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Transformation of antibacterial agent roxithromycin in sodium hypochlorite disinfection process of different water matrices

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ABSTRACT

The effects of water matrices on the reaction kinetics and transformation products of roxithromycin (ROX) with sodium hypochlorite (NaClO) were investigated. It was found that the removal efficiency of ROX was dependent on the type of disinfected water. For simulated fresh water, marine culture water and seawater, the reaction rate constant was 0.0521 min^{-1}, 0.0757 min^{-1} and 0.106 min^{-1}, respectively. The bromide ions in seawater and marine culture water not only promoted the reaction of ROX with NaClO but also caused the generation of brominated DBPs (Br-DBPs). Four DBPs including one chlorinated DBP (Cl-DBP) and three Br-DBPs were identified. The cladinose moiety and C14 atom were the main reaction centers which were easily attacked by disinfectant in fresh water. The desosamine moiety was also broken away from the parent compound ROX in the simulated marine culture water and seawater. Adsorbable organic halogen (AOX) analysis demonstrated that the Br-DBPs in water samples containing bromide ions were generally more carcinogenic than the Cl-DBPs formed in fresh water.

1. Introduction

Recirculating aquaculture systems (RAS) have been widely used to reduce waste discharge and improve water quality in marine culture over the past years [1–3]. Disinfection of marine culture water is essential in RAS to prevent disease outbreak and pathogen contamination [4]. Chlorine, chlorine dioxide, chloramines, and sodium hypochlorite (NaClO) are chlorination disinfectants used frequently in marine culture [5]. The disinfectants inactivate any residual pathogenic microorganisms, meanwhile, they can also react with the organic matter and inorganic ions (e.g., bromide ions and iodine ions) in source water to generate unintended halogenated disinfection byproducts (DBPs) such as trihalomethanes (THMs) and haloacetic acids (HAAs). Toxicological studies have also shown that halogenated DBPs are genotoxic or carcinogenic that cause threat to human health [6–9].

To enhance growth rate and feed efficiency, extensive antibiotics were used in animal feed [10,11]. However, about 75% of antibiotics can be excreted through faeces and enter into the recycled water with the uneaten antibiotic feed together [12,13]. A lot of researches have shown that the constant increasing of residual antibiotics cause antibiotic pollution in the coastal environment [14–18]. Indeed, various macrolides antibiotics, such as erythromycin, clarithromycin, spiramycin, azithromycin, tylosin, and roxithromycin (ROX) have been frequently detected at the maximum concentration of 630 ng/L in coastal water [19,20]. Antibiotic residues in water are not only pollutants but also act as precursors of halogenated DBPs in chlorine disinfection [21,22]. Nevertheless, the reported researches mainly focused on the transformation products of macrolides antibiotics generated in fresh water during chlorine, chlorine dioxide and ozone disinfection processes [23–26]. For example, Radjenovic et al. reported that five new products of ROX were originated from the oxidation of ROX by ozone. The deprotonated dimethylamino group was attacked and the clasinose moiety was broken [27].

The above researches were performed in fresh water, and only chlorinated DBPs (Cl-DBPs) were identified. Water quality parameters (e.g., pH, background inorganic matrix, especially bromide ions concentration) will influence the formation species of DBPs [28–30]. High concentrations of chlorine, bromide ions and residual antibiotics were included in the marine culture water. Bromide ions can be oxidized by hypochlorous acid (HClO) to hypobromous acid (HOBr), which is a stronger oxidant compared to HClO. Furthermore, the active oxidant can react with organic pollutants to form brominated DBPs (Br-DBPs). Symons et al. [31] reported that HOBr can react more rapidly with natural organic matter (NOM) than HOCl. The distribution of THMs and HAAs shifted to more brominated species in the presence of the bromide ions [32–34]. Among all halogenated DBPs, Br-DBPs are of

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increasing concern because they are usually more toxic than their chlorinated analogs. The conclusion have been proved through the comparative toxicity study on haloaliphatic DBPs in bacteria, chinese hamster ovary cells and human cells [35–38].

The residual macrolide antibiotic in marine culture water would act as the organic precursor and directly react with the disinfectants to form various toxic halogenated DBPs [39–41]. This prompted us to investigate the reaction kinetics of ROX with NaClO, the DBPs species, reaction mechanisms and toxicity of halogeno-DBPs, especially the Br-DBPs during the disinfection process. ROX which was frequently detected at concentrations of 0.25–458 ng/L in shrimp ponds was selected as the model macrolide antibiotic [42,43]. Its molecular structure consists of a 14-membered lactone ring and the two sugar residues cladinose and desosamine as shown in Fig. S1 [44]. NaClO commonly used in marine culture was chosen as the chlorine-containing disinfectant. This paper mainly focused on identifying the new DBPs especially Br-DBPs, and investigating the reaction kinetics, primary reactive center and reaction pathways of ROX in the NaClO disinfection process of different water samples.

2. Materials and methods

2.1. Chemicals

Analytical grade ROX was purchased from the Shanghai Yuanye Biological Technology Company and used without further purification. NaCl, NaBr and $Na_2S_2O_3$ were obtained from the Chengdu Jinshan Chemical Reagent Company, China. NaClO was obtained from the Tianjin Damao Chemical Reagent Company at 10% purity. HPLC grade methanol and acetonitrile were obtained from the Anhui Fulltime Specialized Solvents & Reagents Co., LTD. Formic acid was purchased from the Chengdu Kelong Chemical Reagent Company. Buffer was purchased from the Shanghai Hongyi Instrument & Meter Co., LTD. The reaction pH was maintained by 0.2 mM phosphate (pH 5–8) or borate buffer (pH > 8) during experiments conducted in reagent water systems. All reagent solutions deionized water was prepared using by a Millipore Mili-Q Ultrapure Gradient A10 purification system.

2.2. Analytical methods

The loss concentration of ROX in sodium hypochlorite disinfection during kinetic experiments was measured with an Agilent 1050 series HPLC system equipped with a Zorbax RX-C18 column (2.1 mm × 50 mm, 1.7 μm), a thermostat (30 °C), fluorescence detector, and UV diode-array detector. The detection wavelength for ROX was set at 210 nm. The mobile phase consisted of 0.025 mol/L phosphoric acid (A) and acetonitrile (B). Isocratic elution at a flow rate of 0.25 ml/min was carried out using A: B = 40%:60%. The total organic carbon (TOC) was measured by analyzer of Shimadzu. The adsorbed organic halides (AOX) was measured with the micro-coulometric titration method [45] using a total organic halogen analyzer (XPLORER; TE Instruments B.V.). Each sample was analyzed in triplicate.

2.3. Batch kinetic experiments

Free chlorination experiments for each roxithromycin antibiotic were carried out in 25 ml conical flask in triplicate. To avoid missing some of the transformed products, a lot of literatures on the DBPs identification set the initial precursors concentration higher than that in actual water samples [46]. The initial concentration of ROX was set higher than its possible concentration in real marine cultural water and in sea water. Reaction was initiated by adding 1 ml of 0.3 mol/L NaClO into solutions containing 20 ml of 0.05 mmol/L ROX. The molar ratio of NaClO was at least 30 times higher than that of target compound to ensure that it is completely transformed in the kinetic experiments. Reaction solutions were constantly mixed using thermostatic oscillator. Sample aliquots were taken periodically, immediately quenched by adding 1 ml of 0.06 mol/L of Na_2SO_3, and then analyzed by the 1050 Agilent HPLC system for the loss of target ROX. The kinetics equation of ROX oxidation could be describe as follows:

$$\frac{d[ROX]}{dt} = -k[ROX]^n \quad (1)$$

where k represents the reaction rate constant, n represents the reaction order.

The kinetics data revealed that all of the reactions between ROX and NaClO followed the pseudo first order with R^2 values ranging from 0.95 to 1.0. The rate constants for losses of ROX were obtained from the slopes of fitted linear plots of ln ([NOR]) vs. time with unit of min^{-1}.

2.4. Product identification

Reaction products were analyzed using a Thermo Fisher LC-MS/MS (Q-Exactive) system equipped with a Zorbax SB-C18 column (2.4 × 150 mm, 5 μm), a UV diode-array detector, and a mass spectrometer. Analyte peaks were resolved using gradient elution with acetonitrile and 0.2% formic acid at a flow rate of 0.30 ml min^{-1}. MS analyses were conducted using positive mode electrospray ionization (ESI^+) over a mass scan range of 50–1000 *m/z* and with a mass resolution in increments of 0.0001 *m/z*. Halogen compounds were analyzed by mass spectrometry. Isotopic ion peaks can be found in the mass spectra of organic compounds with non-single isotopic composition, especially for compounds containing bromine and chlorine elements.

The DBPs of ROX reacted with NaClO were analyzed by LC-MS/MS in the following procedures: first, a full-scan mass spectrum was obtained simultaneously using the positive and negative modes; then, the Thermo Qual Browser of XCalibur was used to assign molecular formulae to each candidate mass, and ChemSpider databases were used to help identify the DBPs. Then, the proposed structures were further verified using Mass Frontier 7.0 software.

3. Results and discussion

3.1. Reaction kinetics of ROX with NaClO

According to the components of the actual sea water, the seawater samples used in the experiments were synthesized by adding the main inorganic cations (Na^+: 10.76 g L^{-1}, Ca^+: 0.41 g L^{-1}, Mg^{2+}: 1.29 g L^{-1}, K^+: 0.40 g L^{-1}) and anions (Cl^-: 19.35 g L^{-1}, Br^-: 65 mg L^{-1}, SO_4^{2-}: 2.71 g L^{-1} and HCO_3^-: 0.142 g L^{-1}) to the fresh water obtained by Milli-Q pure water system. The synthetic marine culture water was a mixture of sea water and fresh water with proportion of 1:2 as in the actual breeding process. Then, all the ionic concentrations of marine culture water were one third of that in seawater. The rate constants provide the necessary information to predict the fate of ROX during the oxidation of NaClO. As can been seen from Fig. 1a, after reaction with NaClO for 30 min, the removal efficiency of ROX was 99.2%, 90.4% and 80.5% in synthetic sea water, marine culture water and fresh water, respectively. Therefore, the reaction rates of ROX oxidation in various mediums followed the order seawater > marine culture water > fresh water (Fig. 1b). As mentioned above, there are many anions and cations in the water samples. The effects of each anion and cation on the reaction rates were analyzed respectively. The experiments were conducted by fixing the ions concentrations except for the investigated parameter. The results showed that all cations did not affect the rate of reaction. For the main anions, HCO_3^- negligibly affected the reaction rate of ROX with NaClO, SO_4^{2-} and Cl^- showed promotion of the reactions (Fig. S2a). Bromide ion has a certain inhibitory effect on the reaction (Fig. S2b). The reason for above phenomenon remains to be further examined.

The activation energy that material required to transform from the normal state to the active state can also explain for the rate of reaction.

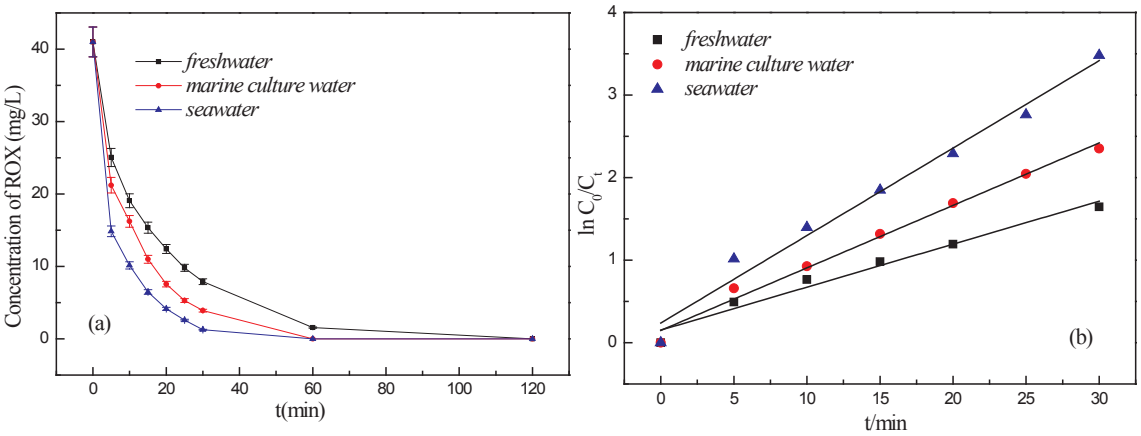


Fig. 1. Transformation of ROX reacted with NaClO in different water samples and the linear fit of the kinetic data ($[ROX]_0$ = 0.05 mM, 20 ml, $[NaClO]_0$ = 0.3 M, 1 ml, pH = 7, T = 298.15 K).

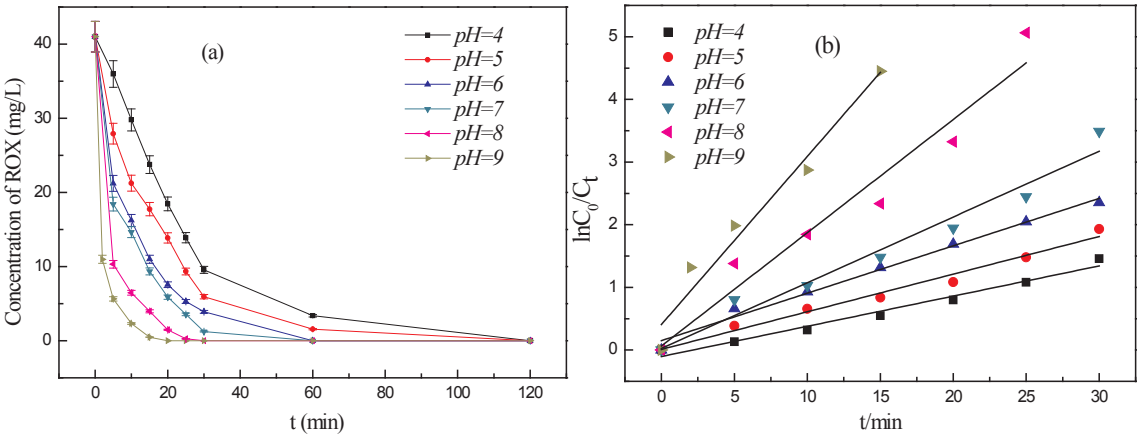


Fig. 2. Transformation of ROX reacted with NaClO at different pH values in the synthetic marine culture water and the linear fit of the kinetic data ($[ROX]_0$ = 0.05 mM, 20 ml and $[NaClO]_0$ = 0.3 M, 1 ml, pH = 7, T = 298.15 K).

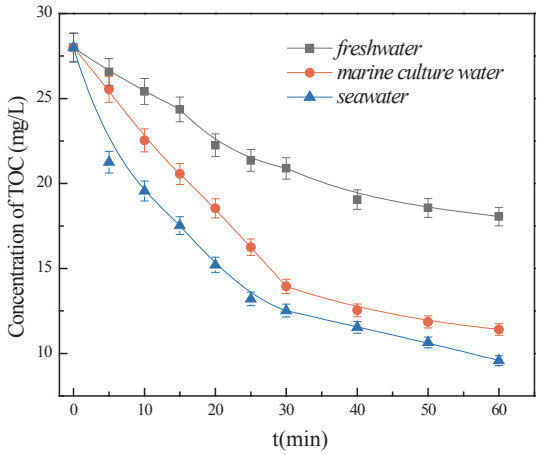


Fig. 3. The variation of TOC during the reaction of ROX with NaClO in different water samples ($[ROX]_0$ = 0.05 mM, 20 ml, $[NaClO]_0$ = 0.3 M, 1 ml, pH = 7, T = 298.15 K).

The activation energies of reactions between ROX and NaClO were analyzed in fresh water, simulated brackish marine culture water and sea water. The Arrhenius expression can be applied on elementary reactions. The thermodynamic parameters can be calculated by the following equations [47,48]:

$$k = A\exp\left(\frac{-Ea}{RT}\right) \quad (2)$$

$$\ln K = \ln A - \frac{Ea}{RT} \quad (3)$$

where k represents the reaction rate constant, Ea represents the reaction activation energy, J mol^{-1}, R represents the molar gas constant, 8.314 J/(K·mol), A is the pre-exponential factors and T represents the reaction thermodynamic temperature [49,50].

The reaction rates variations on temperature were shown in Fig. S3. The corresponding activation energies of reaction between ROX and NaClO in fresh water, simulated brackish marine culture water and sea water were then calculated to be 79.335 KJ/mol, 70.928 KJ/mol and 63.827 KJ/mol, respectively (Fig. S3a–c). The results indicated that the transformation of ROX should occur more easily in sea water and brackish marine culture water than that in fresh water. The smaller activation energies required for the reactions in sea water and brackish marine culture water also further explained the reason for the faster reaction rates.

Fig. 2 presents the variations on the rate of ROX oxidation in synthetic marine culture water with different pH values. The degradation of ROX followed the pseudo-first-order model ($0.939 < R^2 < 0.986$) well. As shown in Fig. 2b, the reactivity of ROX with NaClO obviously favored higher pH within the range of 4.0–9.0. The rate constants increased from 0.0482 min^{-1} to 0.2682 min^{-1} when the pH value raised from 4.0 to 9.0. The influence of pH on the reaction of ROX with NaClO in sea water showed the same trend with that in the synthetic marine

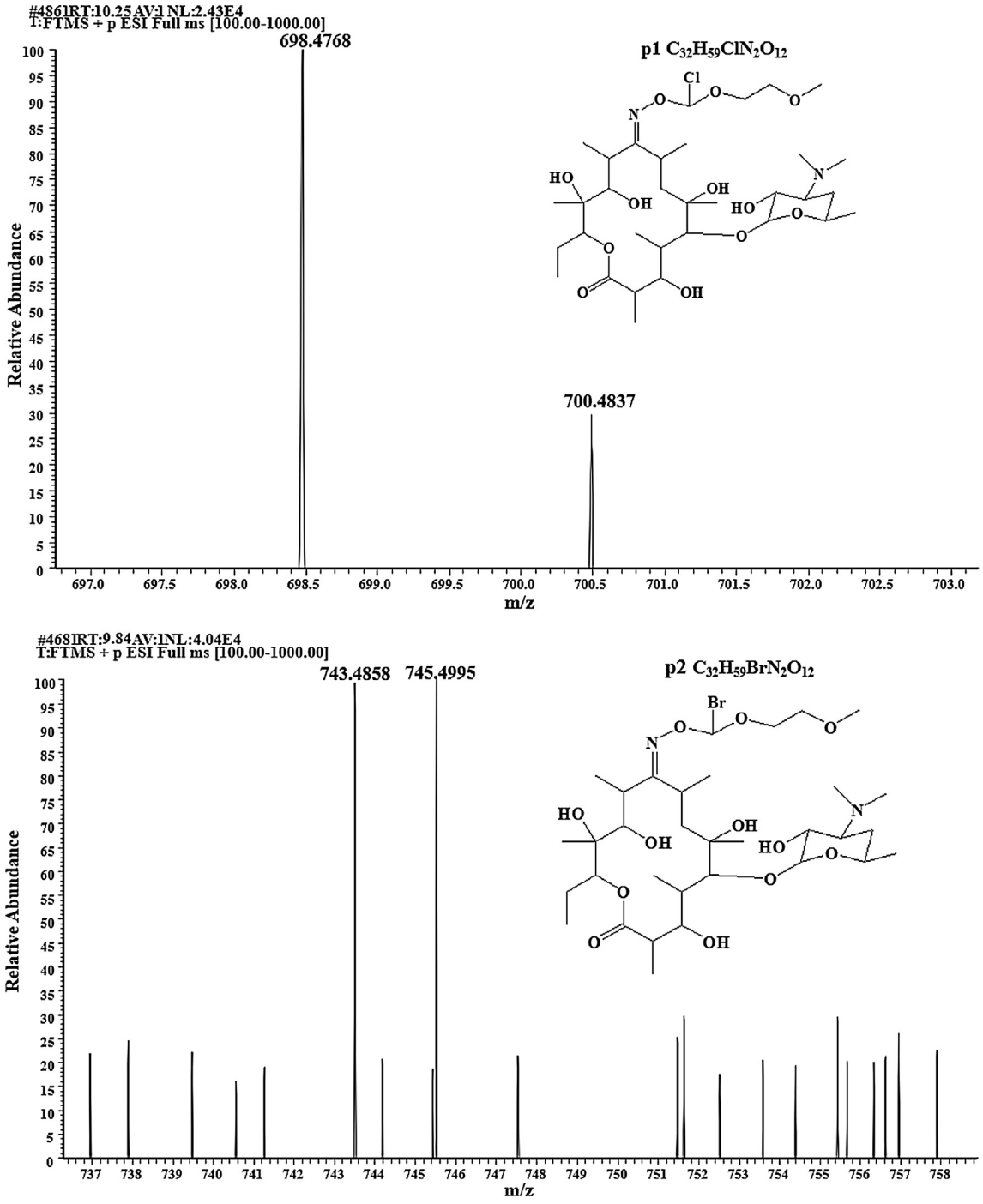


Fig. 4. LC/MS-ESI$^+$ spectra for final products of the reaction between ROX and NaClO in different systems (pH = 7, $[ROX]_0$ = 0.05 mM, 20 ml, $[NaClO]_0$ = 0.3 M, 1 ml, available chlorine content 10%, reaction (2) hours).

culture water. The rate constants increased from 0.0781 min^{-1} to 0.3458 min^{-1} when the pH value raised from 4.0 to 9.0. The results indicated that the reactivity of ROX toward NaClO highly depended on pH value. NaClO and ROX species (cationic, neutral and anionic) under different pH values should both account for the phenomenon. The halogen dissociation effect on the reaction of chlorine ($HOCl/OCl^-$) with organic matter during water treatment could be precluded as reported by Westerhoff [51]. Therefore, ROX functional dissociation may mainly account for the reaction rate difference between the different pH values [23,52]. For ROX, pKa (pH at which a group dissociated in half of the total concentration) has been reported to be 8.8 [26]. ROX would be mainly present in the form of protonated tertiary amine in the synthetic marine culture water and sea water which made this group inactive for attacks. Faster reaction rates at higher pH values indicated that ROX may be mainly attacted at the deprotonated dimethylamino group [27].

The changes of TOC during the oxidation processes of ROX were measured to determine the mineralization rate. As shown in Fig. 3, when the initial concentration of TOC was 28 mg/L, after 60 min reaction of NaClO, the residual TOC concentration in the simulated fresh water, marine culture water and sea water was 18.05 mg/L, 11.41 mg/L and 9.58 mg/L, respectively. The corresponding removal efficiency of TOC was 35.52%, 59.25% and 65.78% in the three water samples, respectively. The mineralization efficiencies were much lower than the corresponding removal efficiencies of ROX as shown in Fig. 1 indicated

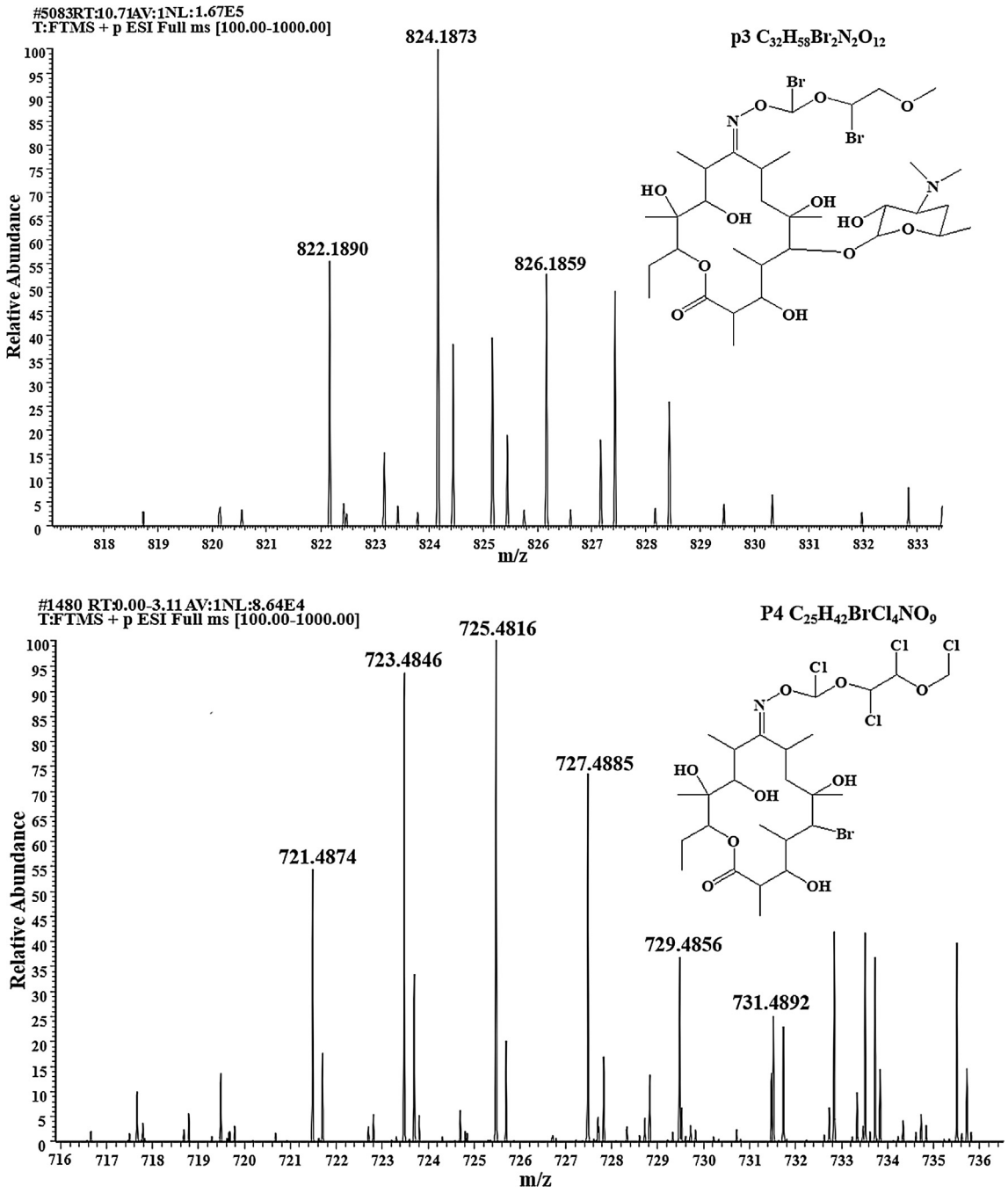
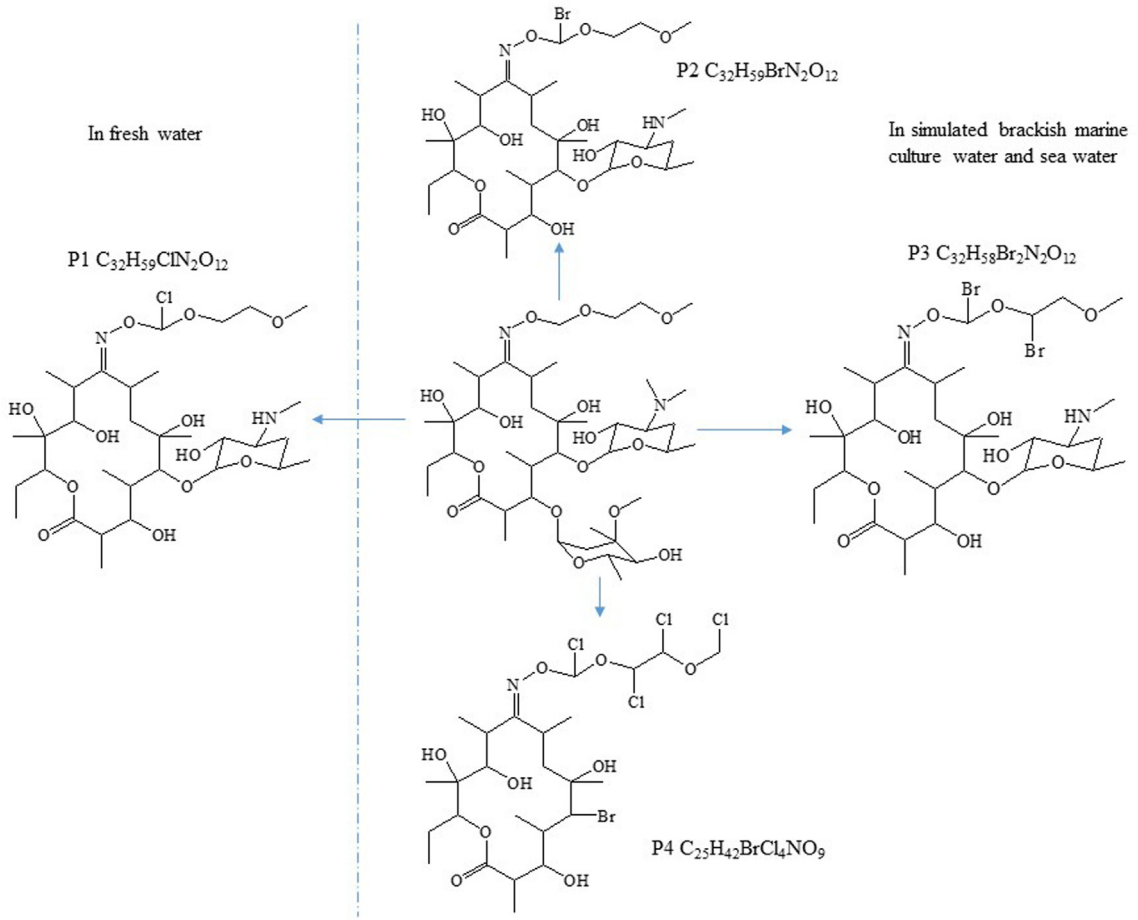


Fig. 4. (*continued*)

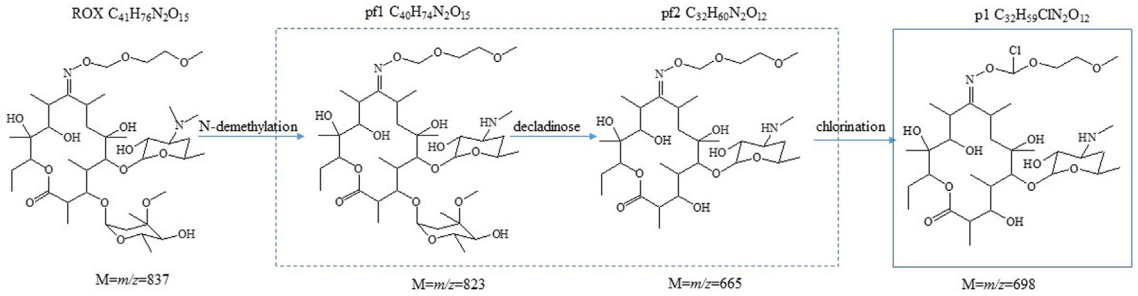
that ROX was not completely mineralized and some organic byproducts were produced.

3.2. Final products identification

The final transformation products of ROX reacted with excess NaClO in the simulated fresh water, brackish marine culture water and seawater reaction systems of were evaluated. The DBPs were analyzed by LC/MS based on the exact molecular weight and halogen isotope peak ratios information as shown in Fig. 4. LC/MS/MS-ESI$^+$ spectra for final products were given in Fig. S4. The fragmentation and formation mechanisms obtained from Mass Frontier 7.0 were shown in Table s1. The mass loss or gain of parent compound ROX with m/z = 837 was used to determine the final transformation products. As shown in scheme 1, four final products were identified for reaction of ROX with NaClO. The cladinose moiety of ROX was lost after reaction with NaClO in fresh water for 2 h. Chlorine substitution occurred at the C14 atom and a mono-chlorinated compound p1 (m/z = 698/700 for MH$^+$) was formed. The formation of p1 suggested that the cladinose moiety and C14 atom were the main reaction centers which were easily attacked by disinfectant in fresh water. However, the water conditions of the simulated brackish marine culture water and seawater differed from those of the fresh water. The other three DBPs produced in simulated brackish marine culture water were the same as products in sea water. The p2 was a mono-brominated compound with m/z = 743/745, p3 was a dibrominated compound with m/z = 822/824/826, p4 was a tetrachloro-mono-brominated compound with m/z = 721/723/725/727/729/731. Except for the loss of cladinose moiety, multiple halogen substitution reactions occurred on the oxime side chain such as the new Br-DBPs P2 and P3. It is worth noting that the structure of multi



Scheme 1. Final products of ROX reacted with NaClO in different water matrices ($[ROX]_0$ = 0.05 mM, 20 ml and $[NaClO]_0$ = 0.3 M, 1 ml, pH = 7, reaction (2) hours).



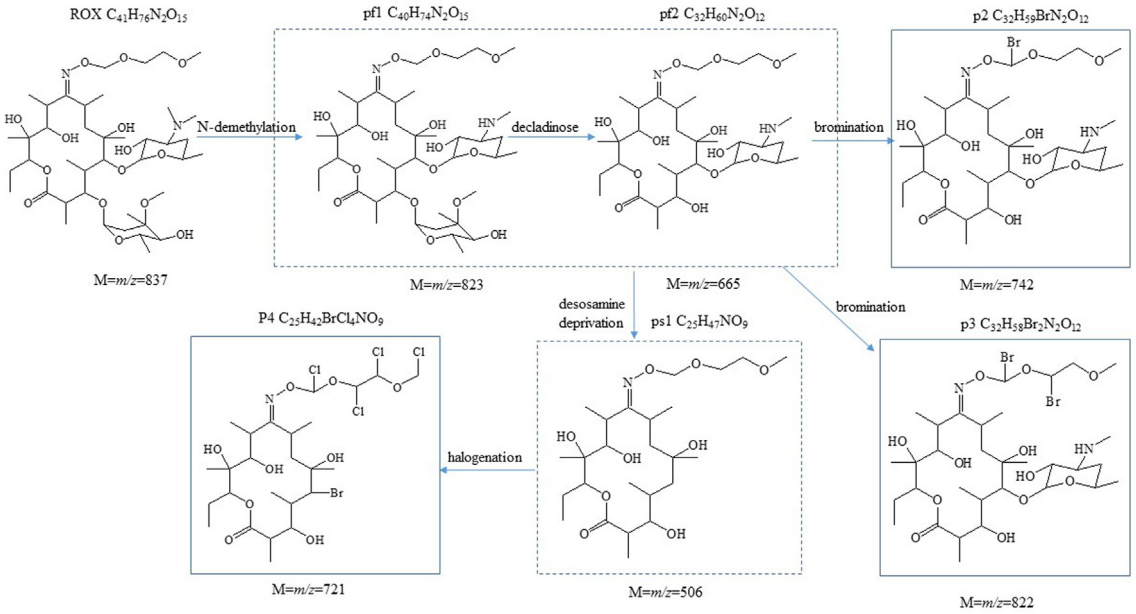
Scheme 2. Products and proposed pathways for ROX reacted with NaClO in fresh water ($[ROX]_0$ = 0.05 mM, 20 ml, $[NaClO]_0$ = 0.3 M, 1 ml, pH = 7).

halogen compound P4 was especial. The desosamine moiety was lost and substituted by bromine.

3.3. Reaction mechanisms

In fresh water The intermediate products of ROX reacted with NaClO were analyzed to infer the proposed reaction mechanisms. Mass spectral data for these organic intermediates were confirmed by LC/MS/MS as shown in Fig. S5. The fragmentation and formation mechanisms were also obtained from Mass Frontier 7.0 (Table S1). Based on the organic intermediates, the pathways for the transformation of ROX in fresh water were proposed. As shown in Scheme 2, the dashed boxes and solid boxes represented the intermediate products and the final products, respectively. As reported, oxidative dealkylation of the alkylether side chain, hydrolytic cleavage of the sugar cladinose, and *O*-demethylation at the oxime side chain were the major metabolic pathways of ROX in humans [53]. The research on ozonation of ROX indicated that the degradation products were formed by the attack of C14 atom, cleavage of its cladinose moiety and N-demethylation at desosamine moiety [27]. Therefore, the cladinose moiety, methyl of the alkylether side chain and desosamine moiety may be relatively fragile and easily to be attacked. The intermediates were inferred both according to the LC-MS-MS spectra and the above conclusion. After reacted with NaClO in freshwater for 5 min, pf1 with m/z = 823 was found indicating the N-demethylation on the desosamine moiety of ROX. Subsequently, the formation of pf2 with m/z = 665 indicated that the cladinose moiety was lost. After reaction of 2 h, p1 was finally formed as a result of chlorination on the C14 atom of the oxime side chain of ROX.

In simulated brackish marine culture water and seawater. The intermediate products obtained from the simulated brackish marine culture water and sea water were analyzed. The reaction pathways of ROX with



Scheme 3. Products and proposed pathways for ROX reacted with NaClO in the simulated brackish marine culture water and seawater ($[ROX]_0$ = 0.05 mM, 20 ml, $[NaClO]_0$ = 0.3 M, 1 ml, pH = 7).

NaClO in the two water samples were essentially the same. As shown in Scheme 3, the intermediate products pf1 and pf2 were also formed in these two reaction systems in the first 5 min. Mono-brominated compound p2 (m/z = 742) and dibrominated compound p3 (m/z = 822) were formed by bromine substitution of the oxime side chain followed with the N-demethylation on the desosamine moiety and loss of the cladinose moiety ROX. Moreover, the formation of the new intermediate product ps1 with m/z = 506 (Fig. S5) indicated that the desosamine moiety was also broken away from the parent compound ROX. Then, multi-halogenated compound p4 was formed by the bromine/chlorine substitution of the oxime side chain.

Considering the organic matter, other than ROX will react with NaClO to generate other typical Br-DBPs, the DBPs were checked in the actual marine culture water collected from a shrimp pond in Qinzhou. The results showed that the concentration of ROX in the real marine culture water was 635 ng/L and the above identifiable Br-DBPs in the simulated water samples were also found in the LC/MS/MS spectrogram after NaClO was added. The typical Br-DBPs were quantitatively determined. For example, bromoform (TBM), dibromoacetic acid (DBAA), bromodichloromethane (BDCM), bromochloromethane (BCM) and dibromochloromethane (DBCM) was determined to be 125.4 μg/L, 25.6 μg/L, 12.5 μg/L, 2.2 μg/L and 18.5 μg/L, respectively. Moreover, absorbable organic halogen (AOX) as a reference indicator to measure the water toxicity was also detected [54]. The concentration of AOX obtained from the fresh water, marine culture water and sea water were 1.9807 mg/L, 3.0980 mg/L and 6.4365 mg/L, respectively. The results showed that the DBPs in marine culture water possessed stronger toxicological properties than the DBPs in fresh water and the existence of bromide ions may be one of the main reasons [55,56].

4. Conclusions

This report described the fate of ROX which could react with NaClO in fresh water, simulated brackish marine culture water and sea water. The results showed that the reaction rate constants increased with the increase of bromide ions concentration and pH values. The reaction activation energies corresponding to the reaction of NaClO with ROX in the fresh water, simulated brackish marine culture water and sea water were calculated to be 79.335 KJ/mol, 70.928 KJ/mol and 63.827 KJ/mol, respectively. During the transformation of ROX, four DBPs were identified in the different water samples. In fresh water, methyl on the desosamine moiety and the cladinose moiety of ROX were lost. Chlorination on the C14 atom of the oxime side chain resulted in the formation of p1. The other products (p2-p4) were formed by the attack of the desosamine and cladinose moiety, followed by the bromine and chlorine substitution in simulated brackish marine culture water and seawater. The concentration of AOX obtained from the fresh water, marine culture water and sea water were 1.9807 mg/L, 3.0980 mg/L and 6.4365 mg/L, respectively. The results demonstrated that the Br-DBPs in water samples containing bromide ions were generally more toxic than the Cl-DBPs in fresh water.

Acknowledgements

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.seppur.2018.11.061.

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