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## **Irradiation damage of uridine molecules with MeV heavy ions**

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Abstract:

In order to study the mechanism of the nucleotide directly damaged by energetic heavy ions, the residual ratio of uridine molecules after irradiation was measured by means of High Performance Liquid Chromatography (HPLC). The experimental results show that the irradiation damage probability depends on the electronic energy loss rate ( $S_e$ ) of incident ions: first it increases quickly with  $S_e$ , then becomes stable when  $S_e$  reaches 800 eV/nm. The contribution of the nuclear collisions can be neglected compared with that of the electronic process. This is not only because that the nuclear energy loss rate ( $S_n$ ) is much smaller than  $S_e$  for MeV heavy ions, but also because the energy deposition through the electronic process is more efficient in damaging molecules than through the nuclear process.

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**Key words:** Irradiation damage, HPLC, heavy ion, energy loss

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## 1. Introduction

The irradiation damage due to energetic heavy ions depends on the linear energy transfer (LET) to the sample. For most of the heavy ions the LET value reaches a maximum for energies is in the MeV range. Therefore it is very important to study the irradiation damage mechanism of MeV heavy ions in view of practical applications, such as cancer therapy, radiation protection and so on <sup>[1,2,3,4]</sup>.

Numerous studies have been performed on the irradiation damage of living cells or bio-molecules in aqueous solution, while there are very few experimental studies on dry samples. The mechanism of energetic ions damaging dry samples is very important to understand some of the irradiation applications, such as the mutation effect due to heavy ion irradiation of plant seeds <sup>[5-9]</sup>.

When energetic heavy ions bombard dry bio-molecules samples, the molecules can be damaged directly by the nuclear collision or by the secondary electrons induced by the incident ions. When the ion energy is low, the ion energy is deposited to the sample mainly by nuclear collisions and most of the irradiation damage results from this process. This nuclear damaging process has been widely studied on vary samples, such as DNA bases <sup>[10-14]</sup>, nucleotides <sup>[15-16]</sup> and DNA molecules <sup>[17-19]</sup>.

When the ion energy is in MeV range, most of its energy is transferred to the target *via* the electronic process. It was reported that about  $10^5$  secondary electrons can be produced per MeV energy loss. Although the energies of these secondary electrons are usually less than 20 eV <sup>[20]</sup>, they are able to break molecules. Some

reports show that electrons can damage nucleotide molecules even when their energy is lower than 1eV<sup>[21-25]</sup>.

Giustranti *et al.* have studied the single strand break (SSB) damage of plasmid DNA induced by high-energy heavy ions, and have found that the relationship between SSB and the ion dose was linear<sup>[27]</sup>. Bowman et al. found that for 100 MeV/u Ar<sup>+</sup> the cross section for producing SSB at 77K is about 122 nm<sup>2</sup> which indicates that damaging bio-molecules with secondary electrons is very easy<sup>[28]</sup>. Up to now, there has been no report on the LET effect on the damaging probability of dry nucleotide samples by MeV heavy ions.

In the present paper, we study the irradiation damage of uridine molecules induced by MeV heavy ions. The High Performance Liquid Chromatography (HPLC) method was used to count the intact uridine molecules after irradiation. The influences of the ion fluence and of the LET value on the damaging probability were investigated.

## **2. Experimental details**

### **2.1 Sample preparation**

Uridine (>99.7%) was purchased from the Sigma Company and used without further purification. The samples were prepared in very thin films, in order to allow the incident ions to penetrate the whole sample. Firstly, the uridine was dissolved in pure water with a concentration of 200mg/mL; then 35 $\mu$ l of this solution was transferred onto a clean flat glass of area 2.4 $\times$ 2.4cm<sup>2</sup> and spread on the glass surface homogeneously. After being naturally dried at room temperature, an uridine film with a

mass thickness of  $0.2\text{mg}/\text{cm}^2$  was left, and its geometric thickness was around 1600 nm.

## 2.2 Irradiation

$\text{He}^{2+}$  and  $\text{C}^+$  ions with energies of several MeV were produced by the  $2\times 1.7\text{MV}$  tandem accelerator of the Institute of Heavy Ion Physics (IHIP), Peking University. The ion fluence ranged from  $1\times 10^{12}$  to  $1\times 10^{14}$  ions  $/\text{cm}^2$  (details of the ion parameters are listed in table 1). The beam current density was kept lower than  $5\text{ nA}/\text{cm}^2$  in order to keep the sample temperature as low as possible.

$30\text{keV Ar}^+$  ions were also used in our experiment in order to clarify the contribution of nuclear collisions to the final damaging probability, and its fluence ranged from  $1\times 10^{15}$  to  $2\times 10^{16}$  ions $/\text{cm}^2$ .

The SRIM2003 code was used to calculate the electronic energy loss rate ( $S_e$ ) and the nuclear energy loss rate ( $S_n$ ) of these ions in uridine material, and the calculation results are shown in Table 1.

## 2.3 HPLC measurement

After irradiation, the sample was dissolved into 1.5mL of pure water, and 20  $\mu\text{l}$  was fetched for HPLC analysis. The HPLC facility used in this experiment was a Varian ProStar HPLC system with a C-18 (4.6 mm $\times$ 250 mm) analytical column, and the spectra were detected with a UV detector at the wave length of 254nm. In the measurement, the solvent was the mixture of water and acetonitrile (1:1) , and the flow rate was kept at 1.0 mL/min. The peak areas were calculated automatically with

the software provided by the Varian company.

The molecule number is proportional to the area of the corresponding peak, so the residual molecule number ( $N$ ) can be calculated with:  $N=N_o \times S/S_o$ , where  $S$  and  $S_o$  are the uridine peak areas after and before irradiation,  $N_o$  being the original uridine molecule number.

In order to test the experimental error, we have analyzed three samples treated with the same process. The discrepancy in the final peak areas of these three samples was less than 5%, so we consider the experimental error to be 5%.

### 3. Experimental results

#### 3.1 HPLC spectra for the irradiated samples

Fig.1 shows the HPLC spectra for uridine samples before and after being irradiated with 1.5MeV C ions. The large peak with the retention time of 700 (about 2.5mins) corresponds to intact uridine molecules, other small peaks being due to the radiation products or sample impurities. In this work, we were only interested in the intact uridine molecules, and neglected others.

If we define the damage probability  $P$  as the number of molecules broken by one incident ion, then the residual molecule number and the ion fluence ( $D$ ) have the following relationship:

$$N = N_o \exp(-P \cdot D) \quad (1)$$

$N_o$  is the original molecule number before irradiation.

Fig.2 shows the residual ratio ( $N/N_o$ ) as a function of ion fluence of 1.5 MeV He ions ( $1 \times 10^{12} \sim 1 \times 10^{14}$  ions/cm<sup>2</sup>). When the incident ion fluence increases, the residual

ratio decreases exponentially. By fitting this curve with equation (1), the  $P$  values for the incident ions were obtained.

However, a large amount of experiments was needed to obtain the  $P$  values for each kind of incident ions. It is possible to estimate the  $P$  with an approximated method. Equation (1) can be extended with the Taylor method, and considering only the first order term allows to calculate  $P$  if the ion fluence is very low:  $N = N_0 \exp(-P \bullet D) = N_0(1 - P \bullet D)$ . Then the  $P$  values can be calculated as:  $P = (N_0 - N)/D$ . In the measurements, the ion fluence was always  $5 \times 10^{12}$  ion/cm<sup>2</sup>. In the following section, the values of  $P$  were obtained with this simple method.

### 3.2 LET effect on the molecule damaging probability

Fig.3 shows the measured results of damaging probability as a function of the  $S_e$  of incident ions, and the line in the figure is only used to guide the eye. The results show that in the low  $S_e$  region  $P$  increases rapidly when  $S_e$  increases; however,  $P$  becomes nearly stable when  $S_e$  is higher than 800eV/nm.

The molecular damaging is dominated by the secondary electrons, and the contribution of the nuclear collisions could be neglected (this will be discussed in section 3.3). Here we just estimate the damaging probability by MeV ions. A large number of secondary electrons are produced by the incident ions, and then these electrons will escape from the ion track and lose their energies to the target atoms/molecules gradually. In the energy loss process, some of them interact with the molecules bond and thus break it, which results into molecule damaging. If the

density of secondary electrons in a certain region is  $N(r, \epsilon)$ , and the cross-section for an electron of energy  $\epsilon$  to break a molecule is  $\sigma(\epsilon)$ , then the damaged molecule number  $N$  per unit distance along the beam direction can be calculated as following:

$$N = \int_0^{R_{max}} \int_0^{E_{max}} \rho \times N(r, \epsilon) \sigma_e(\epsilon) d\epsilon dr \quad (2)$$

where  $\rho$  is the number density of undamaged molecules,  $R_{max}$  is the maximum range of secondary electrons,  $E_{max}$  is the highest kinetic energy of secondary electrons (usually it is 20 eV as mentioned above). If we assume that the  $N$  value is the same inside the whole sample, then  $P=N \times L$ , where  $L$  is the sample thickness.

It can be seen that  $P$  depends on the number of secondary electrons. When  $S_e$  increases, the number of secondary electrons becomes larger, and then the value of  $P$  also increases. However, if the secondary electron number is too large, one molecule could be damaged several times by secondary electrons, but the final number of damaged molecules does not increase. This is the reason for the slowly changes of  $P$  when  $S_e$  is higher than 800 eV/nm.

It is impossible to make a quantitative calculation on the  $P \sim S_e$  relation due to the lack of experimental data on  $\sigma(\epsilon)$  and  $N(r, \epsilon)$ .

### 3.3 Contribution of the nuclear collisions to the irradiation damaging probability

In order to investigate the contribution of nuclear collisions to the damaging probability  $P$ , 30 keV  $Ar^+$  with different ion fluences were used to irradiate samples, and the results are shown in Fig.4. For 30 keV  $Ar^+$ , the nuclear energy loss is dominant. As the range of 30 keV  $Ar^+$  is only 34 nm whereas the MeV ions can



penetrate the samples of thickness 1600 nm, it is not suitable to compare the damaging effects in terms of numbers of damaged molecules per incident ion. Instead, for a better comparison, we used the number of damaged molecules by unit of energy loss.

Fig.4 shows that one  $\text{Ar}^+$  ion can break 188 uridine molecules, nearly 0.023 molecules/eV. For 1.5 MeV C ions, this value is 0.15 molecules/eV, about 5 times more. This difference comes from the different interaction mechanisms of the nuclear energy loss and electronic energy loss processes. In the nuclear collision process, a target atom must get an energy higher than a critical value (binding energy) to be able to leave its original location and induce the molecular break up. The binding energy of the molecules is usually above 10 eV, therefore the deposited energy in a single collision should be higher than 10eV in order to damage the molecule. However, for secondary electrons, 0.3eV is enough to cause the molecule bond to be broken through the electron-bond interaction<sup>[21-22]</sup>. As a result, the energy deposition through electrons is more efficient than by nuclear collisions.

By using 0.023 molecules/eV, the contribution of nuclear collisions to  $P$  for 1.0 MeV C ions, which has the highest  $S_n$  in table 1, is at most 300 molecules/ion. Therefore, the effect of nuclear collisions could be neglected for these MeV heavy ions.

#### **4. summary**

Energetic heavy ions were used to irradiate dry uridine samples, and the residual uridine molecules were counted with the HPLC method. The residual rate of uridine molecule drops exponentially when the incident ion fluence increases. The damaging probability by incident ions depends on their electronic energy loss rate. In the low  $S_e$  region, P increases quickly when  $S_e$  increases; however, P becomes nearly stable when  $S_e$  is higher than 800eV/nm.

For 30 keV Ar ions, 1eV of deposited energy can break 0.023 uridine molecule, while 1.5 MeV C ions can break 0.149 molecules/eV. This result indicates that, for damaging nucleotide molecules, the energy deposition through electronic way is more efficient than through nuclear collisions.

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Table 1 Parameters of the energetic heavy ions used in the irradiation experiments; the  $S_e$ ,  $S_n$  and ranges were calculated with the SRIM2003 code.

Ion species	Energy (keV)	$S_e$ (eV/nm)	$S_n$ (eV/nm)	Range (nm)
He	1000	287	0.3	4000
He	2000	209	0.2	8100
C	1000	887	7	2400
C	2000	1113	4	3600
C	3000	1134	3	4700
Ar	30	203	550	42

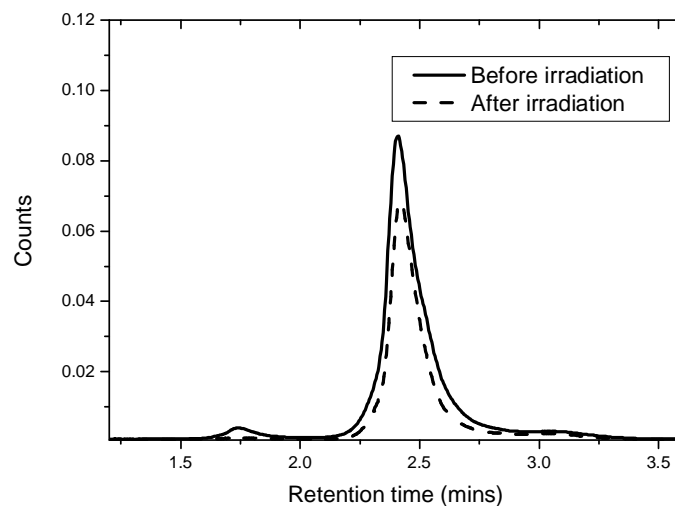


Fig.1 HPLC spectra for Uridine samples before and after being irradiated with 1.5MeV C ions. The peak around the retention time of 2.4 minutes is for intact uridine molecules, it drops down after being irradiated.

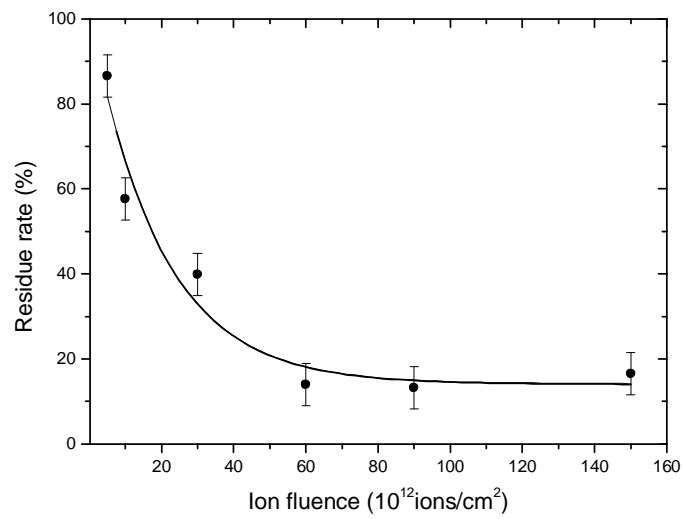
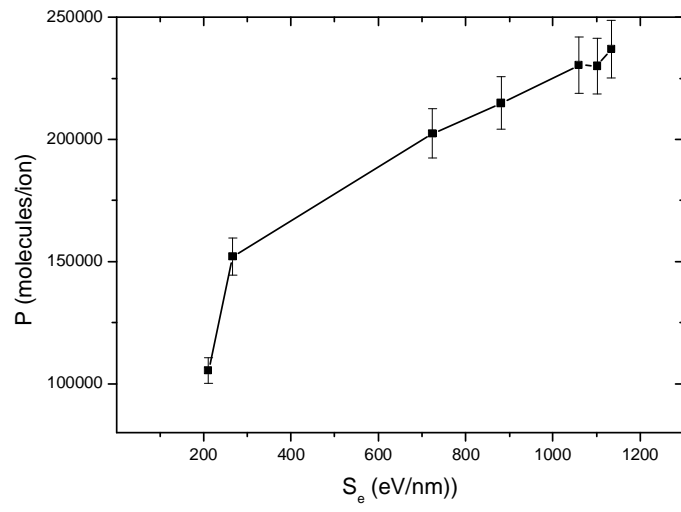
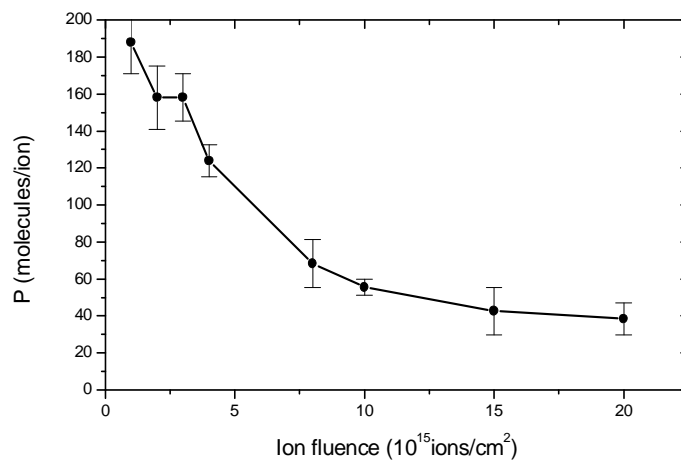


Fig.2 Uridine molecule residual rate as a function of 1.5MeV He ions fluence; the line is the fitting curve with an exponential function.



**Fig.3 The relationship between the molecule damaging probability and the electronic stopping power for the incident ions**





**Fig 4 The damaging probability as function of the fluence of 30 keV Ar<sup>+</sup> ions**