Ion induced fragmentation of 5BrU pure and hydrated clusters: role of the environment in radiosensitising mechanisms and resulting mutagenesis

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Exposure of a living organism to ionizing radiation causes alterations that begin at the DNA level [1] and evolve in biological malfunctioning as well as mutation and cellular death. On the other hand, the same pathogenic effects of radiation damage are proficiently used in radiotherapy for cancer treatment. The major drawback in radiotherapy is that it produces an unselective damage in both tumour and healthy cells, with significant side effects for the patients. This issue led to the search for new strategies with targeted drugs, the radiosensitizers [2,3], that enhance the lethal effect of radiation specifically on tumor rather than on normal cells.

Among the different classes of radiosensitisers the halosubstituted pyrimidinic bases and their nucleosides analogues have reached the stage of clinical trials [4]. Among halopyrimidine nucleobases, 5-bromouracil (5BrU) [5,6] is the fundamental building block of bromo-deoxyuridine that, thanks to the similar steric hindrance of the Br atom and the methyl group, can replace thymine into the DNA of fast replicating tumor cells. In the present work we have investigated the $^{12}C^{4+}$ ion induced fragmentation of 5BrU embedded in clusters of molecules of the same species (pure clusters) or with the addition of water molecules (nano-hydrated clusters). Both situations mimic 'realistic' biological media, because of the planar bonding of nucleobases in the cluster, similar to base pairing configuration, as well as the presence of water, the main constituent of human bodies.

These studies indicate that the environment, on one hand, protects the system against the complete break-up in small fragments but on the other, triggers 'new' fragmentation pathways (OH loss). The most striking results are i) the observation in the nano-hydrated clusters, of series of hydrated fragments, which highlights a strong interaction between 5BrU and water molecules with a consequent blocking of specific fragmentation pathways active in the pure cluster (BrC_2H loss) and ii) the evidence that a sufficient number of water molecules can mediate the keto-enol tautomerisation responsible of mutagenesis. This sheds light on the radiosensitising and mutagenic effects of this DNA base analogue.

The present results prove for the first time the 5BrU potential to produce harmful effects on a biological system in terms of both mutagenicity, due to water-mediated tautomerisation, and enhanced fragility, due to ultrafast radiation damage mechanisms. The latter enhances the molecular fragmentation against a statistical redistribution of the absorbed energy, leading to the release of several types of 'hydrated fragments', never observed in other nitrogenous bases.

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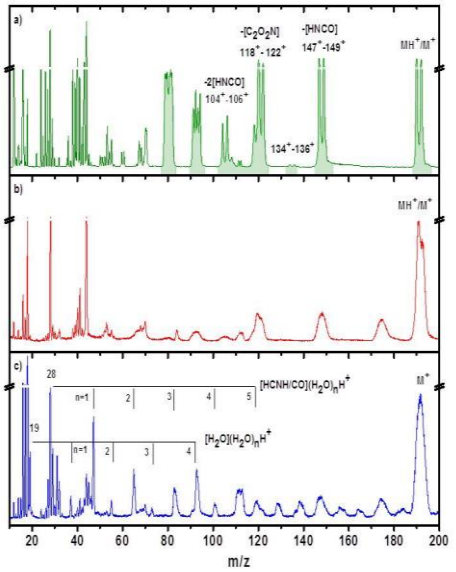

Figure 1. The 36 keV $^{12}C^{4+}$ ion induced mass spectra 5BrU molecules isolated (a) and embedded in pure (b) and nano-hydrated (c) clusters in the m/z region up to the monomer (M^+). Singly charged fragments containing the Br atom display the typical $^{79}Br(^{81}Br)$ isotopic structure and are highlighted as green areas in a). The peaks belonging to the protonated water clusters $(H_2O)_nH^+$ and hydrated $[HCNH/CO](H_2O)_nH^+$ series are indicated in (c).

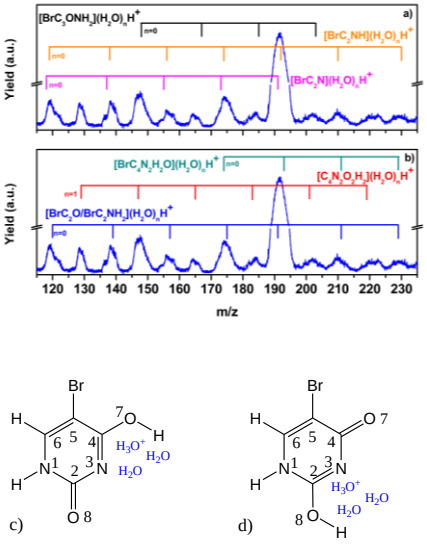

Figure 2. On the top: the 36 keV $^{12}C^{4+}$ ion induced mass spectrum of the nano-hydrated 5BrU clusters in the m/z region 115-235. The peaks belonging to hydrated series are shown. On the bottom: a schematic of the eno-tautomeric forms induced in the nano-hydrated cluster by at least three water molecules.

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