Action of secondary ions on biomolecules: anisotropy and radio-sensitization properties

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Abstract. The charge transfer process of carbon ions on biomolecular targets is analyzed with regard to the action of radiation on the biological medium. The theoretical treatment is performed in a wide collision energy range by means of \textit{ab-initio} quantum chemistry molecular methods. The process has been investigated for a series of target molecules, thymine, uracil and 5-halouracil corresponding to a similar skeleton with different substituent. The charge transfer appears markedly anisotropic in the whole energy domain, and interesting specific features may be pointed out at low energies. In addition, such a study may provide information on the radio-sensitivity of the different bases with regard to ion-induced radiation damage.

1. Introduction
The interaction of ionizing radiation with biological tissues can induce severe damage to DNA [1] as single- and double-strand breaks which can create important biological lesions and may lead to cancer. Apart from the radiation, secondary particles, electrons, or ions generated along the track after interaction of the ionizing radiation with the biological medium, have been shown to induce significant damage [2]. Numerous studies focused on the behaviour of the DNA building blocks under irradiation with slow-electrons, photons or ions with the aim to analyze the mechanisms involved at the molecular level. Low-energy electrons have been extensively investigated and they are shown to induce important damage even at very low kinetic energies, down to 3eV [3-6]. However, experimental and theoretical studies have also been performed on interactions of ions with the biological medium, first of all in the keV energy range corresponding to the region of the Bragg peak where the damage is maximum [7-16] and makes heavy-ion therapy such a promising technique in cancer treatment [17]. More recently, studies have been extended to lower collision energies [18-22] where specific physico-chemical interactions with the biological medium can occur. Collisions of ions with biomolecular targets may induce different processes: excitation and fragmentation of the biomolecule, ionization of the gaseous target, and also charge transfer from the multiply charged ion towards the biomolecule [23]. Experimentally, excitation and fragmentation cross sections are determined from mass spectra [7-9]. But theoretically, the charge transfer process may be investigated in the framework of the molecular representation of the collisions [24]. Fragmentation and charge transfer processes have been shown to be complementary processes and a strong influence of the charge of the projectile has been pointed out [11]. We have thus investigated the collision of the same...
ion on a series of biomolecular targets of similar structure, the DNA base thymine, the RNA base uracil and the corresponding 5-halouracil molecules corresponding to the same skeleton, but with a different substituent on the carbon C5 (see figure 1b). This extended study allows the analysis of the charge transfer mechanism with regard to both steric and electronic effects as groups of different size and electro-negativity are involved. We have chosen for this study the C⁴⁺ projectile ion which was shown to induce efficient charge transfer, weakly dependent on the collision energy [7,11], and which presents similar features as the C⁶⁺ ion used in hadrontherapy treatments [25]. The calculation has been performed in a wide collision energy range, from keV incident ions where incident damage is supposed to be maximum, to lower collision energies in order to exhibit a possible specific behaviour which could be of importance in ion-induced radiation damage. We focused our attention on the anisotropy of the process with regard to the substituent, as well as on the radio-sensitivity properties of halouracil molecules widely used in radiation therapy [26]. Ab-initio quantum chemistry methods have been used for the determination of the potential energies and non-adiabatic coupling matrix elements followed by a semi-classical collision treatment.

2. Theoretical approach

The charge transfer is described as the evolution of the quasi-molecular ion-target system. For such a polyatomic collision system, a simple model may be proposed by means of the one-dimensional reaction coordinate approximation [27-29], the polyatomic C⁴⁺ - biomolecule complex being considered as a pseudo-diatomic molecule whose evolution is driven by the reaction coordinate corresponding to the distance between the centre-of-mass of the target and the colliding carbon ion. Of course, such an approach does not consider the degrees of freedom of the complex and the internal motions of the molecule but it appears 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 collision system is presented in figure 1a,b. The different molecular states involved in the charge transfer process are calculated along the reaction coordinate R for different approaches θ from the perpendicular (θ=90°) to a planar or 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, from 0.5Å to 9Å, for a number of specific values of the angle θ. The angle ϕ has been kept fixed at ϕ=60° which corresponds to a direction opposite to the X substituent. The geometry of the ground state of the different biomolecular targets have been optimized and kept frozen during the collision process.

![Figure 1](image)

**Figure 1.** (a) Internal coordinates for the C⁴⁺ + biomolecule system. (b) Geometry of the biomolecule: thymine, X=CH₃; uracil, X=H; 5-fluorouracil, X=F; 5-chlorouracil, X=Cl; 5-bromouracil, X=Br.

The molecular calculations have been carried out using the MOLPRO suite of ab-initio programs [30]. As spin-orbit coupling is negligible in the energy range of interest, only singlet states have been considered in the calculation. An all-electron calculation has been performed with no symmetries for
non-planar geometries using Cartesian coordinates with the origin of coordinates at the centre-of-mass of the target molecule. For the planar approach, calculations have been performed in the C\textsubscript{6v} symmetry group. Only the states coupled by means of radial coupling matrix elements have been taken into account in the calculation, the rotational coupling being neglected in a first step [31]. The potential energies and non-adiabatic coupling matrix elements (NACME) have been determined by state-averaged CASSCF calculations. Even if dynamic correlation effects are not taken into account at this level of theory, a correct description of the relative energies of the different excited states can be expected. Besides, some calculations at the higher MRCI (Multireference Configuration Interaction) level of theory have been performed for a few critical points. A similar active space has been considered for the different targets. It includes the six highest valence orbitals constructed mainly on the 2\textit{pz} orbital on CH\textsubscript{3} for thymine, the 2\textit{pz}, 3\textit{pz}, 4\textit{pz} orbitals centered, respectively, on fluorine, chlorine, and bromine for halouracil molecules, and, in all cases, the 2\textit{pz} orbitals centred on the oxygen atoms, the 2\textit{pz}(C\textsubscript{5}) and 2\textit{pz}(C\textsubscript{6}) orbitals (describing the molecular orbital called by extension \pi(C\textsubscript{5}C\textsubscript{6}), see figure 1b), and the 2\textit{px}, 2\textit{py} and 2\textit{pz} orbitals of the colliding carbon ion. The 1\textit{s} orbitals of carbon, nitrogen and oxygen are treated as frozen core. The valence electrons have been described using the 6-311G** basis set of atomic orbitals.

The charge transfer process is driven mainly by the non-adiabatic interactions at the vicinity of the avoided crossings [32,33] and corresponding non-adiabatic radial coupling matrix elements between all pairs of states of the same symmetry have been calculated numerically by means of the finite difference technique [34]:

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

which, taking account of the orthogonality of the eigenfunctions |\psi_K (R)\rangle and |\psi_L (R)\rangle for \( K \neq L \) reduces to

\[
g_{KL}(R) = \langle \psi_K | \partial / \partial R | \psi_L \rangle = \lim_{\Delta \to 0} \frac{1}{\Delta} \langle \psi_K (R) | \psi_L (R + \Delta) \rangle. \tag{2}
\]

The stability with regard to the differentiation step has been tested and the value \( \Delta = 0.0012 \text{ a.u.} \) has been chosen [35] using the three-point numerical differentiation method for reasons of numerical accuracy. The centre of mass of the target has been taken as origin of electronic coordinates.

The collision dynamics has been treated from keV to eV energies using the EIKONXS program based on an efficient propagation method [36] taking into account of all the transitions driven by radial coupling matrix elements. The calculations have been performed in the framework of the sudden approximation hypothesis assuming that electronic transitions occur so fast that vibration and rotation motions remain unchanged. Effectively the collision time to travel a distance \( L, \) \( T_{\text{coll}} \approx L(\mu / 2E_{\text{coll}})^{1/2} \) [37], appears much shorter than the typical vibration time \( T_{\text{vib}} \approx \Delta E_{\text{vib}}, \) and \textit{a fortiori} typical rotation time. The ratio \( T_{\text{vib}} / T_{\text{coll}} \) has been shown to be about \( 10^2 \) at keV collision energies [12]. It depends of course of the collision velocity and decreases by a factor 10 between 1keV and 10 eV, remaining still in the approximation limit. The total and partial cross sections, corresponding to purely electronic transitions, are thus determined by solving the impact-parameter equation as in the usual ion-atom approach, considering the geometry of the molecular target fixed [29]. Such a treatment is, of course, relatively crude, but it has proved its efficiency in a number of ion-diatomic or polyatomic collisions [38,39,11] for energies higher than \( \sim 10 \text{eV/amu} \). Recently we have extended this approach to lower collision energies [20,22] with regard to our comparative analysis of time-dependent quantal wave packet and semiclassical approaches in charge transfer processes showing that semiclassical methods can give quite reasonable cross sections up to 10-20 eV, the discrepancy with quantal calculations appearing only for lower energies [40].
3. Anisotropic effect

For all biomolecular targets, the charge transfer process appears to be highly anisotropic. The cross sections calculated for a series of angles $\theta$ (see figure 1a) corresponding to different orientations of the projectile towards the target from perpendicular to planar geometries, show indeed very strong variations, as presented in figure 2 for the $\text{C}^{4+}$ + uracil charge transfer system. For this system, the charge transfer is clearly favoured for geometries close to the perpendicular orientation. The cross sections are maximum for the angle $\theta=70^\circ$, about 2 orders of magnitude higher than in the planar or near-planar orientation. This result is observed for collision energies in the keV range as presented in figure 2a, but also at lower collision energies, down to 30 eV, as exhibited in figure 2b. Globally speaking, the charge transfer process appears thus clearly more efficient for the $\text{C}^{4+}$ + uracil collision in a solid angle about 20° around the perpendicular geometry.

![Figure 2](image)

Figure 2. Charge transfer cross sections (given in $10^{-16}$ cm$^2$) for the $\text{C}^{4+}$ + uracil collision system. (a) $\rightarrow$, $E_{lab}=$3 keV; $\leftarrow$, $E_{lab}=$27 keV; $\rightarrow$, $E_{lab}=$75 keV; $\leftarrow$, $E_{lab}=$147 keV; (b) $\rightarrow$, $E_{lab}=$3 keV; $\leftarrow$, $E_{lab}=$750 eV; $\rightarrow$, $E_{lab}=$120 eV; $\leftarrow$, $E_{lab}=$30 eV.

Such effect is also observed for the halouracil targets. The results for collision energies between 3 keV and 30 eV are presented in figure 3a,b,c for, respectively, the 5-fluoro, 5-chloro and 5-bromouracil targets. The charge transfer process is clearly favoured near the perpendicular direction for the $\text{C}^{4+}$ + 5-fluouracil collision, with a maximum around the angle $\theta=70^\circ$. On the contrary, the process appears more efficient for an orientation around $\theta=45^\circ$ for 5-chlorouracil or 5-bromouracil targets. A similar behaviour appears also at higher energies, in the keV energy range [12] and could certainly be attributed to the influence of a strong steric effect. The atomic radius of fluor is indeed small and cannot hinder the access of the projectile ion, leading to a mechanism quite similar to the one observed for the $\text{C}^{4+}$ + uracil system with a preferred collision around the perpendicular geometry. This conclusion can also be extended to the thymine target molecule [22]. On the other hand, for a heavy substituent as chlorine or bromine of higher atomic radius, the access of the colliding ion in the perpendicular geometry is reduced and thus an approach further from the heavy halogen atom is favoured, as shown by the preferential cross section values in the $\theta=45^\circ$ geometry.

Some specific behaviour can be pointed out for the $\text{C}^{4+}$ + thymine charge transfer at eV collision energies. The corresponding cross sections in the [7.5–480] eV energy range are presented in figure 4 and show clearly a strong decrease of the charge transfer cross sections for the lowest energy, $E_{lab}=$7.5 eV. This effect is quite significant as charge transfer cross sections are lowered by a factor up to 10$^2$ at eV energies compared to cross sections at 500 eV. The effect is reduced with increasing energy, still marked at $E_{lab}=$30 eV, it disappears for collisions energies of the order of 100–500 eV. The cross sections appear to be highly anisotropic with a maximum for the orientation angle $\theta=20^\circ$–$30^\circ$. This
result may be discussed with regard to a previous analysis of the C⁴⁺ + uracil collision system involving the theoretical determination of charge transfer cross sections [11] and the experimental fragmentation yield [7]. In collisions of ions with biomolecular targets, excitation, ionization, fragmentation and charge transfer are strongly related processes and depend on a great number of factors, velocity, projectile charge, target state, but a qualitative correlation may be pointed out between fragmentation and charge transfer. For example, at low collision energy, the C²⁺ + uracil system appears experimentally to drive almost complete fragmentation, in relation with a very low charge transfer cross section and the fragmentation yield decreases with increasing collision energy, when the charge transfer cross section increases [7,11]. Conversely, for the same reactions with the C⁴⁺ projectile ion, the experimental fragmentation yield is lower, almost independent of the collision energy, and the calculated charge transfer cross sections are significantly higher than in the collision with the C²⁺ projectile, and similarly almost independent of the collision energy. These observations remain of course completely qualitative and have to be handled with care; anyway they would suggest that a correlation could be established between both processes. Considering the present results, fragmentation could thus be enhanced in the collision of C⁴⁺ ions on thymine for specific orientations at very low collision energies. This result is in accordance with experimental studies at hyperthermal energies [18,19] pointing out a complex mechanism in ion-induced radiation damage. This result has to be brought together with a similar enhancement observed for collisions with very low-energy electrons [3,4] and could be of interest for ion induced radiation damage.

Figure 3. Charge transfer cross sections with regard to the orientation angle θ (given in 10⁻¹⁶ cm²). (a) C⁴⁺ + 5-fluorouracil; (b) C⁴⁺ + 5-chlorouracil; (c) C⁴⁺ + 5-bromouracil. —, E_lab=3 keV; —, E_lab=750 eV; —, E_lab=120 eV; —, E_lab=30 eV.

Figure 4. Charge transfer cross sections for the C⁴⁺+ thymine system at low collision energies as a function of the θ angle (in 10⁻¹⁶ cm²). —, E_lab=7.5 eV; —, E_lab=30 eV; —, E_lab=120 eV; —, E_lab=270 eV; —, E_lab=480 eV.
4. Radio-sensitivity properties

Independently of the anisotropic effect discussed in the previous paragraph, charge transfer cross sections have also to be analyzed with regard to their order of magnitude for the different biomolecular targets. The results are summarised in table 1 for a wide range of collision energies.

Table 1. Charge transfer cross sections averaged over the different orientations for a series of C⁴⁺-biomolecule collision systems (in 10⁻¹⁶ cm²).

| Elab (eV) | C⁴⁺+thymine [22] | C⁴⁺+uracil [20,22] | C⁴⁺+fluorouracil [20,22,15] | C⁴⁺+chlorouracil [20,22,15] | C⁴⁺+bromouracil [20,22,15] |
|----------|------------------|--------------------|-----------------------------|-----------------------------|-----------------------------|
| 30       | 9.10             | 5.73               | 0.015                       | 0.085                       | 0.006                       |
| 120      | 8.68             | 6.45               | 0.020                       | 0.072                       | 0.009                       |
| 270      | 9.01             | 7.74               | 0.029                       | 0.056                       | 0.008                       |
| 3×10³    | 14.93            | 5.79               | 0.031                       | 0.047                       | 0.013                       |
| 27×10³   | 12.12            | 3.97               | 0.018                       | 0.025                       | 0.004                       |

The cross sections are of the same order of magnitude for the thymine and uracil targets; the values are slightly higher for thymine with a maximum of 14.9 10⁻¹⁶ cm² whereas the charge transfer cross sections do not exceed 7.7 10⁻¹⁶ cm² for uracil. From our previous discussion, this supposes that fragmentation would be somewhat less efficient for collisions with the thymine target than observed for uracil. However, the effect would remain relatively smooth, compared with the completely different order of magnitude observed for the charge transfer cross sections involving halouracil targets. The corresponding cross sections are indeed at least a factor 100 lower than previously noticed for uracil or thymine targets. The rate reaches even up to 10⁵ for 5-bromouracil. This point is crucial with regard to the radio-sensitivity of halouracils. Effectively, 5-bromouracil has been shown early to enhance DNA damage [25], but such sensitivity to ionizing radiation is also recognized for other 5-halouracil molecules and widely used in radiation therapy [41,42]. The very low values obtained for the charge transfer cross sections with halouracils would induce a very high efficiency for fragmentation, in complete agreement with the enhancement of DNA damage observed with 5-halouracils. Even if our approach remains qualitative, it could provide an order of magnitude of the effect. Effectively, the cross sections are numerically lower for the 5-bromouracil target supposed to be the most efficient radio-sensitizer. Such specific behaviour of halouracils could be attributed to an important electronic effect. Halogen atoms present indeed a high electro-negativity compared to the corresponding substituent, hydrogen atom or the CH₃ group, present in uracil or thymine targets which could compete with the electronic transfer from the target to the colliding carbon cation and charge transfer would be then less efficient.

5. Concluding remarks

The charge transfer in collisions of C⁴⁺ ions with thymine, uracil and halouracil, has been investigated using *ab-initio* methods in the one-dimension reaction coordinate approximation followed by a semiclassical collision treatment in the framework of the sudden approximation approach. Such approach provides information on the molecular states involved in the process, considering neutral and ionized target levels. The charge transfer process has been shown to be highly anisotropic, clearly favoured around the perpendicular geometry for thymine, uracil and fluorouracil, but quite sensible to steric effects as shown for chloro- and bromouracil targets for which the charge transfer is favoured in an orientation opposite to the heavy atom. A comparison with experimental measurements at given orientations would be highly desirable. Besides, a specific decrease of the C⁴⁺ + thymine charge...
transfer cross sections at eV energies, in an orientation close to the planar geometry, has been exhibited. This could lead to an interesting enhancement of the fragmentation process at very low energies, as observed for collisions with low-energy electrons and further investigations would be welcome. Taking into account the correlation pointed out between charge transfer and fragmentation processes, a strong radio-sensitization effect may be pointed out for the halouracil targets, in particular the 5-bromouracil, which would induce an enhancement of DNA damage through ionizing radiation in agreement with medical observations.

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