpendicular geometry. The same features already pointed out for the C^{4+}+uracil collision [15] with a strong avoided crossing at long range around 6 Å between the 4 ^1A entry channel and the excited 5 ^1A, 6 ^1A, 7 ^1A charge transfer levels are clearly observed for all the C^{4+}+halouracil systems. The main process is a double excitation of both electrons of the $2p_{\mathrm{O}}$ orbital on 5-halouracil (the $2p_{\mathrm{O}}$ orbital is a linear combination of the $2p_z$ orbitals on atoms O2 and O4 of the halouracil molecule with a contribution of the p_z orbitals on halogen) to the $2p$ components of the colliding carbon, and to the π_{C5C6} orbital constructed on $2p_{z(\mathrm{C5})}$ and $2p_{z(\mathrm{C6})}$ orbitals of 5-halouracil. The position of the avoided crossing is very close, around $R=6.4$ Å, for

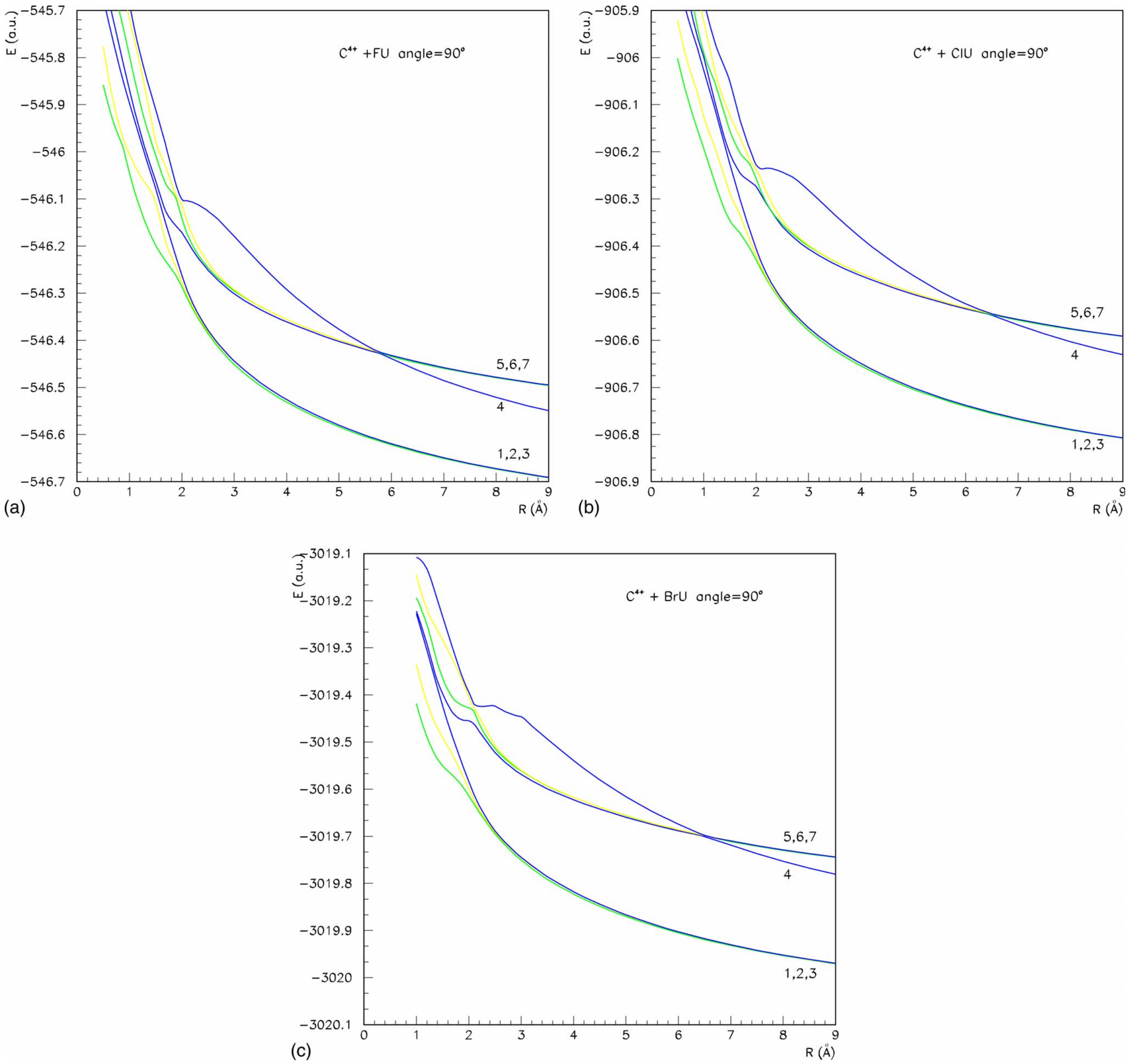

FIG. 2. (Color online) Adiabatic potential energy curves for the C^{4+}+halouracil collision systems in the perpendicular geometry (numbering by increasing energy). (a) C^{4+}+5-FU, (b) C^{4+}+5-ClU, (c) C^{4+}+5-BrU. 1 (green/medium gray): ^1A state corresponding to the configuration $\{2p_O 2p_z\}$, 2 (yellow/light gray): ^1A state corresponding to the configuration $\{2p_O 2p_y\}$, 3 (blue/black): ^1A state corresponding to the configuration $\{2p_O 2p_x\}$, 4 (blue/black): ^1A state corresponding to the configuration $\{(2p_O)^2\}$, 5 (green/medium gray): ^1A state corresponding to the configuration $\{\pi_{C5C6} 2p_z\}$, 6 (yellow/light gray): ^1A state corresponding to the configuration $\{\pi_{C5C6} 2p_y\}$, 7 (blue/black): ^1A state corresponding to the configuration $\{\pi_{C5C6} 2p_x\}$.

5-chlorouracil and 5-bromouracil; it appears at a lower internuclear distance, R=5.8 Å, for 5-fluorouracil. It is depending also on the geometry of the collision system. The main features are displayed in Figs. 3(a)–3(c) for three characteristic orientations of the C^{4+}+5-fluorouracil system. Generally speaking, the interaction appears at lower internuclear distances when the approach angle θ decreases and moves from the perpendicular geometry (θ=90°) to a geometry closer to the planar one. The values calculated for a series of angles θ show a smooth variation of the position of the main avoided crossing between θ=90° and 70°, but the effect becomes significant when the approach angle reaches θ=45° leading to a wide distance range interaction around R=4–5 Å. At lower angle such as θ=20°, the molecular system is dominated by short range avoided crossings between the different potentials. A similar behavior is observed for the C^{4+}+5-chlorouracil and C^{4+}+5-bromouracil collision systems.

III. COLLISION DYNAMICS

As for the collision of C^{q+} ions with uracil [15,16], the collision dynamics has been performed in the [0.1–0.7] a.u.

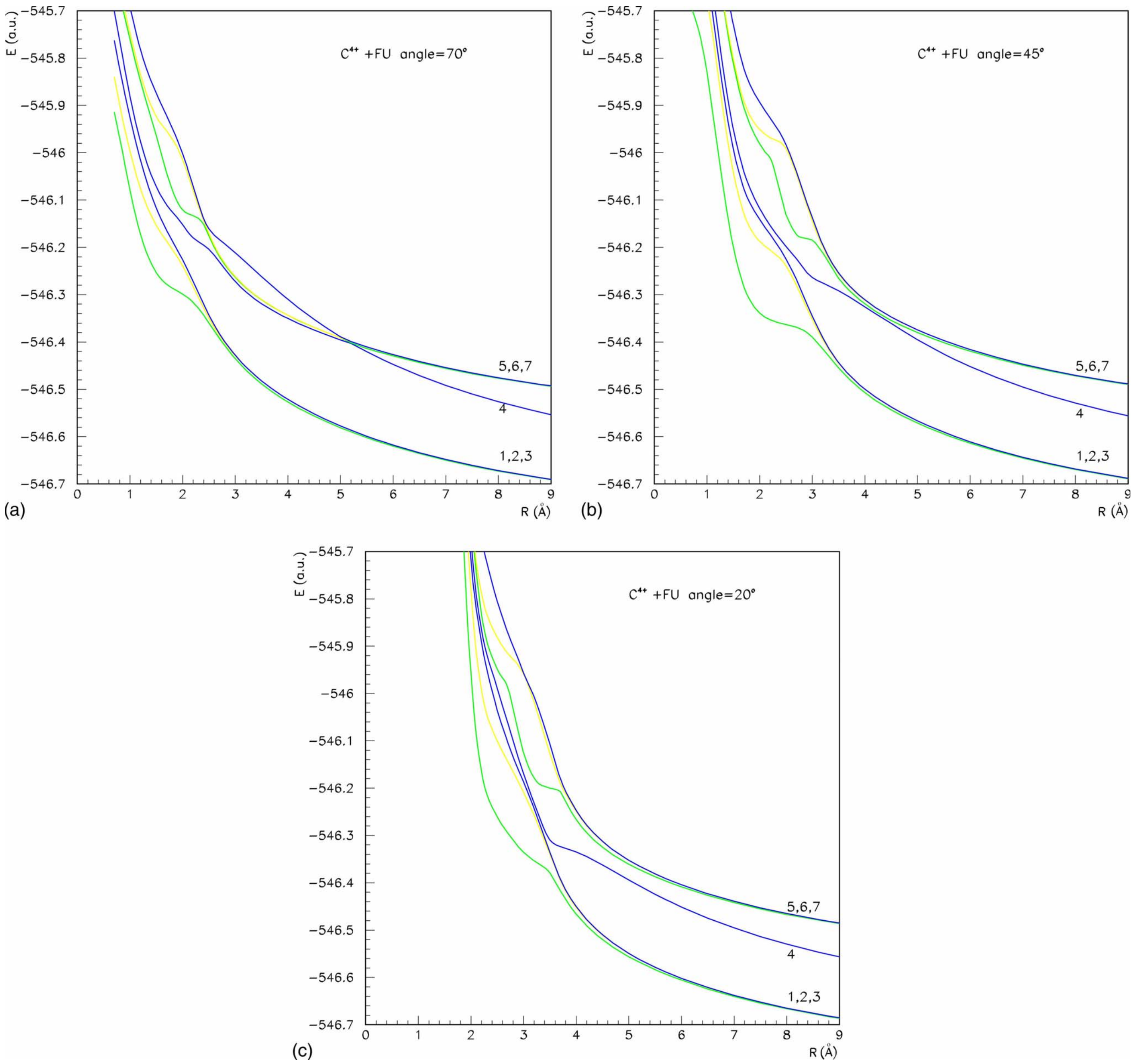

FIG. 3. (Color online) Adiabatic potential energy curves for specific geometries of the C^{4+}+5-fluorouracil collision system (same labels as in Fig. 2). (a) θ=70°; (b) θ=45°; (c) θ=20°.

collision velocity range ([3–147] keV laboratory energies) by means of semiclassical approaches using the EIKONXS code based on an efficient propagation method [21]. The calculation has been carried out in the framework of the sudden approximation hypothesis assuming electronic transitions to occur so fast that vibration and rotation motions could be considered as frozen during the collision. Effectively, as we detailed in previous work [16], a factor 100 may be assumed for the ratio between the vibration and collision times for collisions in the keV energy range we are dealing with. This first order approximation, widely used in ion-diatomics collisions [22–24], has been shown to give reliable results for energies greater than ~100 eV/amu [24].

The collision dynamics for velocities between 0.1 and 0.7 a.u. has been carried out for the different orientations taking into account all the transitions driven by radial coupling matrix elements with origin of electronic coordinates at the center-of-mass of the halouracil molecule. The coupled equations have been solved with a step size such that an accuracy of 10^{-4} for the symmetry of the S matrix is achieved. The charge transfer cross sections for selected velocities as a function of the θ angle are displayed in Figs. 4(a)–4(c) for the collision of C^{4+} on 5-fluorouracil, 5-chlorouracil, 5-bromouracil, respectively. These results may be compared to the previous ones obtained for the C^{4+} +uracil system [16]. The first very important remark is that the order of magnitude of the cross sections is completely different: the cross sections are at least a factor 100 lower in the collision systems including a halouracil molecule, compared to the uracil target [15,16]. This can be pointed out more precisely by looking at the averaged values over the different orientations displayed in Table II and Fig. 5. For all

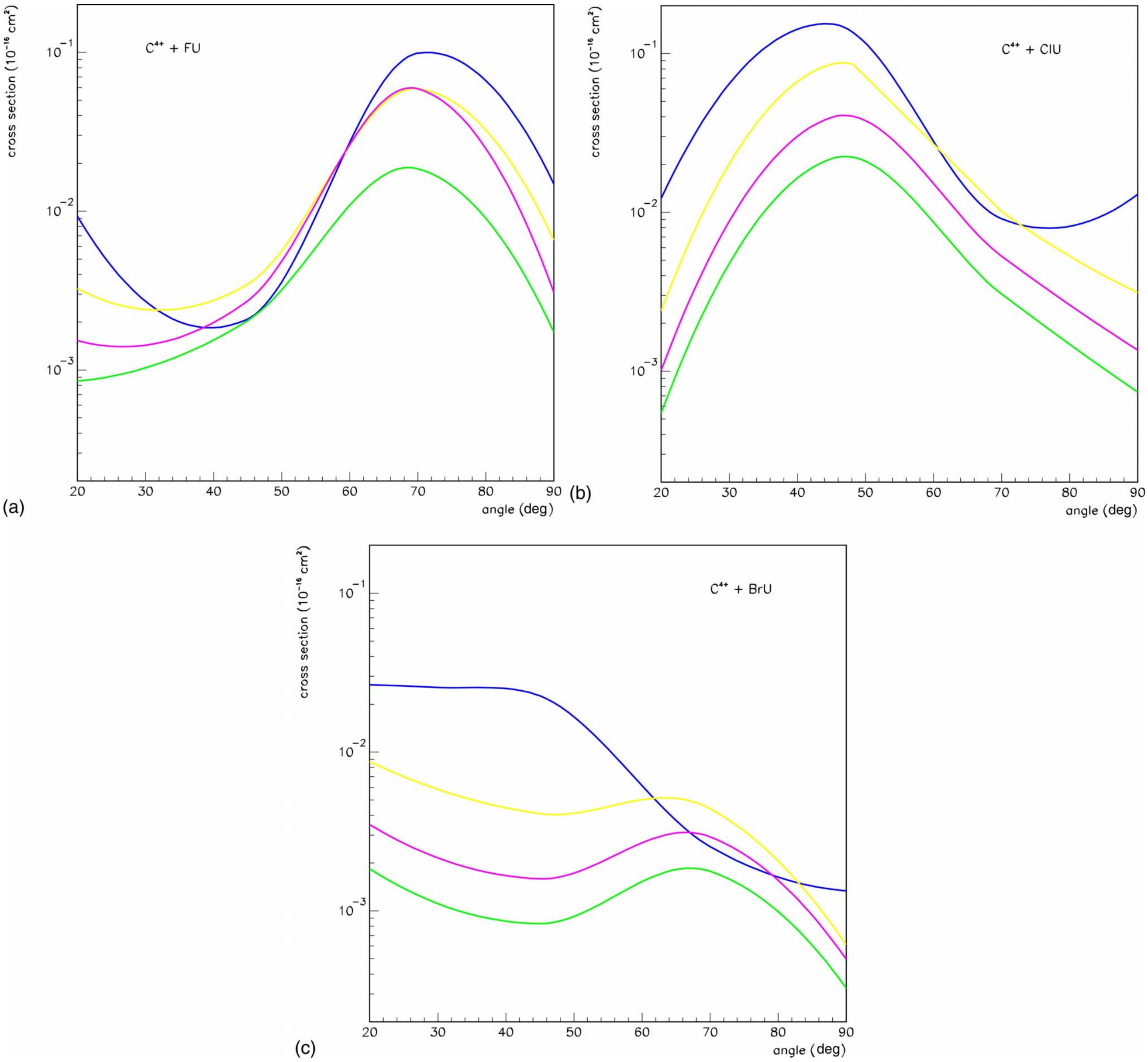

FIG. 4. (Color online) Charge transfer cross sections for the C^{4+}+halouracil systems as a function of the θ angle for selected collision velocities (in 10^{-16}cm^2). (a) C^{4+}+5-FU; (b) C^{4+}+5-ClU; (c) C^{4+}+5-BrU. Blue/black: v=0.1 a.u. (E_{lab}=3 keV); yellow/light gray: v=0.3 a.u. (E_{lab}=27 keV); magenta/dark gray: v=0.5 a.u. (E_{lab}=75 keV); green/medium gray: v=0.7 a.u. (E_{lab}=147 keV).

systems, the cross sections are slightly decreasing with collision energy, from about 0.04×10^{-16} cm^2 to 0.006×10^{-16} cm^2 for 5-fluorouracil and 5-chlorouracil targets; they are significantly lower, from about 10^{-2} to $10^{-3}\times10^{-16}$ cm^2 for 5-bromouracil. This point is crucial with regard to the radiosensitivity of the halouracils. Effectively, as charge transfer and fragmentation have been shown to be complementary processes [15], low charge transfer cross sections mean a high efficiency for the fragmentation process, in complete agreement with the enhancement of DNA damage observed with 5-halouracil molecules. Numerically, the cross sections are lower for the 5-bromouracil target which would be supposed to be the most efficient radiosensitizer. Such a lowering of charge transfer cross sections for halouracil targets compared to uracil could be attributed to an important

TABLE II. Charge transfer cross sections averaged over the different orientations for the C^{4+}+halouracil collisional systems (in 10^{-16} cm^2).

Velocity (a.u.)	E_{lab} (keV)	C^{4+}+5-FU	C^{4+}+5-ClU	C^{4+}+5-BrU
0.1	3	0.031	0.047	0.013
0.2	12	0.024	0.038	0.007
0.3	27	0.018	0.025	0.004
0.4	48	0.013	0.017	0.003
0.5	75	0.010	0.012	0.002
0.6	108	0.007	0.009	0.002
0.7	147	0.006	0.006	0.001

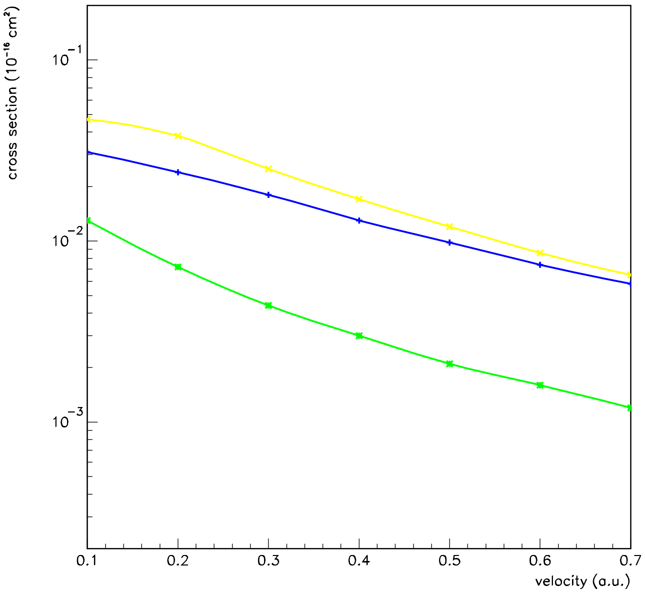

FIG. 5. (Color online) Charge transfer cross sections averaged over the different orientations for the C^{4+}+halouracil collisional systems (in 10^{-16}cm^2). Yellow/light gray: C^{4+}+5-ClU; blue/black: C^{4+}+5-FU; green/medium gray: C^{4+}+5-BrU.

electronic effect relied to the difference of electronegativity between halogen and hydrogen atoms. The analysis may be completed by looking at the anisotropy of the process in the different cases. For the C^{4+}+5-fluorouracil collision system, the charge transfer is clearly favored near the perpendicular direction with a maximum around the angle θ=70°. The atomic radius of fluor appears to be small enough to allow the approach of the C^{4+} ion around the perpendicular geometry, as in the collision with uracil. Furthermore, the charge transfer cross sections decrease with increasing collision velocity. Such behavior is completely similar, except for the order of magnitude of the cross sections, to the features previously observed for the C^{4+}+uracil system. The situation is slightly different for the C^{4+}+5-chlorouracil collision system. We still observe a decrease of the charge transfer cross sections with increasing collision velocity, but in that case the process appears to be favored for an orientation around θ=45°. This could be attributed to a steric effect relied to the higher atomic radius of chlorine which could effectively reduce the access of the colliding ion to 5-chlorouracil in the perpendicular geometry and then favor an approach further from the chlorine atom. The conclusions are less clear for the C^{4+}+5-bromouracil system. Numerically, the charge transfer cross sections decrease with increasing collision velocity as observed for the two other halouracil targets, but they appear to be less dependent on the geometry of the system. At low collision velocities, the approach angles between θ =20°−30° seem, however, preferred in accordance with a possible steric effect, as mentioned for the C^{4+}+5-chlorouracil collision, considering the large bromine atomic radius. But for higher velocities, the orientation dependence is less significant and the cross sections for the C^{4+}+5-bromouracil charge transfer process remain small for every orientation. They present, however, a decrease in the perpendicular approach which appears to be particularly unfavored.

IV. CONCLUDING REMARKS

The charge transfer in the C^{4+}+5-halouracil reactions has been investigated using *ab initio* potential energy curves and couplings calculated in the one-dimensional reaction coordinate approximation model followed by a semiclassical collision treatment in the framework of the sudden approximation approach. This work shows a strong lowering of the charge transfer cross sections, by at least a factor 100, for collision systems involving a halouracil target compared to the previous results with a uracil target. This may lead to an enhancement of the fragmentation process, in complete agreement with the radiosensitization properties already noticed for the 5-halouracil molecules, in particular for 5-bromouracil. As already pointed out for C^{4+}+uracil, the charge transfer appears to be an anisotropic process and the preferred orientation depends on the halouracil target considered. In such reaction, two effects seem to have to be taken into account simultaneously: a global electronic effect with regard to the electronegativity of the halogen atom, and a more specific steric effect relied to the size of the halogen which could induce preferred orientations for the collision reaction.

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