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Correlation Analysis of Oxidation of Thio Acids by Halogens and Their Compounds

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ABSTRACT: Naturally produced halogenated compounds are ubiquitous across all domains of life where they perform a multitude of biological functions and adopt a diversity of chemical structures. Accordingly, a diverse collection of enzyme catalysts to install and remove halogens from organic scaffolds has evolved in nature. Accounting for the different chemical properties of the four halogen atoms (fluorine, chlorine, bromine, and iodine) and the diversity and chemical reactivity of their organic substrates, enzymes performing biosynthetic and degradative halogenation chemistry utilize numerous mechanistic strategies involving oxidation, reduction, and substitution. Biosynthetic halogenation reactions range from simple aromatic substitutions to stereoselective C-H functionalizations on remote carbon centers and can initiate the formation of simple to complex ring structures. Dehalogenating enzymes, on the other hand, are best known for removing halogen atoms from man-made organohalogenes, yet also function naturally, albeit rarely, in metabolic pathways. This review details the scope and mechanism of nature's halogenation and dehalogenation enzymatic strategies, highlights gaps in our understanding, and posits where new advances in the field might arise in the near future.

I.INTRODUCTION

Halide ions in aqueous solution have absorption edges below ~260 nm and therefore do not photolyze at solar wavelengths. However, recent studies indicate that photo-sensitization by DOM may be an important source of RHS in natural waters [7,8]. Irradiation of DOM with solar light generates a short-lived excited singlet state (¹DOM*) that can relax to the ground state or intersystem crosses (ISC) to a much longer-lived excited triplet state (³DOM*). ³DOM* is a mixture of excited triplet states of diverse structures with energies ranging from 94 kJ·mol⁻¹ to above 250 kJ·mol⁻¹ [9]. While the nature of the chromophoric groups of DOM giving rise to triplet states is not known for certain, it has been said that aromatic ketones and other carbonyl-containing groups (e.g., coumarin and chromone moieties) are candidates for production of the high-energy triplet states of DOM [10]. The steady-state concentration of ³DOM* is estimated to be 10⁻¹⁴ to 10⁻¹² M, depending on light intensities, [DOM] and [O₂] [10] and, undoubtedly, the nature of DOM in the water parcel.[1,2]

³DOM* is a known precursor of photochemically-produced reactive oxygen species (ROS) such as singlet oxygen (¹O₂) and hydroperoxyl/superoxide (HO₂·/O₂⁻, pK_a = 4.88), and is a suspected precursor of hydroxyl (HO·). In addition, ³DOM* also can engage in triplet energy transfer or oxidation reactions with itself and with other solutes. It has been shown that ³DOM* can oxidize or reduce various organic compounds [11], and that model triplet ketone sensitizers with similar reactivity as ³DOM* can oxidize CO₃²⁻ to CO₃⁻, NO₂⁻ to NO₂[·] [12], etc.

The question arises whether ³DOM* can oxidize halide ions. The standard reduction potential of ³DOM* obtained in different studies of terrestrial and freshwater NOM reference standards is estimated to be "centered near 1.64 V" [10] and about 1.6–1.8 V [8]. The estimated one-electron reduction potentials of the halogens E^o_{X·/X⁻} are 2.59 V (Cl), 2.04 V (Br), and 1.37 V (I) in water [13]. These values are about 0.4–0.5 V lower in polar organic solvents—an important consideration

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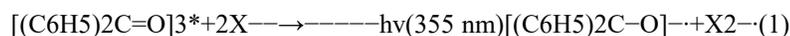
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because DOM exists as supramolecular aggregates and colloids, in which the electric field in the vicinity of the chromophoric site may be somewhere in between water and polar organic solvents. It thus appears that bromide and iodide, and possibly chloride, are potentially susceptible to one-electron oxidation by ${}^3\text{DOM}^*$. [5,6]

Jammoul et al. [7] found that the triplet excited state of benzophenone, which can be regarded as a surrogate for aromatic carbonyl compounds in seawater DOM, can oxidize halide ions to X_2^- , Reaction (1):



The rate constant for Reaction (1) follows the order, $\text{I}^- (\sim 8 \times 10^9) > \text{Br}^- (\sim 3 \times 10^8) > \text{Cl}^- (< 1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1})$ which is consistent with the order in their reduction potential. The triplet state of anthraquinone derivatives was observed to oxidize bromide and chloride [12,14].

Building on previous theory [15], Loeff et al. [12] modeled reactions sensitized by simple organic compounds according to Scheme 2.

According to this model, halide ion reacts with the triplet excited state (${}^3\text{M}$) to form a charge-transfer binary exciplex, ${}^3(\text{M}^- \cdots \text{X})$, or, at higher halide concentrations, the ternary exciplex, ${}^3(\text{M}^- \cdots \text{X} \cdots \text{X}^-)$. Both the binary and ternary exciplexes can decay to the ground state (paths a or c) or dissociate to the radical pair (paths b or d). The ternary exciplex has a lower tendency than the binary exciplex to decay to the ground state because it has weaker spin-orbit coupling of the incipient radical. Therefore, the ternary exciplex more favorably dissociates to the radical products, $\text{M}^{\cdot-}$ and X_2^- . In seawater, the mixed dihalogen radical anion, $\text{BrCl}^{\cdot-}$, is expected to predominate, since bromide is more readily oxidized [16], while chloride is more abundant.

Comparing artificial seawater with ionic strength controls (NaClO_4), Parker and Mitch [8] report that ${}^3\text{DOM}^*$ contributes to RHS formation, which, in turn, affects the oxidation of certain added organic compounds. Using a series of radical quenching agents, they found a strong linear correlation between the observed rate constant for degradation of the marine algal toxin domoic acid sensitized by a DOM reference standard, and the same rate constant sensitized by bromoacetophenone which generates Br^{\cdot} upon photolysis. In Scheme 2 for DOM, the researchers found that chloride enhances bromination in samples containing bromide. [13]

In summary, Scheme 2 has been able to rationalize the behavior of simple sensitizer molecules. Even though the scant data available on DOM is consistent with it, it is far from being “established” for DOM and further studies are called for.

II. DISCUSSION

Oxidation of Halide Ions by Secondary Photo-Products

Sunlight directly or indirectly produces OH^{\cdot} , ozone (O_3), ${}^1\text{O}_2$, $\text{HO}_2^{\cdot}/\text{O}_2^{\cdot-}$, and hydrogen peroxide (H_2O_2) in natural waters. Such ROS are important in many AOPs, as well. Halide ions are susceptible to oxidation by several of these ROS.

One of the most important is HO^{\cdot} . Hydroxyl originates from direct photolysis of H_2O_2 , NO_3^- , NO_2^- , DOM, and dissolved iron species, and can also be produced by (dark) Fenton-type reactions of H_2O_2 catalyzed by redox-switchable transition metal ions, especially Fe. Which of these sources are most important depends on local conditions and is difficult to ascertain in most situations. The exact mechanism of HO^{\cdot} generation from DOM has been the subject of debate for many years, without consensus [17,18,19]. Hydroxyl reacts with halides via the adduct HOX^{\cdot} to form the corresponding halogen and dihalogen radicals:



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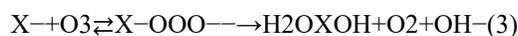
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Reaction (2) is fast, reversible, and dependent on $[X^-]$ and $[H^+]$ [20]. Reactions with bromide and iodide lie far to the right at any normal environmental pH, while the oxidation of chloride to Cl^- and Cl_2^- is favorable only under acidic conditions and comparatively high halide concentrations. For example, at pH 3, oxidation of chloride is significant whenever $[Cl^-]$ is much above a few millimolar [21]. However, oxidation of chloride can be important in aerosols, where the pH can be as low as 2. Bromide and iodide are important OH^\bullet scavengers in seawater [17]. Scavenging of OH^\bullet does not necessarily protect other solute molecules from oxidation, as the resulting RHS are themselves strong oxidants, albeit more selective (see Section 4).

Ozone is an important component of the troposphere due to the action of sunlight on nitrogen oxides and organic vapors. Ground-level ozone concentrations can be appreciable especially in urban and industrial areas [15]. The reaction of ozone with halide initially produces hypohalite or hypohalous acid (XO^-/XOH ; $pK_{a,HOCl} = 7.82$ (0 °C), 7.54 (25 °C); $pK_{a,HOBr} = 8.55$; $pK_{a,HOI} = 10.5$), via a transient halo-ozonide intermediate [15]:



The observed rate constants for overall Reaction (3) differ by more than twelve orders of magnitude among the halogens ($k_{Cl^-} < 3 \times 10^{-3} M^{-1} s^{-1}$; $k_{Br^-} = 258 M^{-1} s^{-1}$; $k_{I^-} = 1.2 \times 10^9 M^{-1} s^{-1}$) [13]. Given normal seawater halide concentrations, the ratio of rates for ozone oxidation of iodide, bromide, and chloride is thus approximately 2300:130:1.

Reaction with O_3 is suggested to be a principal source of bromo- and iodo-RHS in seawater [17]. Since HOI can react with Br^- and Cl^- to form molecular bromine and chlorine species and regenerate I^- (see Section 2.4), iodide has been implicated as a catalyst for volatilization of bromine and chlorine from marine aerosol microdroplets [18].

Halides react only slowly with 1O_2 ; second order rate constants are 1×10^3 for Cl^- (in D_2O); $< 1 \times 10^6$ for Br^- (in acetone/bromobenzene solution), and $8.7 \times 10^5 M^{-1} s^{-1}$ for I^- (in water)—too slow to compete with physical quenching of 1O_2 by water ($2.5 \times 10^5 s^{-1}$ [19]). The halides do not react with HO_2^\bullet/O_2^- in water at environmentally significant rates. A few other oxidation reactions of halides are important in aerosol systems [13]

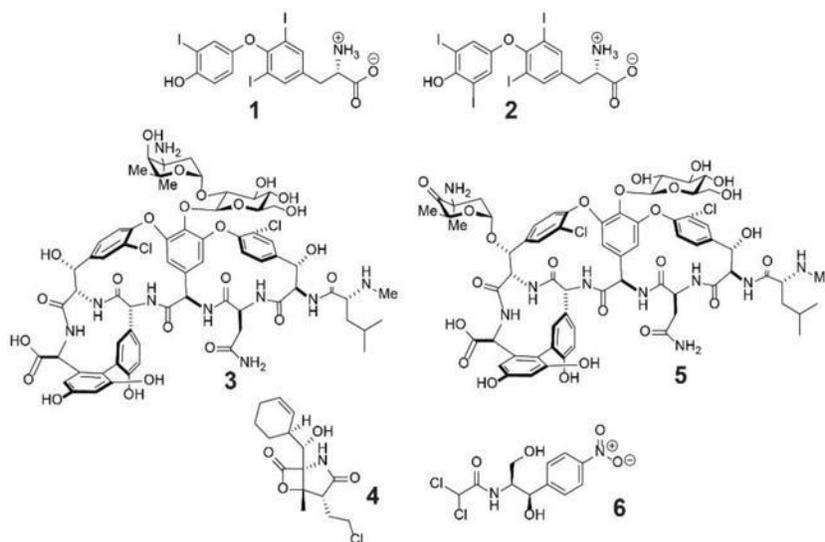


Fig. 1: Examples of halogenated natural products relevant to human health and disease.

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III.CONCLUSION

In addition to naturally produced halogenated molecules, the environment also bears a heavy load of halogenated anthropogenic molecules that are often recalcitrant to degradation and are toxic to humans and wildlife. Indeed, all molecules on the list of persistent organic pollutants regulated by the Stockholm convention, are polyhalogenated. As a result, degradation and bioremediation of organohalogen pollutants has brought renewed interest to studies that have suggested a native role for microbial dehalogenation as part of a biogeochemical halogen cycle in marine and terrestrial environments.[16,17,20] A large number of biocatalysts capable of removing halogens from anthropogenic compounds through processes coupled to respiration or carbon metabolism have been described. However, in contrast to the abundance of reported halogenated natural products, the biochemical transformations leading to their natural formation and degradation remain largely unexplored. While the link between biological halogenation and dehalogenation may be tenuous, the authors of this review hope that the inclusion of a brief overview of dehalogenation will stimulate the investigation of the cognate process of dehalogenation from the fresh perspective of natural product biosynthesis[19].

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