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Anisotropy and charge effect in collisions of ions with biomolecules

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HIGHLIGHTS

- Charge transfer in ion–biomolecule collisions.
- *Ab-initio* calculations of potential energy curves and couplings.
- Anisotropy and charge effect.
- Interest with regard to action of radiations on the biological medium.

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ABSTRACT

Charge transfer dynamics induced by collision of carbon ions with biological targets has been investigated theoretically by means of *ab-initio* quantum chemistry molecular methods. The series of pyrimidine nucleobases, thymine, uracil and 5-halouracil with similar skeleton and different substituents have been considered. The charge effect between C^{6+} and C^{4+} carbon ions is analyzed as well as the anisotropy of the electron exchange process.

1. Introduction

Ionizing radiations may induce severe damage to biological tissues (von Sonntag, 1987). The radiation itself interacts directly with biomolecules, but important damage may be caused by the secondary particles, low-energy electrons or ions, generated along the track after interaction of the ionizing radiation with the biological medium (Michael and O'Neill, 2000). Numerous experimental and theoretical studies focused on the behavior of the DNA building blocks under irradiation with slow-electrons, photons or ions have thus been developed in order to explore the mechanism underlying radiation-induced DNA damage at the molecular level. It has been shown in particular that low-energy electrons drive single- and double-strand breaks of plasmid DNA via dissociative attachment, even at very low kinetic energies (Boudaiffa et al., 2000; Martin et al., 2004; Pan et al., 2003). But collisions of ions on biomolecular targets, in particular DNA building blocks, have been also investigated, first of all in the keV range since these energies are relevant for the heavy-ion-induced biological radiation damage in the region of the Bragg peak (Alvarado et al., 2006; Bacchus-Montabonel et al., 2005, 2009; Champeaux et al., 2010; Coupier et al., 2002; de Vries et al., 2002; López-Tarifa et al., 2011; Schlathölter et al., 2006). In this region, the damage is maximum inducing a selectivity that makes heavy-ion therapy such a promising technique in cancer treatments (Lacombe et al., 2004), as for example hadron therapy by C^{6+} carbon ions for the treatment of deeply seated tumors (Bacchus-Montabonel, 2012; Wambersie, 1995). Experimental and theoretical studies on ion induced damage have however been extended more recently at lower energies where specific physico-chemical interactions with the biological medium khave been pointed out (Bacchus-Montabonel and Tergiman, 2011a, 2012; Deng et al., 2005a, 2005b).

Collisions of ions with biomolecular targets are driven by complex mechanisms involving different processes: charge transfer from the multiply charged ion toward the molecular target, excitation, ionization and fragmentation of the biomolecule. From the experimental point of view, fragmentation cross sections are determined from mass spectra (de Vries et al., 2002). But these experimental measurements cannot give any information on charge transfer between the incident ion and the biomolecular target. Such process may be investigated however theoretically in the framework of the molecular representation of the collisions. We have indeed developed a theoretical approach in order to study the charge transfer of carbon ions with different biomolecular targets (Bacchus-Montabonel et al., 2005, 2009; Bacchus-Montabonel and Tergiman, 2006, 2011b). We consider presently a series of pyrimidine nucleobases, thymine, uracil and 5-halouracil corresponding to the same skeleton, with different substituents on the carbon C5 as presented in Fig. 1b. Such a study allows the analysis of both steric and electronic effects in the charge transfer mechanism as groups of different sizes and electronativities are

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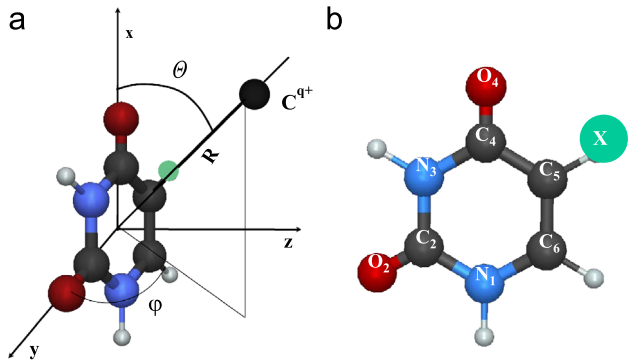

Fig. 1. (**a**) Internal coordinates for the C^{q+} +biomolecule system, and (**b**) geometry of the biomolecule: thymine, X=CH_3; uracil, X=H; 5-fluorouracil, X=F; 5-chlorouracil, X=Cl, 5-bromouracil, X=Br.

considered. We have analyzed in particular the influence of the substituent on the anisotropy of the process with regard to the orientation of the projectile toward the biological target. The collision has been studied for different charged ions, the C^{6+} ion used in hadron therapy by carbon ions as well as the C^{4+} ion in order to evaluate the influence of the charge of the projectile in the charge transfer process. *Ab-initio* quantum chemistry methods have been used for the determination of the potential energies and non-adiabatic coupling matrix elements. The collision dynamics has been performed in a wide energy domain, from keV to eV energies, in order to investigate the region of the Bragg peak as well as possible specific behavior at low energies.

2. Theoretical treatment

2.1. Molecular calculations

The molecular description of the collisions considers the charge transfer process as the evolution of a quasi-molecular system formed by the projectile ion and the molecular target. For complex systems, a simple model may be proposed using the one-dimension reaction coordinate approximation (Salem, 1982). The ion–biomolecule system may thus be considered as a pseudo-diatomic molecule in which evolution is driven by the reaction coordinate corresponding to the distance between the center-of-mass of the biomolecule and the colliding carbon ion. Of course such an approach does not consider the internal motions of the biomolecule 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 (Bacchus-Montabonel et al., 2000).

Fig. 1a and b presents the geometry of the collision system for the series of pyrimidine nucleobases. The molecular states involved in the process are calculated along the reaction coordinate R for different orientations θ 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 interacting region, from 0.5 Å to 9 Å for a number of specific values of the angle θ. The calculation has been performed from the perpendicular ($\theta=90^\circ$) to the planar geometry ($\theta=0^\circ$). The angle φ has been kept fixed at $\varphi=60^\circ$ which corresponds to a direction opposite to the X substituent and thus minimizes the steric hindrance in the collision process. The geometry of the ground state of the different targets has been optimized and kept frozen during the collision process.

The molecular calculations have been carried out with the MOLPRO suite of *ab-initio* programs (Werner and Knowles, 2010) using the 6-311G** basis set of atomic orbitals. Spin–orbit coupling being negligible in the energy range of interest, the electron spin can be assumed to be conserved during the collision process and only singlet states have been considered. 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 biomolecule. The potential energies and non-adiabatic coupling matrix elements (NACME) have been determined by state-averaged CASSCF (Complete Active Space Self-Consistent Field) calculations. Although, dynamical correlation effects are not taken into account at this level of theory, we can expect a correct description of the relative energies between excited states. Similar active spaces have been considered for the different targets in order to compare each system at the same level of accuracy, including the $2p_x$, $2p_y$ and $2p_z$ orbitals of the colliding carbon ion, the HOMO (highest occupied molecular orbital) mainly constructed on the $2p_z$ orbitals centered on both oxygen atoms and the $2p_{z(C5)}$ and $2p_{z(C6)}$ orbitals describing the molecular orbital called by extension $\pi_{(C5C6)}$ (see Fig. 1b). This excited orbital $\pi_{(C5C6)}$ is delocalized also on the $2p_z$ orbital on CH_3 for thymine, and on the $2p_z$, $3p_z$, and $4p_z$ orbitals centered, respectively, on fluorine, chlorine, and bromine for halouracil molecules. The 1s orbitals of carbon, nitrogen and oxygen are treated as frozen core. For both projectiles a complex mechanism may be observed, with a direct excitation of the HOMO on the molecular target to the 2p orbitals of the colliding carbon ion, together with a double excitation process with both excitation of the $\pi_{(C5C6)}$ orbital of the ring and the HOMO to the 2p components of the colliding ion (Bacchus-Montabonel, 2012; Bacchus-Montabonel and Tergiman, 2011b). Analysis of inner excitations could be performed by including deeper molecular orbitals in the active space although this would lead to quite heavier calculations.

The charge transfer process is being driven mainly by non-adiabatic interactions in the vicinity of avoided crossings (Baloïtcha et al., 2001); the non-adiabatic radial coupling matrix elements between all pairs of states have thus been calculated numerically by means of the finite difference technique (Bacchus-Montabonel et al., 2003):

$$g_{KL}(R) = \langle \psi_K | \partial/\partial R | \psi_L \rangle = \lim_{\Delta \to 0} \frac{1}{\Delta} \langle \psi_K(R) | \psi_L(R+\Delta) \rangle \qquad (2-1)$$

The stability with regard to the differentiation step Δ has been tested and a value of $\Delta=0.0012$ a.u. has been chosen (Bene et al., 2008). The center-of-mass of the biomolecule has been taken as origin of electronic coordinates.

2.2. Collision dynamics

The collision dynamics has been developed by semiclassical methods using the sudden approximation hypothesis assuming that the electronic transitions occur so fast that vibration and rotation motions remain unchanged during the collision time. The total and partial cross sections, corresponding to purely electronic transitions, are then determined by solving the impact-parameter equation with a frozen geometry for the molecular target. Such a crude treatment has proved its efficiency in a number of ion-diatomic or polyatomic collisions (Stancil et al., 1998; Bene et al., 2009). As shown in a recent analysis of time-dependent quantum wave packet and semiclassical methods for charge transfer processes (Chenel et al., 2010), the method could be extended to lower collision energies, down to the eV range (Bacchus-Montabonel and Tergiman, 2010, 2011a).

The collision dynamics has been performed using the EIKONXS program based on an efficient propagation method (Allan et al., 1990). The calculation has been carried out taking into account all the transitions driven by radial coupling matrix elements with