Free Radical Research

ISSN: 1071-5762 (Print) 1029-2470 (Online) Journal homepage: https://www.tandfonline.com/loi/ifra20

High-energy ionizing radiation-induced degradation of amodiaquine in dilute aqueous solution: radical reactions and kinetics

Krisztina Kovács, Ádám Simon, György Tibor Balogh, Tünde Tóth & László Wojnárovits

To cite this article: Krisztina Kovács, Ádám Simon, György Tibor Balogh, Tünde Tóth & László Wojnárovits (2020): High-energy ionizing radiation-induced degradation of amodiaquine in dilute aqueous solution: radical reactions and kinetics, Free Radical Research, DOI: 10.1080/10715762.2020.1736579

To link to this article: https://doi.org/10.1080/10715762.2020.1736579

FREE RADICAL RESEARCH
https://doi.org/10.1080/10715762.2020.1736579

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

High-energy ionizing radiation-induced degradation of amodiaquine in dilute aqueous solution: radical reactions and kinetics

Krisztina Kovács[a], Ádám Simon[a,b], György Tibor Balogh[c,d], Tünde Tóth[a,b] and László Wojnárovits[a]

[a]Institute for Energy Security and Environmental Safety, Centre for Energy Research, Budapest, Hungary; [b]Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary; [c]Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, Budapest, Hungary; [d]Department of Pharmacodynamics and Biopharmacy, University of Szeged, Szeged, Hungary

ABSTRACT

The widely used antimalarial drug amodiaquine (AQ) contains a 7-Cl-quinoline unit, a substituted 4-aminophenol part connected through the amino group and a tertiary amine part. The 4-aminophenol unit can be easily oxidized through radical intermediates to iminoquinone. This reaction also takes place *in vitro* and *in vivo* enzymatic reactions. The reaction is expected to have an important role in degradation of AQ in surface waters and also during degradation in advanced oxidation processes. In this paper by means of radiation chemical techniques the one-electron oxidation and reduction of AQ were studied using transient kinetics, kinetics of AQ degradation, formation and decay of end-products of radical reactions. The hydroxyl radicals were shown to add both to the quinoline (∼ 38%) and aminophenol (∼ 50%) parts *via* formation of hydroxycyclohexadienyl radicals and by H-abstraction or by an electron removal from the tertiary amine part of the molecule (∼ 12%). The dihydroxycyclohexadienyl radical formed on the aminophenol part is suggested to transform to aminophenoxy radical. The hydrated electrons can also effectively contribute to AQ degradation. Chemical oxygen demand and total organic carbon content investigations were also made in order to characterize the ionizing radiation-induced oxidation and mineralization. In aerated 0.1 mmol dm^{-3} solution, at 2.5 kGy absorbed dose AQ and its higher molecular mass degradation products demolished completely. Ionizing irradiation is a capable technique for degradation of AQ under both oxidative and reductive circumstances.

ARTICLE HISTORY
Received 6 November 2019
Revised 4 February 2020
Accepted 25 February 2020

KEYWORDS
Aminophenoxy radical; degradation efficiency; one-electron oxidation; oxidative degradation; pharmaceuticals

Introduction

The highly effective, and in Africa widely used, antimalarial drug amodiaquine (AQ) [1] may cause hepatotoxicity in man [2]. The molecule (with IUPAC name 4-[(7-chloroquinolin-4-yl)amino] - 2-[(diethylamino)methyl]phenol) contains a 7-Cl-quinoline unit, a substituted 4-aminophenol part connected through the amino group and a tertiary amine part (Figure 1). AQ is a diprotic weak base with pK_a at 8.14 and 7.08. These pK_a's correspond to the proton reaction involving the side chain terminal nitrogen and the first proton reaction involving the quinoline nucleus [3]. The 4-aminophenol unit can be easily oxidized through a radical intermediate to iminoquinone. The free radical has been reported to form also in *in vitro* and *in vivo* enzymatic reactions [2,4]. In the last decades, with the aim of removal of harmful organic contaminants from water/wastewater, a family of new techniques, called advanced oxidation processes is under developed. In these processes inorganic radicals, mainly hydroxyl radicals (•OH), are produced in photolytic, photocatalytic, radiolytic, etc., processes. These radicals attacking the organic molecules produce organic radicals. AQ is a frequently detected contaminant of wastewater in certain areas [5]. Thus studies on the radical reactions of AQ have importance from both biochemical and environmental protection point of view.

Radiolysis techniques provide an excellent tool for studying radical reactions. In the radiolysis of water hydroxyl radical (•OH), hydrated electron (e_{aq}^-) and hydrogen atom (H•) reactive radical intermediates (Reaction (1)) form with yields (*G*-values) of 0.28, 0.27 and 0.06 μmol J^{-1} (N_2 saturated solution) [6]:

$$H_2O \rightarrow OH,\ e_{aq}^-,\ H^\bullet \qquad (1)$$

In the radiation chemical practice the •OH reactions are generally investigated in N_2O saturated solution (0.025 mol dm^{-3}) in order to transform e_{aq}^- to •OH in

CONTACT Krisztina Kovács kovacs.krisztina@energia.mta.hu Institute for Energy Security and Environmental Safety, Centre for Energy Research, Budapest, Hungary.

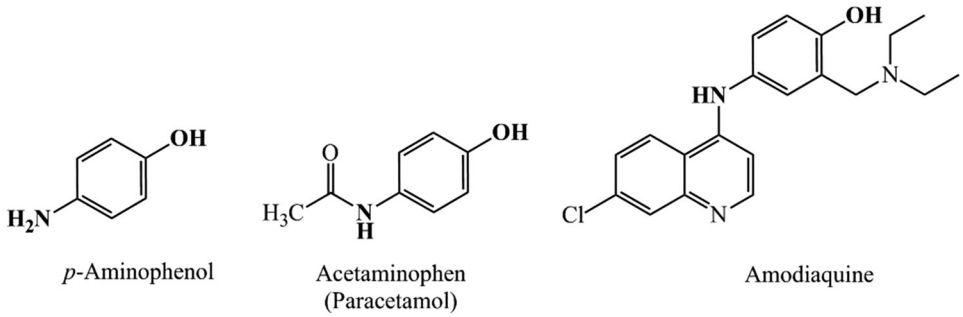


Figure 1. Structures of *p*-aminophenol, acetaminophen, and amodiaquine.

Reaction (2). The e_{aq}^- reactions are usually studied in the presence of *tert*-butanol, which solute removes the hydroxyl radicals from the system (Reaction (3)). In the presence of dissolved O_2 (air saturated solution), $O_2^{-\bullet}$/$HO_2^\bullet$ pair ($pK_a = 4.8$) forms in e_{aq}^- and $H^\bullet$ reactions (Reactions (4) and (5)). In this case, the main reacting agents are $^\bullet OH$ and $O_2^{\bullet-}/HO_2^\bullet$:

$$e_{aq}^- + N_2O + H_2O \rightarrow N_2 + {}^\bullet OH + OH^- \quad (2)$$

$$^\bullet OH + (CH_3)_3COH \rightarrow H_2O + {}^\bullet CH_2(CH_3)_2COH \quad (3)$$

$$e_{aq}^- + O_2 \rightarrow O_2^{\bullet-} \quad (4)$$

$$H^\bullet + O_2 \rightarrow HO_2^\bullet \quad (5)$$

Using pulse radiolysis technique, the radical reactions of AQ were studied by Bisby [2]. However, the radical reactions of its structural unit 4-aminophenol [7,8] and also of the analgesic and antipyretic type drug molecule acetaminophen (paracetamol) [9–14] were investigated by several research groups. The hydroxyl radicals in their reactions with the aromatic molecules generally add to the conjugated ring, direct oxidation (i.e. picking up an electron from the attacked molecule) rarely occurs. In pulse radiolysis studies direct oxidation experiments applying $N_3^\bullet$, $Cl_2^{\bullet-}$, $(SCN)_2^{\bullet-}$ or $Br_2^{\bullet-}$ one-electron oxidants were also conducted with all the three compounds. In these experiments such radical intermediates were observed whose characteristics were different from that of the phenoxyl radical (radical site on the oxygen atom) generally observed in one-electron oxidation of phenol type molecules. In Reaction (6) the direct oxidation reaction is shown on the example of the $N_3^\bullet$ reaction with 4-aminophenol:

$$N_3^\bullet + NH_2C_6H_4OH \rightarrow NH_2C_6H_4O^\bullet + H^+ + N_3^- \quad (6)$$

The phenoxyl radicals have characteristic absorption bands around 400 nm with well-defined fine structure and molar absorption coefficients of c.a. 3000 mol^{-1} dm^3 cm^{-1} [15]. However, in the cases of the formerly mentioned compounds (e.g. 4-aminophenol), the band is shifted to longer wavelength by about 50 nm and the molar absorbance is higher by at least a factor of two. Tripathi devoted several papers to the radical intermediate that forms in 4-aminophenol reaction [7,16–18]. The structure of the radical was established to be more similar to that of a semiquinone than to that of the phenoxyl radical. It means a considerable part of spin density is concentrated on the nitrogen atom. The radical is also called aminophenoxy radical.

In the transient spectrum of the $^\bullet OH$ + acetaminophen reaction 1 μs after the pulse (solute concentration 0.5 mmol dm^{-3}) Bisby and Tabassum [10] detected the absorbance of the typical hydroxycyclohexadienyl intermediate with absorption maximum at 330 nm. It means, in the reaction, as a first step, a radical adduct formed. However, 20 μs later a well resolved peak appeared with λ_{max} at 450 nm (Reaction (7)). This absorbance also appeared when acetaminophen was directly oxidized by $N_3^\bullet$, $Cl_2^{\bullet-}$ or $Br_2^{\bullet-}$ to aminophenoxy radical. In $^\bullet OH$ reaction the 450 nm absorbance was also attributed to the aminophenoxy radical forming in dehydration of the hydroxycyclohexadienyl intermediate. The dehydration is fast process taking place on the few μs timescale [10,14,19]. Bisby [2] suggested a similar mechanism for the $^\bullet OH + AQ$ reaction:

$$OH + NH_2C_6H_4OH \rightarrow \underset{\text{hydroxycyclohexadienyl}}{NH_2C_6H_4{}^\bullet(OH)OH} \rightarrow \underset{\text{aminophenoxy}}{NH_2C_6H_4O^\bullet} + H_2O \quad (7)$$

This work serves dual purposes. On the one hand, we determine further details of the radical reactions and suggest mechanism. On the other hand, for the purpose of water purification we follow the course of AQ decomposition and determine the efficiency in irradiation technology.

Materials and methods

AQ hydrochloride, methyl viologen dichloride hydrate (MV), 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), hydroquinone (H_2Q) were supplied by Sigma-Aldrich. KH_2PO_4 and K_2HPO_4

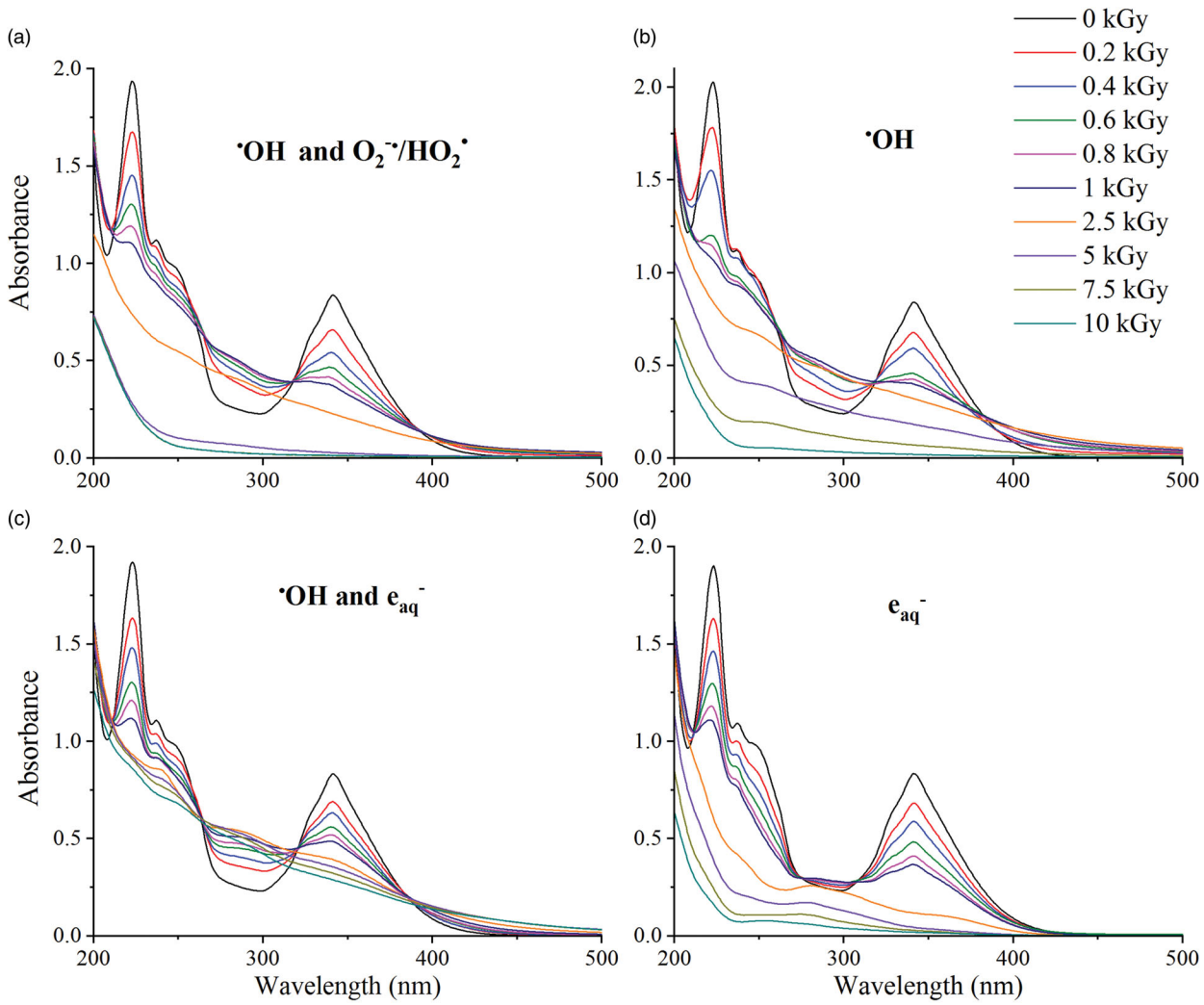


Figure 2. Absorption spectra of 0.1 mmol dm^{-3} unirradiated and irradiated AQ solutions under different conditions: in aerated (a), in N_2O saturated (b), in N_2 saturated (c) and in N_2 saturated *tert*-butanol containing (d) solutions. In order to remain in the absorbance range where the Lambert-Beer low is expected to be obeyed two times dilution was applied.

for preparing buffers were provided by Reanal. *Tert*-butanol was obtained from Molar Chemicals.

The samples in the end-product experiments were irradiated in a panoramic type ^{60}Co-γ irradiation chamber with doses 0, 0.2, 0.4, 0.6, 0.8, 1, 2.5, 5, 7.5 and 10 kGy under different conditions. The γ-irradiations were carried at room temperature at a dose rate of 10 kGy h^{-1}. The dose was determined using alcoholic chlorobenzene dosimetry [20]. The samples were saturated with N_2O, N_2 or air. In some experiments they were gently bubbled during irradiations in order to avoid oxygen depletion. The initial AQ concentration was 0.1 mmol dm^{-3}. The samples before and after irradiation were characterized by using a JASCO 550 ultraviolet–visible (UV–vis) spectrophotometer in 1 cm cell and applying appropriate dilutions before taking the spectra.

The transient intermediates of degradation reactions were investigated by the pulse radiolysis technique. Our microsecond pulse radiolysis experiments were performed using 4 MeV accelerated electrons with electron pulse length of 800 ns and utilizing kinetic spectrophotometric detection with 1 cm path length cell [21]. Pulse dosimetry was carried out with air saturated, 1×10^{-2} mol dm^{-3} KSCN solutions monitoring the transient product, ($(SCN)_2^{\bullet -}$) at 480 nm (λ_{max}) and calculating the dose with a molar absorbance of 7580 mol^{-1} dm^3 cm^{-1} [22]. The dose/pulse values were 20 Gy/pulse. Because AQ exhibits considerable light absorption in the near UV range an optical filter was used to decrease the effect of bleaching below 400 nm.

In order to identify and quantify the participating free radicals (e.g. α-aminoalkyl) with different reduction potentials, redox titration measurements were

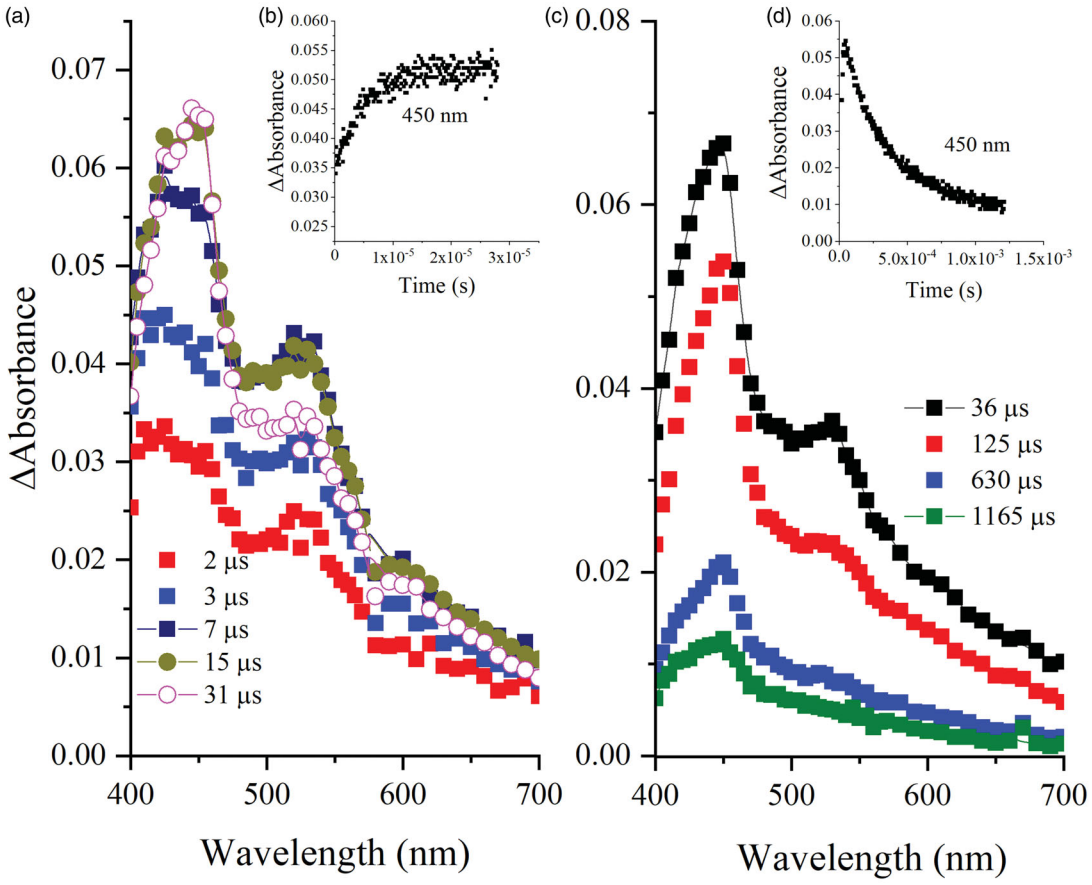


Figure 3. Transient absorption spectra of AQ in 0.1 mmol dm^{-3} N_2O saturated solution containing 1 mmol dm^{-3} phosphate buffer in the 2–31 μs (a) and 36–1165 μs (b) time ranges. Insets of (b) and (c) depict the first-order formation and decay at 450 nm.

conducted. Methyl viologen (MV, $E^\circ(MV^{2+}/MV^{\bullet+}) = -0.448$ V vs. NHE) was applied for the detection of reducing α-aminoalkyl radicals [23]. $MV^{\bullet+}$ absorbs at 600 nm with $\varepsilon_{600} = 11{,}850\ mol^{-1}\ dm^3\ cm^{-1}$ [24]. Oxidizing, nitrogen-centered radicals can be monitored with ABTS and H_2Q ($E^\circ(ABTS^{\bullet+}/ABTS) = 0.680$ V [25] and $E^\circ(Q^{\bullet-}/Q_2^-) = 0.459$ V [23]). The forming radicals were detected at 415 and 430 nm ($\varepsilon_{415} = 36{,}000\ mol^{-1}\ dm^3\ cm^{-1}$ and $\varepsilon_{430} = 7200\ mol^{-1}\ dm^3\ cm^{-1}$), respectively [26,27]. Based on the absorbances of forming radicals the yields of reducing/oxidizing radicals were calculated.

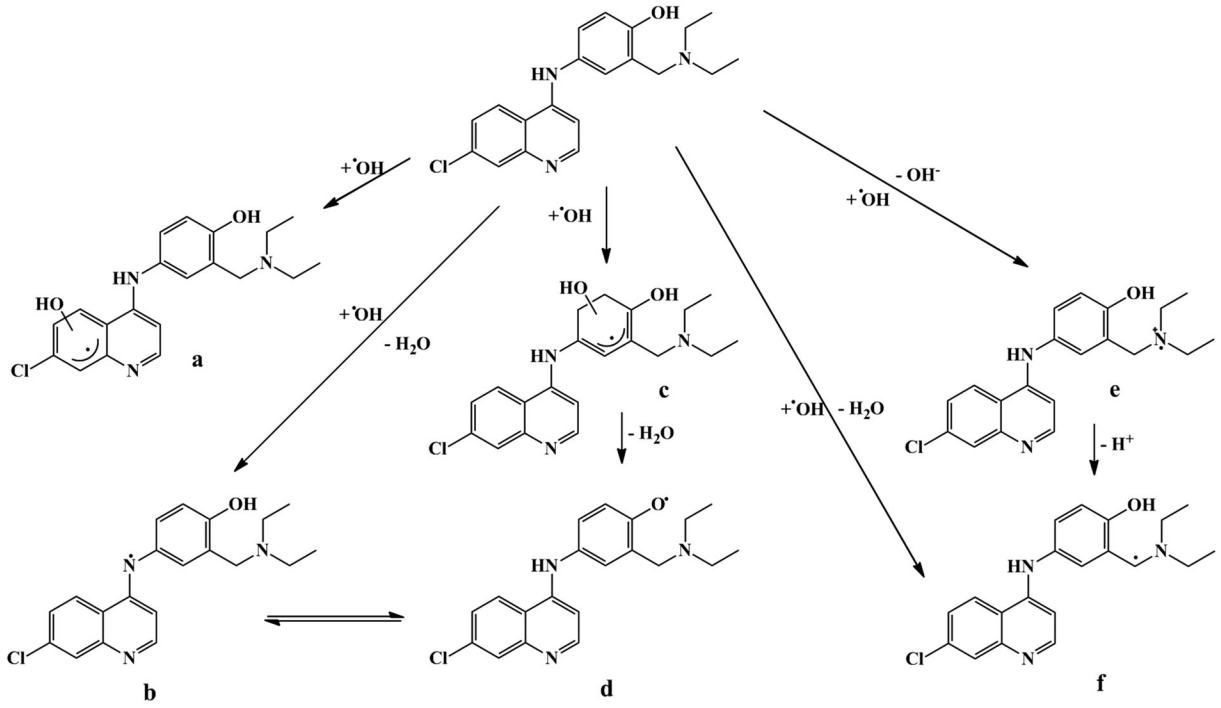
The removal of efficiency was evaluated by using Agilent 1200 LC and Agilent 6410 MS devices. The separation was carried out on a Kinetex XB-C18 column (100 × 2.1 mm, particle size 2.6 μm) at 25 °C. The mobile phase was the mixture of 0.1% formic acid aqueous solution (A) and acetonitrile (B). Gradient elution was performed as follows: the starting composition was 5% B for 1 min, then increased to 10% in 0.5 min, kept this condition for 9 min, than increased to 50% in 0.5 min. The measurements were conducted in positive ionization mode.

The time (dose) dependence of degradation was characterized by the sum parameters, chemical oxygen demand (COD) and total organic carbon (TOC) content measurements used in environmental analysis of water samples. COD values were assessed based on ISO Standard 6060:1989 by a Behrotest TRS 200 COD system. Shimadzu TOC-LCSH/CSN was used for the determination of TOC.

Results and discussion

UV–vis absorption spectra of amodiaquine in γ-radiolysis and pulse radiolysis experiments

The absorption spectra of samples irradiated by γ-rays in air, N_2O and N_2 (without and with *tert*-butanol added) saturated samples are shown in Figure 2 (a–d). Under these conditions the reactive intermediates are $^\bullet OH + O_2^{-\bullet}/HO_2^\bullet$, $^\bullet OH$, $^\bullet OH + e_{aq}^-$, and e_{aq}^-, respectively. The wide band between 300 and 400 nm in the UV–vis spectrum exhibits λ_{max} at 341 nm with ε_{max} of $16{,}400\ mol^{-1}\ dm^3\ cm^{-1}$. The absorbance gradually



Scheme 1. •OH reactions with AQ.

decreases with the increasing dose and disappears at 2.5 kGy.

In air, N_2 and N_2O saturated solutions the •OH reactions are dominant. •OH forms with yields: 0.28, 0.56 and 0.28 μmol J^{-1}, respectively. The transient intermediates in the •OH + AQ reaction were studied using pulse radiolysis in N_2O saturated solution (Figure 3). In the 400–700 nm wavelength range two bands can be distinguished: a strong band at ~450 nm and a smaller one at 525 nm.

•OH is expected to react with the Cl-quinoline, 4-aminophenol and also with the tertiary amine part of AQ. Based on the measured rate constant (9.0×10^9 mol^{-1} dm^3 s^{-1}), at 0.1 mmol dm^{-3} AQ concentration the •OH reaction is completed in c.a. 3 μs. The radical adducts on Cl-quinoline (a, Scheme 1) and 4-aminophenol (c) parts of AQ are expected to exhibit transient absorption between 300 and 400 nm as it is typical for aromatic adduct (hydroxycyclohexadienyl) radicals [8]. Due to the strong absorbance of AQ in this range, we did not take the transient spectrum at wavelengths below 400 nm.

•OH is assumed to react with addition to both rings of the Cl-quinoline part [28,29]. The reaction taking place on this part is supported by the UV–vis spectra of γ-irradiated solutions. In cases when •OH played a key role in degradation the 241 nm peak shifted to shorter wavelength due dehalogenation. Similar shift was also observed in •OH-induced dehalogenation of Cl-substituted phenylureas, e.g. monuron and diuron [30,31]. We expect a moderately fast •OH reaction with the Cl-quinoline part of AQ due to the deactivating electronegative Cl- and N-atoms.

The absorbance above 400 nm can be attributed to reactions on the 4-aminophenol part of AQ in agreement with results on 4-aminophenol and acetaminophen [2, 8, 14]. •OH reaction in these molecules produces 4-aminophenoxy radical with $\lambda_{max} \approx 440$ nm and $\varepsilon_{max} \approx 5000$ mol^{-1} dm^3 cm^{-1} [7,8]. The increasing absorbance above 400 nm after the AQ + •OH reaction is completed is due to transformation of the first formed hydroxycyclohexadienyl radical (c, Scheme 1) to aminophenoxy radical (d) with a rate constant of 2×10^5 s^{-1}. The molar absorbance of this radical at 460 nm, based on AQ reaction with the directly oxidizing $N_3^•$ was suggested to be 14,000 mol^{-1} dm^3 cm^{-1} [2]. Using this molar absorbance and the absorbance measured in our experiment, ~ 50% of the primarily formed organic radicals transform to aminophenoxy radical.

At the pH of our investigations (pH = 6.8) ~ 5% of the N-atoms on the trialkyl amine part of AQ are deprotonated. The rate constant of reaction with deprotonated triethylamine is reported to be high, 1.0×10^{10} mol^{-1} dm^3 s^{-1}, while with the protonated form it is low, 3.8×10^8 mol^{-1} dm^3 s^{-1} [32]. Due to the low percentage, the reaction with the deprotonated form gives low contribution to the overall degradation. In the reaction between •OH and the triethylamine part of AQ α-aminoalkyl radicals are expected (f, Scheme 1)

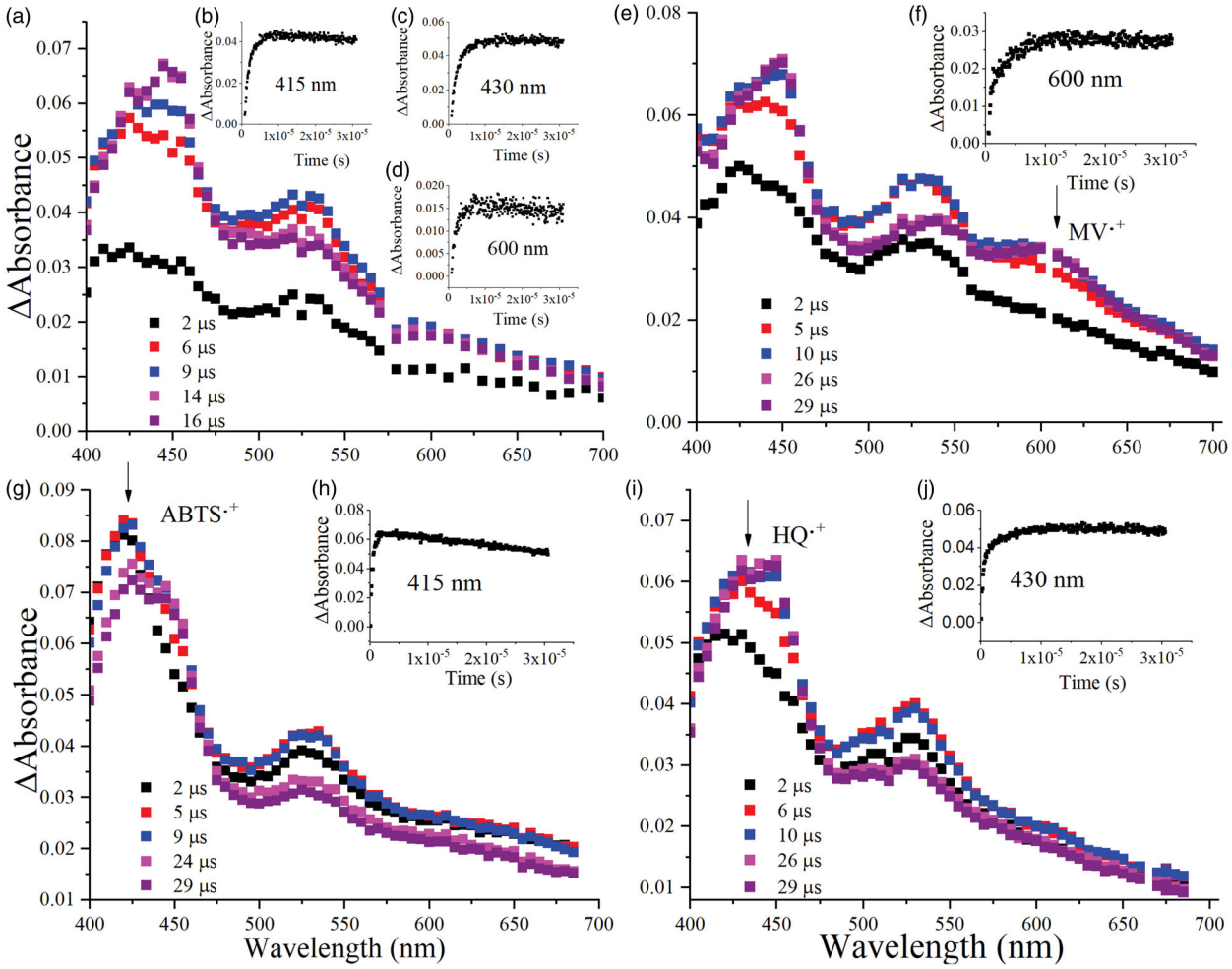


Figure 4. Transient absorption spectra in N_2O-saturated solution containing 0.1 mmol dm^{-3} AQ (a), kinetic traces recorded at 415 nm (b), at 430 nm (c) and 600 nm (d). Redox titration spectra in N_2O saturated solution containing 0.4 mmol dm^{-3} AQ and 0.1 mmol dm^{-3} MV (e), 0.4 mmol dm^{-3} AQ and 0.07 mmol dm^{-3} ABTS (g), 0.4 mmol dm^{-3} AQ and 0.07 mmol dm^{-3} HQ (i). The insets of (e), (g) and (i) show kinetic curves recorded at 600 nm (f), 415 nm (h), and 430 nm (j).

[32,33]. These radicals may form by H-abstraction or by deprotonation of the $R_1N^+(C_2H_5)_2$ cation that can be produced in direct oxidation.

To get a comprehensive picture about $^{\bullet}$OH-induced chemistry of AQ, the yields of α-aminoalkyl and nitrogen-centered radicals were quantified in redox titration experiments at 0.4 mmol dm^{-3} AQ concentration (Figure 4). α-aminoalkyl radicals as strong reducing species react with MV^{2+} *via* electron transfer [33, 34]. $MV^{\bullet+}$ was recorded with a yield of ∼ 0.068 μmol J^{-1}. $^{\bullet}$OH may also react with the triethylamine part of AQ by producing N-centered oxidizing aminium ($R_3N^{\bullet+}$) and aminyl ($R_2N^{\bullet}$) radicals. ABTS ($R_3N^{\bullet+}$) and H_2Q ($R_2N^{\bullet}$) were applied for the quantification of nitrogen-centered radicals. The results showed that aminyl radicals were not produced in the system. Aminium radicals (e, Scheme 1) were produced, albeit with low, ∼ 10% yield. These radicals may transform entirely to α-aminoalkyl radicals (Scheme 1).

The e_{aq}^- reaction was studied in N_2 saturated solutions containing 0.5 mol dm^{-3} *tert*-butanol. Upon γ-irradiation the intensity of the 241 nm band in the UV–vis spectrum (Figure 2(d)) decreased without wavelength shift. In the transient spectrum (Figure 5) the strong absorbance in the 500–700 nm range (the absorbance of e_{aq}^- ($\lambda_{max} \approx 720$ nm, $\varepsilon_{max} \approx 20{,}000$ mol^{-1} dm^3 cm^{-1} [6,35])) decayed within 2 μs, and a wide band remained with lower intensity. The latter is attributed to the AQ electron adduct. The rate constant of e_{aq}^- + AQ reaction was found to be 1.6×10^{10} mol^{-1} dm^3 s^{-1}. It is higher than measured for quinoline or 1-chloronaphthalene (7.1×10^9 and 1.4×10^{10} mol^{-1} dm^3 s^{-1}, respectively, [36,37]) due to the presence of Cl and N electronegative atoms in the

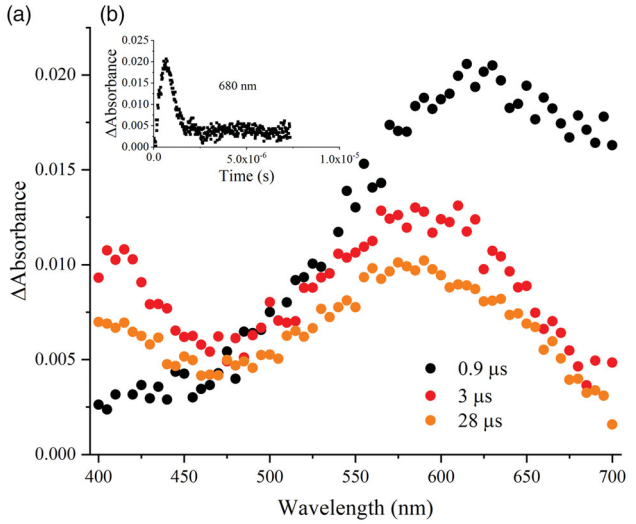


Figure 5. Transient absorption spectrum of AQ taken in 0.1 mmol dm^{-3} N_2 saturated solution containing 0.5 mol dm^{-3} *tert*-butanol and also 1 mmol dm^{-3} phosphate buffer in the 0.9–28 μs time range. Inset displays a kinetic trace at 680 nm (b).

Cl-quinoline part. e_{aq}^- is expected to react preferentially with this part of AQ accommodating on the pyridine ring. Zhu *et al.* [36] published a similar electron adduct spectrum for quinoline molecule as we found for AQ. The reactivity with the aminophenol part is probably low. *p*-Aminophenol and acetaminophen react with e_{aq}^- with rate constants of 2.5×10^8 and 5×10^8 mol^{-1} dm^3 s^{-1}, respectively [8,14]; the rate constants of alkylamines are also in the few times 10^9 mol^{-1} dm^3 s^{-1} range [35].

Removal efficiency of amodiaquine

To get a more reliable and complementary picture about the removal of AQ at each stage of treatment liquid chromatographic separation with mass spectrometry detection (LC-MS), COD, and TOC measurements were conducted.

The samples containing 0.1 mmol dm^{-3} AQ were irradiated in aerated solutions (Figure 6). AQ is a highly polar compound with log $D = -1.4$ (at pH 5) [38]. AQ eluted at 8.49 min, it was detected using the molecular ion ($[M+H]^+$) of 356. The drug concentration decreased gradually with increasing absorbed dose (Figure 6, inset). At 2.5 kGy dose no AQ and its degradation products were detected in the solutions.

Changes in COD values may characterize the rate of oxidation (ΔCOD/dose), while changes in TOC give information on the rate of mineralization. The initial COD and TOC values in 0.1 mmol dm^{-3} AQ solutions were measured as 79 mg (O_2) dm^{-3} and 31 mg (C) dm^{-3}, these values are close to the ones calculated

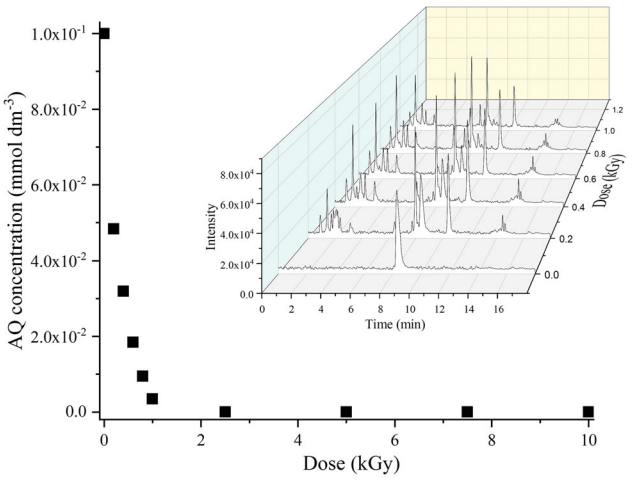


Figure 6. Decrease of AQ concentration in aerated solutions. Inset: chromatogram of AQ and its degradation products.

based on the molecular formula. The COD and TOC values decreased gradually with absorbed dose (Figure 7).

Based on changes in COD values, degradation of AQ can be described by two different linear stages. At low doses (0–3 kGy) the initial ΔCOD/dose slope was 6.6×10^{-3} mg dm^{-3} Gy^{-1}, then, above 3 kGy, the oxidation rate decreased to 1.8×10^{-3} mg dm^{-3} Gy^{-1}. In the first stage the degradation of the initial molecule and its higher molecular mass organic transformation products takes place. At c.a. 2.5 kGy they disappear from the solution (Figures 2(a) and 5). The higher molecular mass products are expected to decay to small molecular mass carboxylic acids, aldehydes and ketones [39] these molecules are known to be oxidized very slowly. The decrease of TOC with absorbed dose was almost linear, the rate of mineralization was 1.6×10^{-3} mg dm^{-3} Gy^{-1}. The initial rate of oxidation and mineralization are different, the decrease in the COD value at 5 kGy dose was about 50%, while in TOC this decrease was only 30%.

The oxidation efficiency (*E*) is defined as the ratio of the number of O_2 molecules used for oxidation (calculated from ΔCOD/dose values) and the number of $^{\bullet}OH$ injected into the solution [40]. When this value is 1, every $^{\bullet}OH$ leads to incorporation of one O_2 molecule, i.e. the attack of the one-electron oxidant $^{\bullet}OH$ leads to four electron oxidations of the organic molecules. Such high values were observed when the organic radical formed in $^{\bullet}OH$ reaction readily reacted with dissolved O_2. If the reactivity of the organic radical with O_2 was low, *E* was well below 1. Aminophenoxy type radicals practically does not react with O_2 [10,40].

For *p*-aminophenol and acetaminophen (also in air saturated solutions) $E = 0.55$ and 0.4, respectively, were measured [40]. Based on the initial ΔCOD/dose slope

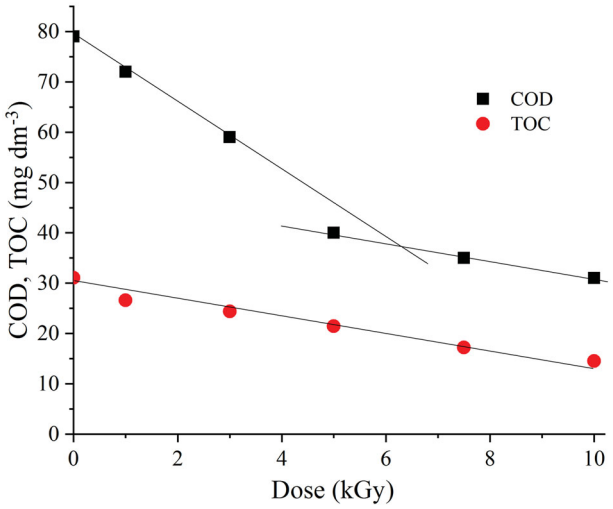


Figure 7. Dose dependence of COD and TOC values in aerated, 0.1 mmol dm^{-3} AQ solution.

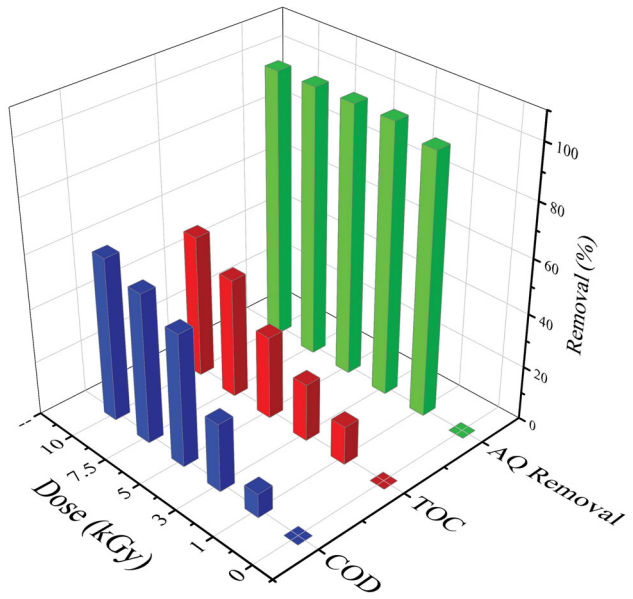


Figure 8. Comparison of removal percentages of AQ, TOC, and COD.

(Figure 7) *E* was found to be 0.7 for AQ. This value for AQ is higher than reported for the two previously mentioned compounds, reflecting more efficient oxidation. In all three cases aminophenoxy type radicals were suggested to be produced in reaction with •OH. AQ is a more complex molecule than *p*-aminophenol and acetaminophen, beyond the central *p*-aminophenol unit it contains also quinoline and tertiary amine parts. Formerly •OH was shown to attack these parts also forming carbon atom centered radicals, which may readily react with dissolved O_2. The higher rate of oxidation of AQ may be related to these reactions.

A comparison of LC-MS, COD and TOC results is shown on the Figure 8. At 10 kGy dose AQ and its main degradation products were entirely consumed. However, the mentioned small molecular mass oxidized organic molecules were yet present in the solution. This high absorbed dose resulted in ∼ 60% COD removal and ∼ 50% TOC removal in course of AQ decomposition.

Conclusion

This study provided a detailed insight into the radical reactions and decomposition of AQ under oxidative and reductive conditions. •OH adds to both Cl-quinoline (∼ 38%) and aminophenol (∼ 50%) parts *via* formation of hydroxycyclohexadienyl radicals and by H-abstraction or by an electron removal from the tertiary amine part of the molecule (∼ 12%). The hydroxycyclohexadienyl radical formed on the aminophenol part is suggested to transform to aminophenoxy radical. The presence of electron withdrawing chlorine atom increases the reactivity of e_{aq}^- towards AQ (1.6×10^{10} mol^{-1} dm^3 s^{-1}) compared to other N-containing molecules such as aminophenols. In aerated 0.1 mmol dm^{-3} solution, at 2.5 kGy absorbed dose AQ and the higher molecular mass degradation products detected by LC-MS disappeared completely. Ionizing irradiation is a capable technique for degradation of AQ under both oxidative and reductive circumstances.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The authors thank International Atomic Energy Agency (IAEA) for support [Coordinated Research Project F23034, Contract no: 23754].

References

[1] Tilley L, Loria P, Foley M. Chloroquine and other quinoline antimalarials. In: Rosenthal PJ, ed. Antimalarial chemotherapy, mechanism of action, resistance and new directions in drug discovery. New York: Springer Science; 2001. p. 87–89.

[2] Bisby RH. Reactions of a free radical intermediate in the oxidation of amodiaquine. Biochem Pharmacol. 1990;39(12):2051–2055.

[3] Hawley SR, Bray PG, Park BK, et al. Amodiaquine accumulation in *Plasmodium falciparum* as a possible explanation for its superior antimalarial activity over chloroquine. Mol Biochem Parasitol. 1996;80(1):15–25.

[4] Bisby RH. Pulse radiolysis, free radicals and antiparasitic drugs. Parasitol Today. 1990;6(3):84–88.

[5] Tella AC, Owalude SO, Olatunji SJ, et al. Synthesis of zinc-carboxylate metal–organic frameworks for the removal of emerging drug contaminant (amodiaquine) from aqueous solution. J Environ Sci. 2018;64: 264–275.

[6] Buxton GV, et al. An overview of the radiation chemistry of liquids. In: Spotheim-Maurizot M, Mostafavi M, Douki T, editors. Radiation chemistry: From basics to applications in material and life sciences. France: EDP Sciences; 2008. p. 3–16.

[7] Tripathi GNR, Schuler RH. Resonance Raman studies of pulse radiolytically produced *p*-aminophenoxyl radical. J Phys Chem. 1984;88(9):1706–1710.

[8] Dwibedy P, Dey GR, Naik DB, et al. Radiation-induced redox reactions of 2-, 3- and 4-amino-phenols in aqueous solutions. Radiat Phys Chem. 2005;74(1): 12–20.

[9] Fischer V, West PR, Harman LS, et al. Free-radical metabolites of acetaminophen and a dimethylated derivative. Environ Health Perspect. 1985;64:127–137.

[10] Bisby RH, Tabassum N. Properties of the radicals formed by one-electron oxidation of acetaminophen––a pulse radiolysis study. Biochem Pharmacol. 1988;37(14):2731–2738.

[11] Andreozzi R, Caprio V, Marotta R, et al. Paracetamol oxidation from aqueous solutions by means of ozonation and H_2O_2/UV system. Water Res. 2003;37(5): 993–1004.

[12] Yang L, Yu LE, Ray MB. Degradation of paracetamol in aqueous solutions by TiO_2 photocatalysis. Water Res. 2008;42(13):3480–3488.

[13] Yang L, Yu LE, Ray MB. Photocatalytic oxidation of paracetamol: dominant reactants, intermediates, and reaction mechanisms. Environ Sci Technol. 2009;43(2): 460–465.

[14] Szabó L, Tóth T, Homlok R, et al. Radiolysis of paracetamol in dilute aqueous solution. Radiat Phys Chem. 2012;81(9):1503–1507.

[15] Wojnárovits L, Kovács A, Földiák G. Spectral characteristics of monosubstituted phenoxyl radicals. Radiat Phys Chem. 1997;50(4):377–379.

[16] Sun Q, Tripathi GNR, Schuler RH. Time-resolved resonance Raman spectroscopy of *p*-aminophenol radical cation in aqueous solution. J Phys Chem. 1990;94(16): 6273–6277.

[17] Tripathi GNR, Schuler RH. Structure of the *p*-aminophenoxyl radical. Faraday Trans. 1993;89(23): 4177–4180.

[18] Tripathi G. Proton reactivity and electronic structure of phenoxyl radicals in water. J Phys Chem A. 1998; 102(13):2388–2397.

[19] Ismail FMD, Drew MGB, Navaratnam S, et al. A pulse radiolysis study of free radicals formed by one-electron oxidation of the antimalarial drug pyronaridine. Res Chem Intermed. 2009;35(4):363–377.

[20] International Organization for Standardization, American Society for Testing and Materials (ISO/ASTM). Practice for use of the ethanol-chlorobenzene dosimetry system. Standard No. ISO/ASTM;51538. ISO/ASTM.

[21] Földiák G, Hargittai P, Kaszanyiczki L, et al. A computer controlled pulse radiolysis laboratory. J Radioanal Nuclear Chem. 1988;125(1):19–28.

[22] Buxton GV, Stuart CR. Re-evaluation of the thiocyanate dosimeter for pulse radiolysis. Faraday Trans. 1995;91(2):279–281.

[23] Wardman P. Reduction potentials of one-electron couples involving free radicals in aqueous solution. J Phys Chem Ref Data. 1989;18(4):1637–1755.

[24] Trudinger PA. On the absorbancy of reduced methyl viologen. Anal Biochem. 1970;36(1):222–225.

[25] Scott SL, Chen WJ, Bakac A, et al. Spectroscopic parameters, electrode potentials, acid ionization constants, and electron exchange rates of the 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) radicals and ions. J Phys Chem. 1993;97(25):6710–6714.

[26] Wolfenden BS, Willson RL. Radical-cations as reference chromogens in kinetic studies of ono-electron transfer reactions: pulse radiolysis studies of 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate). J Chem Soc Perkin Trans 2. 1982;(7):805–812.

[27] Veltwisch D, Asmus K-D. On the reaction of methyl and phenyl radicals with *p*-benzoquinone in aqueous solution. J Chem Soc Perkin Trans 2. 1982;(9): 1147–1152.

[28] Cermenati L, Pichat P, Guillard C, et al. Probing the TiO_2 photocatalytic mechanisms in water purification by use of quinoline, photo-Fenton generated $OH^\bullet$ radicals and superoxide dismutase. J Phys Chem B. 1997; 101(14):2650–2658.

[29] Nicolaescu AR, Wiest O, Kamat PV. Radical-induced oxidative transformation of quinoline. J Phys Chem A. 2003;107(3):427–433.

[30] Kovács K, He S, Mile V, et al. Ionizing radiation induced degradation of diuron in dilute aqueous solution. Chem Cent J. 2015;9:21.

[31] Kovács K, He S, Míle V, et al. Ionizing radiation induced degradation of monuron in dilute aqueous solution. Radiat Phys Chem. 2016;124:191–197.

[32] Simić M, Neta P, Hayon E. Pulse radiolytic investigation of aliphatic amines in aqueous solution. Int J Radiat Phys Chem. 1971;3(3):309–320.

[33] Szabó L, Mile V, Tóth T, et al. On the complex $^\bullet OH/^\bullet O^-$-induced free radical chemistry of arylalkylamines with special emphasis on the contribution of the alkylamine side chain. Free Radic Res. 2017;51(2):124–140.

[34] Rózsa G, Szabó L, Schrantz K, et al. Mechanistic study on thiacloprid transformation: free radical reactions. J Photochem Photobiol Chem. 2017;343:17–25.

[35] Buxton GV, Greenstock CL, Helman WP, et al. Critical review of rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals ($^\bullet OH/O^-$ in Aqueous Solution. J Phys Chem Ref Data. 1988;17(2):513–886.

[36] Zhu D-Z, Sun D-M, Jiang Z-L, et al. Studies on the respective reactions of quinoline and isoquinoline with transient species by pulse radiolysis. Acta Phys Chim Sin. 2008;24:2321–2326.

[37] Aikawa M, Sumiyoshi T, Miura N, et al. Dynamic studies on electron transport across micellar phase. Intermicellar migration of hydrated electrons. BCSJ. 1982;55(8):2352–2355.

[38] Ruscoe JE, Tingle MD, O'Neill PM, et al. Effect of disposition of mannich antimalarial agents on their pharmacology and toxicology. Antimicrob Agents Chemother. 1998;42(9):2410–2416.

[39] Mvula E, Schuchmann MN, von Sonntag C. Reactions of phenol-OH-adduct radicals. Phenoxyl radical formation by water elimination vs. oxidation by dioxygen. J Chem Soc Perkin Trans 2. 2001;(3):264–268.

[40] Homlok R, Takács E, Wojnárovits L. Degradation of organic molecules in advanced oxidation processes: relation between chemical structure and degradability. Chemosphere. 2013;91(3):383–389.