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▶ **To cite this version:**

Mohammad Ghalei, Parastoo Mahdi Khoshouei, Johan Vandenborre, François Guérard, Guillaume Blain, et al.. How radiolysis impacts astatine speciation?. Radiation Physics and Chemistry, 2022, 198, pp.110224. 10.1016/j.radphyschem.2022.110224 . inserm-03668885

HAL Id: inserm-03668885

https://inserm.hal.science/inserm-03668885

Submitted on 16 May 2022

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How Radiolysis Impacts Astatine Speciation?

Mohammad Ghalei[1,3], Parastoo MAHDI KHOSHOUEI[1], Johan VANDENBORRE*[1], François GUERARD[2], Guillaume BLAIN[1], Mojtaba ZAREI[3], Ferid HADDAD[1,4], Massoud FATTAHI[1]

[1]SUBATECH, UMR 6457, Institut Mines-Télécom Atlantique, CNRS/IN2P3, Université de Nantes ; 4, Rue Alfred Kastler, La chantrerie BP 20722, 44307 Nantes cedex 3, France

[2]Université de Nantes, CNRS, Inserm, CRCINA, F-44000 Nantes, France

[3]Institute of Medical Science and Technology Shahid Behehsti University.Velenjak, Tehran, Iran

[4]GIP ARRONAX, 1 rue ARRONAX, CS 10112, 44817 Saint-Herblain Cedex, France

Corresponding author:

Dr. Johan Vandenborre

SUBATECH, UMR 6457, Institut Mines-Télécom Atlantique, CNRS/IN2P3, Université de Nantes

4, Rue Alfred Kastler, La chantrerie BP 20722, 44307 Nantes cedex 3, France

Email : johan.vandenborre@subatech.in2p3.fr

Keywords : Astatine Chemistry, Chloroform, Radiolysis, Hydrogen Chloride, G-yield

ABSTRACT

This work deals with the impact of chloroform radiolysis on astatine chemistry. Astatine-211 is a promising radionuclide for the targeted alpha therapy of cancers. Yet, the production of ^{211}At based radiopharmaceuticals is often complicated by radiolysis due to its own decay, leading to solvent degradation and then impacting astatine chemical state and radiolabeling efficiency. A better understanding of the radiolysis phenomenon is thus necessary. Two experiments are performed: (1) pH measurement during the At extraction in chloroform medium, (2) pH determination calculated from the HCl chemical yield which is obtained during the radiolysis of chloroform medium by γ-ray.

In both cases, the pH values are determined at 2.0 ± 0.5. Then, it is possible to predict the acidic conditions during the ^{211}At production by HCl radiolytic yield determination. This work demonstrated that the radiolysis induced by At during its production in $CHCl_3$ medium should be taken into account as it has a significant effect on acid-basic conditions.

The work helps understanding the mechanisms of production of a major impurity generated from ^{211}At radiolysis in chloroform which alters its radiochemistry, allowing for the identification of solutions to counteract these unwanted effects.

INTRODUCTION

Astatine-211 is a promising alpha-emitter radionuclide with a high potential for applications in targeted alpha therapy of cancers (Guérard et al., 2013). Its intermediate half-life (7.2 h) in comparison with other alpha emitters makes it potentially compatible with various carrier compounds, from small molecules and peptides to large proteins such

as antibodies. Radiolabeling chemistry which is employed for ^{211}At in most cases is similar to other halogens, in particularly to radioiodine. Various strategies have been developed recently which provided biologically relevant molecules labelled with ^{211}At with high radiochemical yields (Navarro et al., 2019; Reilly et al., 2018; Watanabe et al., 2019). Yet, difficulties to obtain robust labelling procedures have been reported when using certain solvents particularly chloroform. Lack of robustness of radiolabeling approaches performed in chloroform, which is clearly evident at high radioactivity , has been attributed to solvent radiolysis, induced by high energy α-particles (5,9-7,4 MeV), which in turn comes from ^{211}At decay. Products of chloroform decomposition may be responsible for the reduction in RCYs due to their reactivity with the reaction precursors (Pozzi and Zalutsky, 2005b) and/or alteration of astatine species necessary for the radiolabelling reaction (Aneheim et al., 2019). Although other solvents (e.g. alcohols or acetonitrile) are now preferred for radiolabeling (in order to reduce issues related to radiolysis), chloroform remains an interesting solvent for astatine recovery after separation from its irradiated bismuth target. The main reason being that it is the only known solvent allowing evaporation to dryness without co-evaporation of astatine activity. This properties is highly interesting since it allows the fractionation of a batch of astatine into several samples that can be evaporated to dryness and then dissolve in any solvent adapted for each experiment (Aneheim et al., 2019).

Thus, the study of chloroform radiolysis appears essential to better counteract issues associated with the use of this solvent.

A large number of reports have previously focused on chloroform radiolysis in various contexts and experimental conditions (Abadie, 1982; Bibler and Hyder, 1968; Chen et al.,

1960; Johnston et al., 1961; Ottolenghi and Stein, 1961; Schulte et al., 1953; Werner and Firestone, 1965). These authors suggested that hydrogen chloride is the main product of chloroform radiolytic degradation. However, all these publications (from the 50's to the 80's) gave equivocal radiolytic yield (G-yield) of generated hydrogen chloride because of differences in the experimental conditions. Either chloroform solutions purity were different which implies discrepancies in G-yield of HCl (Abadie, 1982; Chen et al., 1960; Johnston et al., 1961; Ottolenghi and Stein, 1961) or experimental conditions, for example various temperature, pressure or radiation dose rate (Bibler and Hyder, 1968; Johnston et al., 1961; Schulte et al., 1953; Werner and Firestone, 1965). For these reasons, we planned to revisit the experimental measurements of HCl yield during γ-ray experiments, more easy to be measured and close to the α ones, in specifically well-defined conditions in order to establish the potential quantities of HCl in routine production of astatine-211 solution during radiolabeling and production of [^{211}At]-astatinated radiopharmaceuticals.

MATERIALS AND METHODS

Irradiation experiments

γ-Ray irradiations were performed on an gamma irradiator located at the ARRONAX cyclotron facility (Nantes – France). Irradiation cells made of PEEK (polyether ether ketone) with an internal volume of 42 ml were mounted with a rotulex 19/9 glass tube. These cells were gas-tightened using a screwed joint in a glass-metallic valve. Specificity of each experiment is discussed thereafter. Irradiation of different 20 ml-samples of chloroform was performed from 1 to 7 days under aerated or oxygen free atmospheres under normal pressure (760 mmHg).

γ-Ray irradiation

γ-Ray irradiation was performed with a GSM D1 (Gamma-Service Medical) irradiator containing a 123 TBq ^{137}Cs source. This radionuclide decays to ^{137m}Ba, which delivers 661.7 keV γ-Ray. A dose cartography performed by Fricke dosimetry (Fricke and Hart, 1966) inside gamma irradiation chamber, indicated that the average deposited dose inside the aqueous samples was between 7 and 9 $Gy.min^{-1}$. As γ-Ray is a penetrating radiation, the dose can be considered as homogeneously deposited inside the whole sample.

Analytical procedures

Solutions described in this section were prepared with commercial chemical products as received with no further purification. All reactants were analytical grade and the aqueous samples were prepared with ultrapure (MilliQ) water.

HCl analysis

To quantify HCl, produced by the irradiation of chloroform, it is necessary to extract HCl molecules from chloroform bywater. Extraction experiments were performed to obtain the percentage of HCl extracted from chloroform samples by water. Using 4 different concentrations of HCl in 20 ml of chloroform, samples prepared ahead of time (0.1, 0.2, 0.5 and 1 $mol.l^{-1}$ by addition of 100 µl of aqueous HCl solution) and extraction protocol was performed with a large volume of Ultrapure water (100 ml). After separation of layers, titration of aqueous layer was performed using 0.1 $mol.l^{-1}$ NaOH to determine the percentage of HCl extracted. Similarly, extraction and determination of HCl from irradiated

samples of chloroform was done using a decanter followed by titration of acid with NaOH (**Figure 1**).

The results show on average 75 ± 8 % of HCl from the HCl-chloroform samples was extractable from chloroform to the aqueous phase. This ratio determined by the extraction step that used in this work to establish the realistic HCl concentration obtained during the radiolysis experiments. Therefore, we consider these uncertainties for all data plotted into the figures.

Radiolytic Yield Definition

The radiolytic yield is defined as the amount of a species that is formed or disappeared per unit of deposited energy. It is expressed in the international system in μmol. J^{-1} and is calculated at a time t after transition of the ionizing irradiation according to the following equation:

$$G_t(X) = \frac{[Xt]}{\rho D}$$

where $[X_t]$ is the concentration of the species X at time of t (mol.l^{-1}), ρ is the density of the irradiated solution (kg.l^{-1}) and D the absorbed dose (J.kg^{-1}).

Thus, for the determination of the radiolytic yield of HCl during the irradiation of chloroform, the equation is as following:

$$G_t(HCl) = \frac{[HCl]}{\rho_{CHCl_3}.D}$$

In which ρ_{CHCl_3} is equal to 1.48 kg.l^{-1}.

Production of astatine-211 solutions in chloroform

^{211}At was produced at Arronax cyclotron facility using the ^{209}Bi(α,2n)^{211}At reaction and recovered from the irradiated target in chloroform using a dry-distillation protocol as reported previously (Guérard et al., 2017). The radioactive sample was isolated and shipped to CRCINA laboratory where radiolabelling chemistry is performed. On average there is 300 to 400 MBq activity in a total volume of about 600 µl of chloroform with a contact time of about 2 hours between the end of distillation and the HCl extraction experiments, which corresponds to a dose range of 2.3 to 3.0 kGy received by chloroform solution. Before radiolabeling, and approximately 2 h after recovering of ^{211}At activity in chloroform, the chloroform ^{211}At solution was washed with 200 µl of water (TraceSelect Grade, Fluka). After decantation, both layers were separated. The ^{211}At activity found in the aqueous layer was negligible, nearly all activity being found in the chloroform layer. The pH of the aqueous layer was measured by mean of a pH indicator strip (Merck, pH range 0-6, pH gradation = 0.5). All assays indicated a pH of 1.5 ± 0.5 (n = 4). pH indicator was used to compare it with HCl titration result not as the tool for HCl analysis.

RESULTS AND DISCUSSION

In this study, we investigated the amounts of HCl produced through irradiation of chloroform by γ radiations in two different conditions (presence or absence of oxygen) at low doses of irradiation. The latter one was the dose rate corresponding to the real conditions of exposure of chloroform when performing [^{211}At]-astatinated radiopharmaceuticals for pre-clinical development.

Determination of initial G- values of HCl during irradiation in the aerated and oxygen free atmospheres

Figure 2 presents HCl production as function of dose in aerated and oxygen free atmospheres for $CHCl_3$ irradiated by γ-ray.

According to the data derived from this figure, G-value for HCl in the dose range from 0 to 2580 Gy in the presence of air, is equal to 1.66 ± 0.24 $\mu mol.J^{-1}$ whereas it is only 1.14 ± 0.17 $\mu mol.J^{-1}$ in the presence of Ar. We can see a clear difference between the radiolytic yields of HCl production that can be explained by looking the possible reactions in both conditions.

For the Chloroform irradiation mechanisms, two different behaviors are possible:

(i) One of them, when air is present above the sample, are the chemical reactions of Chloroform with Oxygen in order to produce molecules of HCl, Cl_3COOH and $COCl_2$ which have been proposed in the primarily steps of chloroform irradiation (Schulte et al., 1953):

$$CHCl_3 + O_2 \rightarrow Cl_3COOH \quad (1)$$

$$2CHCl_3 + O_2 \rightarrow 2COCl_2 + 2HCl \quad (2)$$

However, reaction 2 can take place even without ionizing radiation, but it takes too long (some days) (Clover, 1923). As a result, when measuring the radiolytic yield of HCl in presence of air, we consider the HCl concentration zero at no absorbed radiation dose. HCl is produced through reaction (2) while Cl_3COOH is produced through reaction (1).

(ii) The second one, in a free-oxygen environment, is the direct radiolysis of the $CHCl_3$ molecules to produce HCl via H° and Cl° radicals production (Chen et al., 1960):

$$CHCl_3 \rightarrow CHCl_2^{\circ} + Cl^{\circ} \cdot \quad (3)$$

$$CHCl_3 + Cl^{\circ} \rightarrow CCl_3^{\circ} + HCl \quad (4)$$

or

$$CHCl_3 \rightarrow CCl_3^{\circ} + H^{\circ} \cdot \quad (5)$$

$$CHCl_3 + H^{\circ} \rightarrow CHCl_2^{\circ} + HCl \quad (6)$$

Radiolytic products such as dihydrogen (H_2) and dichloride (Cl_2) gases result from recombination of H° and Cl° radicals, respectively (Lainé et al., 2017; Mostafa et al., 2018). This implies that HCl and radiolytic gases compete for formation reactions, which needs to be measured in further studies.

In addition, recent studies by using pulse radiolysis shown that if surrounded chloroform molecules participate with the $CHCl^{+\circ}$ the reaction (7) and (8) are more favorable (Bird et al., 2020):

$$CHCl^{+\circ} + CHCl_3 \rightarrow CCl_3^{+} + CHCl_2^{\circ} + HCl \quad (7)$$

$$CHCl^{+\circ} + CHCl_3 \rightarrow CHCl_2^{+} + CCl_3^{\circ} + HCl \quad (8)$$

At low doses, typically until 3000 Gy, in the first steps of chloroform irradiation, Cl_3COOH (see reaction (1)) has been considered as a major product which produces quantitative amount of peroxide before its reduction (Schulte et al., 1953). According to our results at low doses (< 500 Gy) a difference is observed for the radiolytic yield of acids with and without air. This difference was increased when the dose was increased which means that reactions 2 and 4 are occurring in parallel. It can be concluded that the higher the dose, the more important the effect of oxygen.

Irradiation of chloroform at higher doses

The results obtained in this study was over a wide range of doses, from 0 to 93 kGy, (see **Figure 3**). This dose range corresponds to irradiation times of chloroform in our gamma-irradiator varying from 0 to 10 days.

Based on the results reported in Figure 3 and using the reactions (2-6), the radiolytic yield of HCl production in the dose range of 0-93294 Gy has been determined as 0.82 ± 0.11 $\mu mol.J^{-1}$. Moreover, as already suggested in the previous part, two behaviors append during the HCl formation by chloroform irradiation: (i) in presence and absent of oxygen (ii) in the high dose range (> 3 kGy) the radicals H° and Cl° production by the direct radiolysis of $CHCl_3$ (reactions (3-6)).

The mechanism of abstraction of H and Cl from $CHCl_3$ during dose enhancement, suggested in this work, is consistent with literature (Chen et al., 1960). Authors have proposed that the abstraction of H and Cl atoms from $CHCl_3$ molecules, by Cl° and H° radicals, can be considered as the major reactions producing HCl during the irradiation in the absence of oxygen by γ-rays (Chen et al., 1960).

Most of the reported results regarding irradiation of chloroform in the literature have been obtained in O_2 and water-free situations as in our conditions. However, the literature shows a large discrepancy (see **Table 1**).

All authors have underlined the discrepancy of the G-values (from 0.45 to 1.23 $\mu mol.J^{-1}$). Then, we can explain the difference by temperature, pressure conditions and HCl production behavior due to the impact of oxygen as already suggested. In addition, the range of dose studied in previous works may explain this discrepancy. For example in our study, a neat difference of G-value is observed as a function of the dose range: for low

range (< 3 kGy) G-value = 1.66 µmol.J^{-1}while at high range (< 93 kGy) G-value = 0.66 µmol.J^{-1}. It should be noted that the G-value at higher doses was calculated from obtained data in dose range of 3-93 kGy (cf figure 3).

That is the reason why, we have chosen to use the same dose range (< 3 kGy), determined in the experimental section, for the radiolysis and the ^{211}At extractions experiments in order to determine the realistic quantity of HCl produced by radiolysis which comes from ^{211}At.

Therefore, in the next part, we compare the HCl production for the real dose deposited in chloroform solution defined in the ^{211}At extraction (between 2.3 and 3 kGy), which corresponds to a contact time between At and chloroform solutions of 2 hours, with our γ irradiation conditions in a close range of dose rate in the both cases (27 Gy.min^{-1} for ^{211}At extraction vs. 10 Gy.min^{-1} in the radiolysis ones). However, the possibility of differences in HCl production between γ and α radiolysis may be considered in the context of radiolysis arising from astatine-211. Nonetheless, according to reactions (3-6), HCl production depends on the radicals produced by radiolysis (H°, Cl°). As the linear energy transfer (LET) in α radiation is higher than γ one, therefore the produced radicals are combined faster in spurs therefore, the molecular yield is higher than radical yield in α radiation (Appleby and Schwarz, 1969). That is the main difference between the two types of radiation. Consequently, by considering this difference, the HCl production is, in theory, higher in the case of γ-ray radiolysis and the G-value determined in this work is overestimated in comparison with the one actually occurring during exposition of chloroform to ^{211}At. In order to determine this overestimation, we have measured the HCl production by extraction from batches of ^{211}At in chloroform.

Impact/Consequences for Astatine Extraction/Complexation

Being a radioelement, with only short half-life radioisotopes, astatine chemistry is extremely complex to study. Most work with astatine has been performed with ^{211}At ($t_{1/2}$ = 7.2 h), the most stable isotope, ^{210}At, exhibiting a $t_{1/2}$ of only 8.1 h being avoided for radioprotection concerns. Additionally, the weak amounts produced by accelerators (few pictograms at best), make it nearly impossible to use conventional spectroscopic techniques for precise determination of chemical properties of astatinated species. A major issue in studying astatine chemistry is the evolution over time of the astatinated species in solution, including their oxidation state, which affects the reproducibility of radiolabelling procedures. This phenomenon has been attributed to radiolysis of the solvent, which generates degradation products that may then react with astatine and modify its chemical nature. In the case of chloroform, previous reports have suggested that radicals formed during radiolysis could impact radiolabelling procedures (eg Cl° that may react with precursors instead of astatine and then decrease radiochemical yields (Pozzi and Zalutsky, 2005a), or that recombination of radicals can form species suspected to react with astatine, or adducts affecting its behavior (volatility, extractability, solubility) (Aneheim et al., 2019).

Here we focused our attention on HCl production upon chloroform radiolysis since acidity of the media appears as an essential parameter governing the astatine species in solution as shown in recent reports coupling experimental data with computer simulations to construct the Pourbaix diagram of astatine in water (Champion et al., 2013; Sergentu et al., 2016), and that may impact its use for analysis and radiolabeling chemistry. It is assumed that in acidic and oxidative medium, three species coexist (At^+, AtO^+, and

AtOOH), the predominant species being in part determined by the pH of the solution. Considering this, and since concentration of HCl varies over time in chloroform it is clear that experiments conducted with astatine isolated in chloroform are likely to lack consistency and reproducibility due to the dose deposited in stock solutions when activity in solution and time before radiolabeling and use vary. The solution to this problem is simple to set up, by adding an extraction step in water before use for radiolabeling. Extraction experiments discussed above showed that most of HCl could be extracted from chloroform to water, which was confirmed when applied to ^{211}At stock solutions. This additional step in the purification process of ^{211}At is time-consuming (< 10 min) and generates negligible loss of activity due to the extremely low transfer of astatine to aqueous layer. From the G-yield value determined above (1.66 µmol.J^{-1} in the dose range studied), we can estimate the HCl concentration for the dose applied to the chloroform corresponding to the time between the isolation of astatine in chloroform, to the extraction step (between 2.3 and 3 kGy). The calculated range of HCl concentration is between 3.8 and 5 mmol.L^{-1} (*i.e.* pH = 2.3 ± 0.1) close to the real pH value measured in the Astatine extraction experiments (= 1.5 ± 0.5). The difference can be attributed to the G-values difference between γ and α irradiations and the production of other radiolytic species, which contribute to the acido-basic conditions and must be characterized such as Cl_3COOH. Experiment performed in further studies would be the α irradiation of chloroform solutions using a helium beam to measure the G-yield in these specific conditions and compare them with astatine irradiations (α in the both cases) and the analysis by Infrared Spectrometry of other radiolytic species produced during chloroform irradiation.

CONCLUSION

The gamma radiolysis of chloroform using a ^{137}Cs source was investigated in this study in order to determine the amount of hydrogen chloride (HCl) produced as a major product of chloroform radiolysis. Radiation doses ranged from 0 to 93 kGy, which had an impact on the chemistry of Astatine. According to our finding, during the accumulation of the dose, the amount of HCl acid follows a linear behavior at low dose with a G-value of (1.66 $\mu mol.J^{-1}$) and a linear behavior at high dose with a G-value of (0.82 $\mu mol.J^{-1}$). This different behavior at low and high dose may explain the large discrepancy found in the literature as a function of the dose range studied. Moreover, in the low dose range (< 3kGy), the trichlorohydroperoxymethane (Cl_3COOH) production by chloroform reaction with O_2, must be taken into account for the mechanisms of HCl production.

These experimental results contribute in understanding of chloroform radiolysis mechanisms induced by astatine radioactivity during its extraction/complexation processes. In fact, with the G-value determined in this work we calculated the theoretical pH value in the Chloroform/Astatine solution (pH = 2.3) close to the one measured in the real Astatine complexation/extraction process (pH= 1.5). Then, as a conclusion, the radiolysis mechanism which can explain the acidic pH in the chloroform/astatine solution must be taken into account for this kind of radiochemical experiments as already suggested but not, until now, demonstrated in the literature (Aneheim et al., 2019; Pozzi and Zalutsky, 2005a, 2017). Moreover, synthesis of ^{211}At radiopharmaceuticals such as SAB (N-succinimidyl 3-[^{211}At]-astatobenzoate) suffers from chemical decomposition (Pozzi and Zalutsky, 2005a) and formation of HCl by radiolysis may explain this problem.

Our results may also explain why different oxidation states of ^{211}At exist in chloroform at the same time (Aneheim et al., 2019). It is helpful to measure the radiolytic yield of H_2 and Cl_2 in order to better understand the competition of HCl formation reaction with those gases, as H° and Cl° radicals are involved in these reactions. Moreover, based on this experiment, we would then recommend washing astatine solution with water in order to improve consistency before using for radiolabeling.

ACKNOWLEDGEMENTS

This work has been supported in part by a grant from the French National Agency for Research called “Investissements d''Avenir”, IRON Labex no. ANR-11-LABX-0018-01 and Equipex ArronaxPlus n°ANR-11-EQPX-0004 and ISITE NExT n°ANR-16-IDEX-0007. The authors would like to express their gratitude for the ARRONAX facility teams for their technical support.

REFERENCES

Abadie, M.J.M., 1982. Radiolysis of liquid chloroform in an oxygen free atmosphere. Radiat. Phys. Chem. 19, 63-71.

Aneheim, E., Palm, S., Jensen, H., Ekberg, C., Albertsson, P., Lindegren, S., 2019. Towards elucidating the radiochemistry of astatine – Behavior in chloroform. Scientific Reports 9, 15900.

Appleby, A., Schwarz, H.A., 1969. Radical and molecular yields in water irradiated by γ-rays and heavy ions. J. Phys. Chem. 73, 1937-1941.

Bibler, N.E., Hyder, M.L., 1968. Radiolysis of Chloroform in the Intense Radiation Pulse from a Nuclear Explosion. Nature 219, 374-375.

Bird, M.J., Cook, A.R., Zamadar, M., Asaoka, S., Miller, J.R., 2020. Pushing the limits of the electrochemical window with pulse radiolysis in chloroform. Phys. Chem. Chem. Phys. 22, 14660-14670.

Champion, J., Sabatié-Gogova, A., Bassal, F., Ayed, T., Alliot, C., Galland, N., Montavon, G., 2013. Investigation of Astatine(III) Hydrolyzed Species: Experiments and Relativistic Calculations. J. Phys. Chem. A 117, 1983-1990.

Chen, T.H., Wong, K.Y., Johnston, F.J., 1960. Radiolysis of Chloroform and Carbon Tetrachloride. J. Phys. Chem. 64, 1023-1025.

Clover, A., 1923. The auto-oxidation of chloroform. Journal of the American Chemical Society 45, 3133-3138.

Fricke, H., Hart, E.J., 1966. Chemical Dosimetry, Radiation Dosimetry. Academic Press, New York, USA.

Guérard, F., Gestin, J.F., Brechbiel, M.W., 2013. Production of [211At]-Astatinated Radiopharmaceuticals and Applications in Targeted α-Particle Therapy. Cancer Biotherapy and Radiopharmaceuticals 28, 1-20.

Guérard, F., Navarro, L., Lee, Y.S., Roumesy, A., Alliot, C., Chérel, M., Brechbiel, M.W., Gestin, J.F., 2017. Bifunctional aryliodonium salts for highly efficient radioiodination and astatination of antibodies. Bioorganic & Medicinal Chemistry 25, 5975-5980.

Johnston, F.J., Chen, T.-H., Wong, K.Y., 1961. Effects of Temperature and Added Hexachloroethane on the Radiolyses of Carbon Tetrachloride and Chloroform. J. Phys. Chem. 65, 728-730.

Lainé, M., Balan, E., Allard, T., Paineau, E., Jeunesse, P., Mostafavi, M., Robert, J.-L., Le Caër, S., 2017. Reaction mechanisms in swelling clays under ionizing radiation: influence of the water amount and of the nature of the clay mineral. RSC advances 7, 526-534.

Mostafa, E., Reinsberg, P., Garcia-Segura, S., Baltruschat, H., 2018. Chlorine species evolution during electrochlorination on boron-doped diamond anodes: In-situ electrogeneration of Cl2, Cl2O and ClO2. Electrochimica Acta 281, 831-840.

Navarro, L., Berdal, M., Chérel, M., Pecorari, F., Gestin, J.-F., Guérard, F., 2019. Prosthetic groups for radioiodination and astatination of peptides and proteins: A comparative study of five potential bioorthogonal labeling strategies. Bioorganic & Medicinal Chemistry 27, 167-174.

Ottolenghi, M., Stein, G., 1961. The Radiation Chemistry of Chloroform. Radiation Research 14, 281-290.

Pozzi, O.R., Zalutsky, M.R., 2005a. Radiopharmaceutical Chemistry of Targeted Radiotherapeutics, Part 1: Effects of Solvent on the Degradation of Radiohalogenation Precursors by 211At α-Particles. Journal of Nuclear Medicine 46, 700-706.

Pozzi, O.R., Zalutsky, M.R., 2005b. Radiopharmaceutical Chemistry of Targeted Radiotherapeutics, Part 2: Radiolytic Effects of 211At α-Particles Influence N-Succinimidyl 3-211At-Astatobenzoate Synthesis. Journal of Nuclear Medicine 46, 1393-1400.

Pozzi, O.R., Zalutsky, M.R., 2017. Radiopharmaceutical chemistry of targeted radiotherapeutics, part 4: Strategies for 211At labeling at high activities and radiation doses of 211At α-particles. Nuclear Medicine and Biology 46, 43-49.

Reilly, S.W., Makvandi, M., Xu, K., Mach, R.H., 2018. Rapid Cu-Catalyzed [211At]Astatination and [125I]Iodination of Boronic Esters at Room Temperature. Organic Letters 20, 1752-1755.

Schulte, J.W., Suttle, J.F., Wilhelm, R., 1953. Chemical Effects Produced in Chloroform by γ-Rays1. Journal of the American Chemical Society 75, 2222-2227.

Sergentu, D.-C., Teze, D., Sabatié-Gogova, A., Alliot, C., Guo, N., Bassal, F., Silva, I.D., Deniaud, D., Maurice, R., Champion, J., Galland, N., Montavon, G., 2016. Advances on the Determination of the Astatine Pourbaix Diagram: Predomination of $AtO(OH)_2^-$ over At^- in Basic Conditions. Chemistry – A European Journal 22, 2964-2971.

Watanabe, S., Azim, M.A.-U., Nishinaka, I., Sasaki, I., Ohshima, Y., Yamada, K., Ishioka, N.S., 2019. A convenient and reproducible method for the synthesis of astatinated 4-[211At]astato-l-phenylalanine via electrophilic desilylation. Organic & Biomolecular Chemistry 17, 165-171.

Werner, H.R., Firestone, R.F., 1965. Kinetics of the γ-Ray-Induced Decomposition of Chloroform1. J. Phys. Chem. 69, 840-849.

FIGURE LEGENDS

Figure 1 : Amount of HCl extracted in water from chloroform

Figure 2 : Experimental G-yield values of HCl), produced during irradiation of $CHCl_3$ in aerated (red spots) and oxygen free (blue ones) atmospheres by ^{137}Cs-source irradiator E_γ = 0.667 MeV, DR = 7-9 $Gy.min^{-1}$, Total Dose = 2580 Gy. The obtained data are shown the oxygen in the air can participate in HCl production. When measuring the radiolytic yield of HCl in the presence of air, the HCl concentration is considered zero at no absorbed radiation dose, as explained in results.

Figure 3 : HCl concentration, produced during irradiation of $CHCl_3$ in aerated atmosphere by ^{137}Cs-source irradiator E_γ = 0.667 MeV, DR = 7-9 $Gy.min^{-1}$, Total Dose = 93300 Gy.

TABLE and FIGURES

Table 1: G-yield values of HCl from chloroform irradiation in literature and this work

Dose(kGy)	0.005	320	$4.6-11.8$	$26-210$	$16-420$	93.3
G(HCl)	0.45	1.18	0.59	1.23	0.55	0.82
($\mu mol.J^{-1}$)						
Ref.	(Abadie, 1982)	(Chen et al., 1960)	(Ottolenghi and Stein, 1961)	(Johnston et al., 1961)	(Werner and Firestone, 1965)	This Work

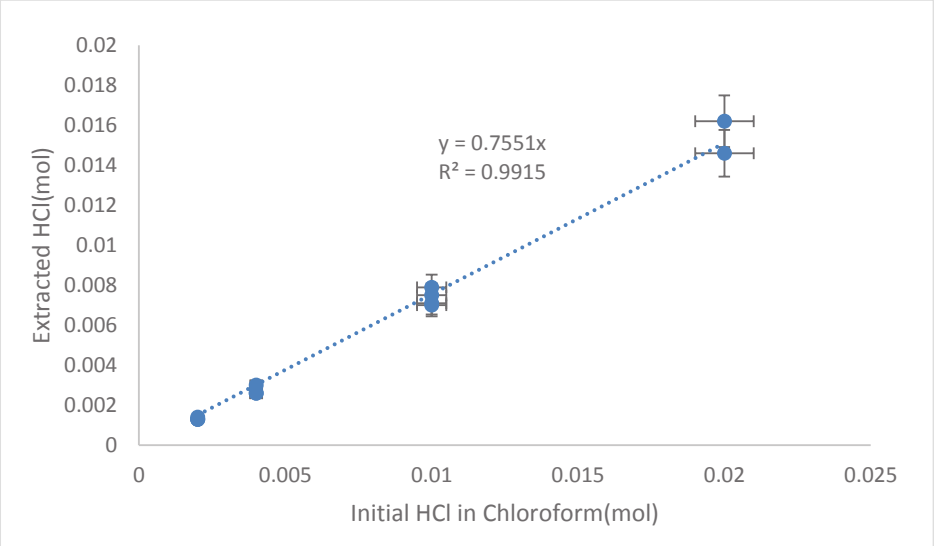


Figure 1 : Amount of HCl extracted in water from chloroform

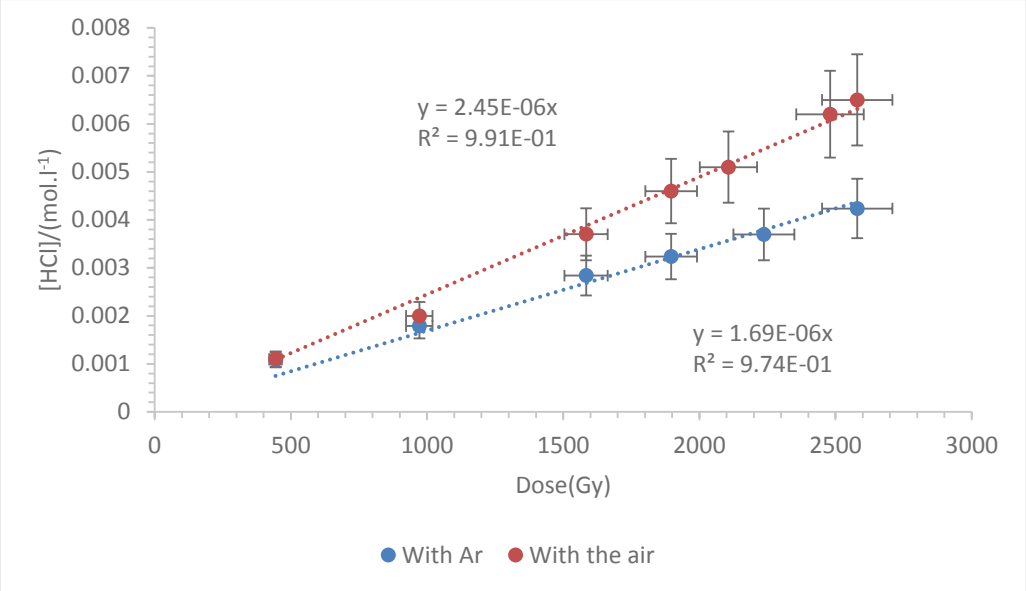


Figure 2 : Experimental G-yield values of HCl), produced during irradiation of $CHCl_3$ in aerated (red spots) and oxygen free (blue ones) atmospheres by ^{137}Cs-source irradiator E_γ = 0.667 MeV, DR = 7-9 $Gy.min^{-1}$, Total Dose = 2580 Gy. The obtained data are shown the oxygen in the air can participate in HCl production. When measuring the radiolytic yield of HCl in the presence of air, the HCl concentration is considered zero at no absorbed radiation dose, as explained in results.

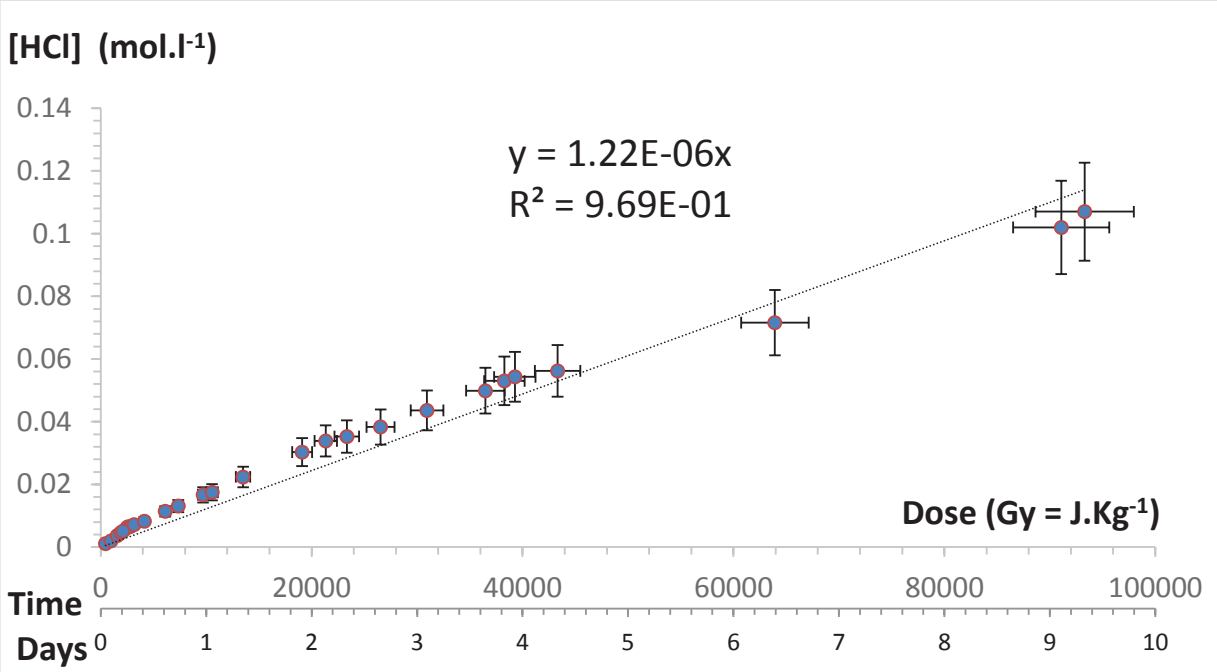


Figure 3 : HCl concentration, produced during irradiation of $CHCl_3$ in aerated atmosphere by ^{137}Cs-source irradiator E_γ = 0.667 MeV, DR = 7-9 $Gy.min^{-1}$, Total Dose = 93300 Gy.

Conflict of Interest

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

- Parastoo Mahdi Khoshouei and Guillaume Blain performed the experiments.
- Johan Vandenborre and Mohammad Ghalei wrote the manuscript with contribution from all co-authors.
- All co-authors contributed to the discussion and interpretation of the data.