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Photochemical Fate of Pharmaceuticals in the Environment: Cimetidine and Ranitidine

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The photochemical fates of the histamine H_2-receptor antagonists cimetidine and ranitidine were studied. Each of the two environmentally relevant pharmaceuticals displayed high rates of reaction with both singlet oxygen ($^1O_2$, $O_2(^1\Delta_g)$) and hydroxyl radical (•OH), two transient oxidants formed in sunlit natural waters. For cimetidine, the bimolecular rate constant for reaction with •OH in water is $6.5 \pm 0.5 \times 10^9$ M^{-1} s^{-1}. Over the pH range 4−10, cimetidine reacts with $^1O_2$ with bimolecular rate constants ranging from $3.3 \pm 0.3 \times 10^6$ M^{-1} s^{-1} at low pH to $2.5 \pm 0.2 \times 10^8$ M^{-1} s^{-1} in alkaline solutions. The bimolecular rate constants for ranitidine reacting with $^1O_2$ in water ranges from $1.6 \pm 0.2 \times 10^7$ M^{-1} s^{-1} at pH 6−$6.4 \pm 0.2 \times 10^7$ M^{-1} s^{-1} at pH 10. Reaction of ranitidine hydrochloride with •OH proceeds with a rate constant of $1.5 \pm 0.2 \times 10^{10}$ M^{-1} s^{-1}. Ranitidine was also degraded in direct photolysis experiments with a half-life of 35 min under noon summertime sunlight at 45 ° latitude, while cimetidine was shown to be resistant to direct photolysis. The results of these experiments, combined with the expected steady-state near surface concentrations of $^1O_2$ and •OH, indicate that photooxidation mediated by $^1O_2$ is the likely degradation pathway for cimetidine in most natural waters, and photodegradation by direct photolysis is expected to be the major pathway for ranitidine, with some degradation caused by $^1O_2$. These predictions were verified in studies using Mississippi River water. Model compounds were analyzed by laser flash photolysis experiments to assess which functionalities within ranitidine and cimetidine are most susceptible to singlet-oxygenation and direct photolysis. The heterocyclic moieties of the pharmaceuticals were clearly implicated as the sites of reaction with $^1O_2$, as evidenced by the high relative rate constants of the furan and imidazole models. The nitroacetamidine portion of ranitidine has been shown to be the moiety active in direct photolysis.

Introduction

Pharmaceuticals and personal care products (PPCPs) have recently gained interest as possible environmental pollutants (*1*−*7*). It has been found that many PPCPs are not completely removed or degraded during the wastewater treatment process (*8*−*14*). Thus, pharmaceuticals have been detected in a variety of surface and groundwaters receiving treated wastewater effluent (*9*, *10*, *12*−*23*). Despite the fact that many pharmaceuticals are produced in quantities rivaling their agrochemical counterparts, relatively little research has been conducted regarding the occurrence and fate of pharmaceuticals in natural waters (*2*). Compared to agrochemicals, PPCPs may pose a greater environmental threat, as they have been designed to have a physiological effect on humans or animals (*1*, *2*, *7*, *24*). It has been hypothesized that some PPCPs may have hormonal mimicking effects at part per trillion levels (*7*). An additional concern regarding the environmental impact of PPCPs is the fact that many of these compounds have been designed to be lipophilic and biologically persistent in order for them to pass through membranes and to remain active until their curing function has been performed (*2*, *7*). Consequently, many PPCPs are reputed to be persistent in the environment.

Two high-use pharmaceutical compounds that may be of environmental importance are the histamine H_2-receptor antagonists cimetidine (**1**) and ranitidine (**2**). Produced under the trade names Tagamet and Zantac, respectively, **1** and **2** are sold worldwide as gastrointestinal drugs. Recent work by Zuccato has identified the presence of ranitidine in European river water samples and sediments, underscoring the need to study the fate of these drugs (*25*). A reconnaissance by the USGS has detected both **1** and **2** in United States waterways (*26*).

Recent work (*15*) has demonstrated that photochemical processes may play an important role in the fate of pharmaceutical compounds in the environment. As a class of compounds, pharmaceuticals are expected to be susceptible to direct photochemical degradation and a wide array of indirect photochemical pathways, including reaction with singlet oxygen ($^1O_2$, $O_2(^1\Delta_g)$), hydroxyl radical (•OH), peroxy radicals (•OOR), photoexcited organic matter, and other reactive species. The present study is an examination of the photochemical fate of two photolabile pharmaceuticals, cimetidine and ranitidine, that display disparate degradation mechanisms. Both drugs contain multiple sites that may be reactive toward reactive oxygen species as they contain conjugated diene, sulfide, and electron-rich alkene functionalities (*27*−*31*). While many potential degradation pathways are available for each pharmaceutical, this study demonstrates that either direct photolysis (ranitidine) or reaction with singlet oxygen (cimetidine) dominates the photoreactivity of these compounds in surface waters.

Experimental Section

Chemicals and Instrumentation. Cimetidine (**1**), *N*,*N*,5-trimethylfurfurylamine (**3**), 2,5-dimethylfuran (**4**), furfuryl methyl sulfide (**5**), sodium metaperiodate, furfuryl alcohol (FFA), diethyl sulfide (**6**), pyridine, perinaphthenone, eosin Y, and Rose Bengal were purchased from Aldrich. Ranitidine hydrochloride ($\mathbf{2H}^+$) was supplied by Sigma, while *N*,*N*′-dimethylnitroacetamidine (**7**) and sodium molybdate dihydrate were purchased from Lancaster Synthesis and Baker, respectively. Diazabicyclo[2.2.2]octane (DABCO) was supplied by Matheson, Coleman, and Bell. Hydrogen peroxide (30%) was purchased from Mallinckrodt. Ferrous sulfate ($FeSO_4 \cdot 7H_2O$) was obtained from Fisher. Acetophenone, *p*-nitroanisole, and D_2SO_4 were purchased from Acros Organics. Deuterium oxide and NaOD were supplied by Cambridge Isotope Labs.

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N-Cyano-*N′*,*N″*-dimethylguanidine (**8**) was prepared as described elsewhere (*32*). Synthesis of ranitidine sulfoxide and cimetidine sulfoxide (**9**) was accomplished by treating the parent compound with sodium metaperiodate as described by Kuzel (*33*). Purification of cimetidine sulfoxide was performed as described in the literature (*33*). The synthesis outlined by Bredereck and Theilig was followed in the preparation of 4,5-dimethyl-1H-imidazole (**10**) (*34*). Treating *N*,*N*,5-trimethylfurfurylamine with HCl afforded the *N*,*N*,5-trimethylfurfurylamine hydrochloride. All other reagents were analytical grade or better and used without purification. Solvents were of HPLC grade.

NMR spectra were recorded on either Varian Inova 300 or 500 MHz or Varian Unity 300 MHz instruments. A VWR Scientific Products Model 8000 pH meter was used to obtain pH measurements. UV−vis absorbance measurements were obtained using a Jasco V-530 Spectrophotometer, and IR spectra were obtained with a Nicolet Magna-IR Spectrometer 550 with Omnic software. Chromatograms were recorded using either an 1100 Series Hewlett-Packard HPLC or a Waters LC Module 1 Plus, each with UV-absorbance detection and a computer driven data acquisition system.

Photolysis in Natural Water with Sunlight. Solutions of cimetidine and ranitidine (each at 100 μM) in DI water and in filtered Mississippi River water (DOC = 16 mg/L, pH = 8.0, see Supporting Information Section S6 for analysis details) were photolyzed in natural sunlight on July 30 and August 13, 2002 in Minneapolis, MN. The samples were contained in capped quartz tubes (o.d. = 1.3 cm, i.d. = 1.1 cm, V = 10 mL). Aliquots of sample (~300 μL) were withdrawn at various intervals and substrate decay was measured by HPLC. In addition to the samples containing the substrate alone, some samples also contained the $^1O_2$ inhibitor sodium azide (10 mM), the radical inhibitor 2-propanol (1%), or both. HPLC peak area decay was monitored as a means of quantifying the loss of substrate.

Steady-State Photolysis Experiments. Between one and four Pyrex-filtered 175 W medium-pressure Hg-vapor lamps (LumaPro lamps, GE HR175A39/CP bulbs) arranged above a turntable were used to irradiate samples. In experiments evaluating the reaction kinetics of ranitidine with singlet oxygen, uncapped borosilicate test tubes containing various concentrations of substrate and 40 μM Rose Bengal (RB) in unbuffered water (pH 7.6) were placed on the turntable apparatus to ensure equal irradiation of the samples. The reactivity of cimetidine with $^1O_2$ was assessed across the pH range of 4−10 using either RB or perinaphthenone as a sensitizer and an appropriate buffer solution used as diluent. In acidic media, the RB did not dissolve, and perinaphthenone was used. The perinaphthenone was delivered from a methanol stock solution yielding a final concentration of 1.3 μM and 1% alcohol in the sample. The tubes were oriented at about a 30° angle to the light source, and the temperature in the photolysis apparatus was 30 °C. Direct photolysis experiments were performed using the same procedure except that no sensitizer was added and quartz tubes were used. Ranitidine (10 μM) direct photolysis was examined in pH 6 and pH 10 phosphate (0.2 M) buffered solutions. At various timepoints, small aliquots (~300 μL) of sample were withdrawn and analyzed by HPLC. Substrate peak area reduction was monitored as a measure of $^1O_2$ reaction with the substrate or of direct photolysis. Chromatographic peak areas were converted to substrate concentrations via calibration curves. Furfuryl alcohol, a $^1O_2$ kinetic probe with well-defined properties, was photolyzed simultaneously in separate tubes with ranitidine and cimetidine samples as a means of quantifying the amount of $^1O_2$ produced during the photolysis experiments. In addition to the singlet oxygen and direct photolysis experiments, this apparatus was used to study the photodegradation of **1** (100 μM) and **2** (10 μM) in Mississippi River water in the presence of various quenchers (sodium azide and DABCO for $^1O_2$ and 2-propanol for $^\bullet$OH).

Laser Flash Photolysis Experiments. The laser flash photolysis apparatus employed in this study was constructed based on systems reported by others (*35*, *36*). Samples containing 40 μM RB or 100 μM eosin Y sensitizer and various substrate concentrations were excited by 4 ns pulses at 532 nm (for RB) or 355 nm (for eosin Y) (Nd:YAG, Continuum Minilite II). Singlet oxygen was produced through the interaction of dissolved oxygen with photoexcited sensitizer. The resultant phosphorescence decay of $^1O_2$ was collected through an 1100 nm long-pass filter (CVI Laser Corp.) and a 1271 ± 18 nm interference filter (CVI Laser Corp.). The luminescent signal was focused by a collimating lens onto the Ge crystal of a liquid nitrogen cooled ultrasensitive Ge detector (Model EI-P, Edinburgh Instruments, Ltd.). The detector output was transferred to a digital storage oscilloscope (Tektronix TDS 430A, 400 MHz) where the transients were recorded (see Supporting Information, Figures S18 and S19 for representative transients). The decay portions of the $^1O_2$ signal from the single laser shot transients of the RB sensitized samples were then fit to single exponential decays (Kaleidagraph) on PC workstations. In the eosin Y sensitized samples, a short lifetime fluorescence spike from the sensitizer was detected along with the $^1O_2$ decay. A biexponential fit was used to deconvolute the $^1O_2$ decay rate from the interfering fluorescence signal.

Fenton Reaction. The second-order rate constant for the reaction of cimetidine and ranitidine with $^\bullet$OH was determined using Fenton's reagent. Previous studies have used Fenton's reagent to study the reaction of a variety of pollutants with $^\bullet$OH (*37*−*39*). It has also been shown that cimetidine and ranitidine are subject to oxidation by the Fenton reaction, though the reaction kinetics reported in previous works were only indirectly monitored (*40*, *41*). Reactors (125 mL serum bottles) contained a solution of the pharmaceutical of interest (~100 μM), acetophenone (~100 μM), Fe^{2+} (0.2 mM), and hydrogen peroxide (5 mM) adjusted to pH 3 with sulfuric acid (*39*). The reactor was wrapped in aluminum foil to exclude light and incubations were performed at room temperature (22 ± 1 °C). Samples (0.5 mL) were withdrawn at predetermined intervals, and the reactions were quenched with an equivalent volume of methanol (*42*).

HPLC Analysis. For the $^1O_2$ experiments, cimetidine was analyzed on an Alltech Econosil C_{18}, 250 × 4.6 mm, 10 μm particle size column, with a mobile phase composition of 70:30 ACN:H_2O and a flow rate of 1.0 mL/min. The column temperature was held constant at 30 °C, and absorbance was monitored at 219 nm. Ranitidine, *N*,*N*,5-trimethylfurfurylamine, and its hydrochloride salt were analyzed using a Supelco Discovery RP-Amide C_{16}, 150 × 4.6 mm, 5 μm particle size column thermostated to 30 °C. Absorbance was monitored at 219 nm. The mobile phase consisted of an aqueous 25 mM KH_2PO_4 buffer (pH 3) and MeOH run at a 90:10 ratio and a flow rate of 1.0 mL/min. This method was used for both cimetidine and ranitidine in the experiments evaluating direct photolysis and the reaction with $^\bullet$OH. The same columns and parameters described for ranitidine and cimetidine were employed in the analysis of FFA. Acetophenone was measured on the RP-Amide column, and the mobile phase was a 50:50 ratio of the pH 3 phosphate buffer described above and MeOH. The absorbance was recorded at 254 nm. The actinometer *p*-nitroanisole was analyzed on a Phenomenex ODS-2, 250 × 4.6 mm, 3 μm particle size column, with a 70:30 ratio of ACN: pH 5 acetate buffer run at 1.0 mL/min. The detector wavelength was 313 nm.

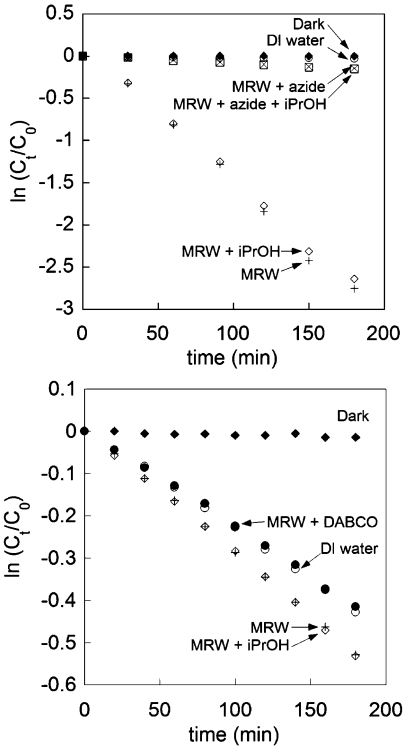


FIGURE 1. Direct photolysis of cimetidine (100 μM) under sunlight (top panel) and ranitidine (10 μM) under four 175 W Hg vapor lamps (bottom panel) in H_2O. Conditions are as follows: ○ = substrate in DI water, + = Mississippi River water (MRW), × = MRW with 10 mM sodium azide, ● = MRW with 10 mM DABCO, ◇ = MRW with 1% 2-propanol, □ = MRW with 10 mM sodium azide and 1% 2-propanol, ◆ = dark control. Similar results were obtained for ranitidine under sunlight (Supporting Information, Figure S24).

Results

Direct Photolysis. The DI water direct photolysis of cimetidine under midsummer sunlight at 45° latitude and of ranitidine under artificial light is shown in Figure 1. Similar results were obtained for ranitidine under natural sunlight (see Supporting Information, Figure S24). Cimetidine did not degrade appreciably by direct photolysis. By contrast, ranitidine degraded rapidly, with a first-order rate constant of $2.8 \pm 0.1 \times 10^{-4}\ s^{-1}$ in midsummer sunlight. The quantum yield for this process (Φ_{direct}), determined using *p*-nitroanisole as an actinometer, was measured to be $5.3 \pm 0.5 \times 10^{-3}$ at pH 6 and $5.5 \pm 0.5 \times 10^{-3}$ at pH 10 after accounting for internal screening, indicating that the direct photodegradation rate was not altered by protonation of the trialkylamine functionality. This finding was consistent with the UV−vis spectrum of **2** being unaltered across the same pH range (see Supporting Information, Figures S22 and S23). The ranitidine conjugate acid model compounds furfurylamine hydrochloride (**3H**$^+$) and *N*,*N*′-dimethylnitroacetamidine (**7**) were also analyzed by direct photolysis. The direct photodegradation rates of the model compounds were compared to that of the ranitidine conjugate acid, **2H**$^+$. The relative rate constants for **3H**$^+$ ($k_{\mathbf{3H^+}}/k_{\mathbf{2H^+}} = 0.1$) and **7** ($k_7/k_{\mathbf{2H^+}} = 1.2$) indicate that the nitroacetamidine functionality of **2H**$^+$ is the chromophore involved in the direct photolysis degradation pathway. This result was also supported by the light absorption spectra of **2H**$^+$, **3H**$^+$, and **7** (see Supporting Information, Figure S20).

Because **2** was also found to react with $^1O_2$ (vide infra), we considered the possibility that its photodegradation was $^1O_2$ mediated even in the absence of known $^1O_2$ sensitizers. For this process to occur, **2** itself must act as a $^1O_2$ sensitizer.

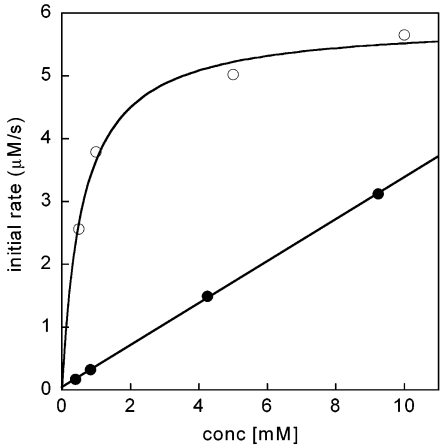


FIGURE 2. Concentration dependence on disappearance rate for the singlet oxygenation of cimetidine (1, ○) and ranitidine hydrochloride (2H$^+$, ●) in EtOH with Rose Bengal (40 μM) sensitizer under two 175 W Hg vapor lamps. For cimetidine, 1, the solid line is a fit to eq 1, for [Q] = 0. For ranitidine hydrochloride, 2H$^+$, the solid line is a fit to eq 2, for [Q] = 0 and ($k_{rxn} + k_{phys}$)[S] ≪ k_{solv}.

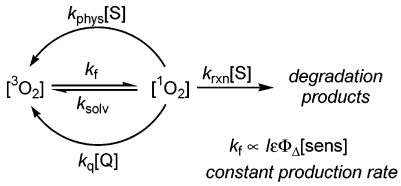
To test this hypothesis, direct photolysis experiments were performed with added $^1O_2$ quencher, sodium azide. No change in the direct photolysis rate was observed with added azide ion, indicating that **2** was not degraded by $^1O_2$ arising from a self-sensitization process.

Photolysis in Natural Water. In addition to the direct photolyses of **1** and **2** in DI water, Figure 1 shows the results of the photolyses of the two drugs in Mississippi River water (MRW). These data show that the sunlight photolysis of **2** in natural water proceeded at a rate that was slightly faster than in DI water ($k_{rel} = k_{MRW}/k_{DI} = 1.2$). The radical inhibitor 2-propanol did not reduce the photolability of **2**, while the $^1O_2$ quencher DABCO suppressed the rate of decay to a value comparable to that in DI water (Figure 1). For cimetidine, photodegradation proceeded much more rapidly in natural water than in DI water. When the natural water samples were spiked with the $^1O_2$ quencher sodium azide, the rate of decay of **1** was diminished to match that in DI water (Figure 1). Comparison of cimetidine photodegradation rates in MRW diluted 50% with DI H_2O or D_2O yielded a solvent isotope effect ($k_H/k_D = 0.52$). The presence of 2-propanol did not alter the photodegradation rate.

Steady-State Photolysis: $^1O_2$ k_{rxn} Measurements. Steady-state photolysis experiments were performed to determine k_{rxn} for the reaction of singlet oxygen with cimetidine (**1**) and the protonated form of ranitidine (**2H**$^+$). In EtOH, substrate **1** displayed saturation kinetics while the slower reacting **2H**$^+$ showed first-order kinetics over the concentration range studied (Figure 2). The results for **1** and **2H**$^+$ were analyzed according to the kinetic model shown in Scheme 1, where $^3O_2$ is triplet ground-state molecular oxygen, S is substrate, k_{phys} is the rate constant for physical quenching by S, k_{rxn} is the rate constant for chemical reaction with S, k_{solv} is the rate constant for deactivation by the solvent, Q is a physical quencher, k_q is the rate constant for quenching by Q, Φ_Δ is the quantum yield for $^1O_2(^1\Delta_g)$ formation, *I* is the intensity of light, ϵ is the absorption coefficient for the sensitizer, and sens is sensitizer. The zero-order $^1O_2$ formation rate constant, k_f, is proportional to $I\epsilon\Phi_\Delta$[sens]. It is also a function of the depth of the solution and the light screening by other components of the solution. The kinetic model predicts the rate of substrate disappearance will follow the rate law given in eq 1.

$$\frac{-\mathrm{d[S]}}{\mathrm{d}t} = \frac{k_f k_{rxn}[\mathrm{S}]}{k_{solv} + k_q[\mathrm{Q}] + (k_{rxn} + k_{phys})[\mathrm{S}]} \qquad (1)$$

SCHEME 1. Kinetic Model for the Formation and Disappearance of $^1O_2$[a]



[a] $^3O_2$ is ground state molecular oxygen, S is the substrate, Q is a physical quencher, k_f is the zero-order formation rate constant, I is light intensity, ϵ is the absorption coefficient of the sensitizer, Φ_Δ is the quantum yield for $^1O_2$ formation, sens is sensitizer, and k_{solv}, k_q, k_{phys}, and k_{rxn} are the rate constants for deactivation by solvent, physical quenching by Q, physical quenching by S, and chemical reaction with S, respectively.

To determine k_{rxn}, the substrates were photolyzed side-by-side with FFA, and a comparison of the rates for the substrates and FFA was made. For these rate comparison experiments, care was taken to work in the first-order kinetic regime described by eq 2:

$$\frac{-d[S]}{dt} = \frac{k_f k_{rxn}[S]}{k_{solv}} \quad \text{for } [Q] = 0 \quad \text{and} \quad (k_{rxn} + k_{phys})[S] \ll k_{solv} \quad (2)$$

Dividing the slope of the substrate curve ($m_S = k_f k_{rxn,S}/k_{solv}$) by the slope of a curve generated simultaneously for FFA ($m_{FFA} = k_f k_{rxn,FFA}/k_{solv}$) yields a ratio of reaction rate constants. By substituting the known rate constant for FFA ($2.0 \pm 0.1 \times 10^7$ M^{-1} s^{-1} in EtOH, $8.3 \pm 0.1 \times 10^7$ M^{-1} s^{-1} in D_2O, as determined by LFP analysis), k_{rxn} values for the substrates were determined. Figure 3 shows rate comparison data for the protonated form of ranitidine (**2H**$^+$) and FFA in pH 7.2 water. For **2H**$^+$, k_{rxn} was calculated to be $0.9 \pm 0.3 \times 10^7$ M^{-1} s^{-1} in EtOH and $2.1 \pm 0.2 \times 10^7$ M^{-1} s^{-1} in pH 7.2 water. For **1**, k_{rxn} was determined to be $1.4 \pm 0.5 \times 10^8$ M^{-1} s^{-1} in EtOH. The reaction rate constants for **1** in various buffer solutions are given in Table 1. The reaction rate constants determined for **1**, under the same conditions as in eq 2, at intermediate pH values were consistent with those calculated from the end-member rate constants (at pH 4.2 and 10.2) once speciation between the parent (S) and conjugate acid forms (SH^+) was taken into account according to eqs 3−5.

$$\frac{-d[S]_T}{dt} = \frac{k_f(k_{rxn,S}[S] + k_{rxn,SH^+}[SH^+])}{k_{solv}} \quad \text{where } [S]_T = [S] + [SH^+] \quad (3)$$

$$\frac{-d[S]_T}{dt} = \frac{k_f[(\alpha)k_{rxn,S} + (1-\alpha)k_{rxn,SH^+}][S]_T}{k_{solv}} \quad (4)$$

$$\alpha = \frac{[S]}{[S] + [SH^+]} = \frac{1}{1 + 10^{(pK_a - pH)}} \quad (5)$$

To test that $^1O_2$ was the active species in the RB-sensitized degradation of ranitidine and cimetidine, sodium azide, a known physical quencher of $^1O_2$, was added to samples of ranitidine and cimetidine prior to photolysis (*43*). The degree of rate suppression upon addition of such a quencher is dependent upon its concentration, as is evident from eq 1. Predictably, the rates of degradation were inversely related to azide concentration for both cimetidine and ranitidine hydrochloride (see Supporting Information, Figures S16 and S17). In the case of **2H**$^+$, the plot of degradation rate constant versus azide concentration was found to have a nonzero asymptote, indicating the presence of a competing photolysis process. The magnitude of this background process is consistent with the direct photolysis rate of **2H**$^+$ found in this study after accounting for the differences in light intensity between the direct and indirect photolysis experiments and did not alter the measurement of k_{rxn}. Similar steady-state photolysis experiments were also conducted to determine the reaction rate ratio of $^1O_2$ with furfurylamine hydrochloride (**3H**$^+$) and its free base (**3**), as shown in Figure 4. This result yielded $k_{rxn,3}/k_{rxn,3H^+} = 2.6$, and thus the more electron rich **3** reacted more quickly than **3H**$^+$.

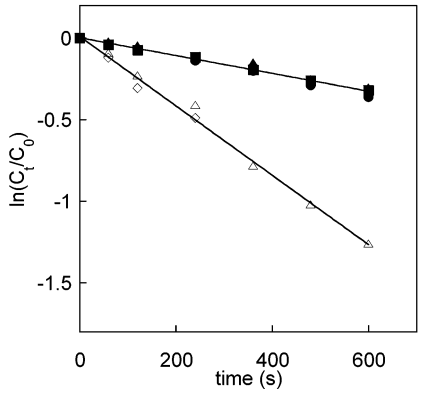


FIGURE 3. Logarithmic decay traces for the singlet oxygenation of ranitidine hydrochloride (2H$^+$, ●, ■, ◆, and ▲) and FFA (◇ and △) in pH 7.2 H_2O with Rose Bengal (40 μM) sensitizer under two Hg vapor lamps. Initial starting concentrations are represented by ● = 4×10^{-5} M, ■ = 8×10^{-5} M, ◆ and ◇ = 9×10^{-5} M, ▲ and △ = 5×10^{-4} M.

Laser Flash Photolysis: $^1O_2$ k_{tot} Measurements. Laser flash photolysis (LFP) was used to measure total quenching rate constants (k_{tot}) for ranitidine, cimetidine, model compounds of both ranitidine and cimetidine, and likely ranitidine and cimetidine reaction products. The data were again analyzed according to Scheme 1, where the sum of k_{phys} and k_{rxn} is k_{tot}. The rate expression for $^1O_2$ decay in the absence of quenchers other than S is given by

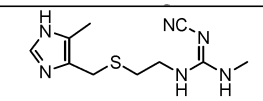
$$\frac{-d[^1O_2]}{dt} = k_{solv} + k_{tot}[S][^1O_2]; \quad k_{tot} = k_{rxn} + k_{phys} \quad (6)$$

For the parent compounds, **1** and **2**, k_{tot} was measured in aqueous (D_2O) buffer solutions. Most of the other LFP data were collected using EtOH as solvent because it affords enhanced solubility of the target compounds and superior signal-to-noise ratios due to the increased solubility, and thus $^1O_2$ signal, of oxygen in it than in water. For **1** and **2**, the D_2O and EtOH values were found to be quite comparable.

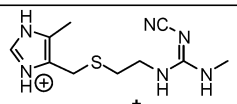
For **1**, k_{tot} was determined to be $1.4 \pm 0.5 \times 10^8$ M^{-1} s^{-1} in a pD 7.1 buffer, where it existed as an equal mix of the parent compound and its conjugate acid (**1H**$^+$, $pK_a = 7.1$ for the conjugate acid) (*44*). A more detailed LFP study of the interaction of **2** with $^1O_2$ was undertaken (Table 1). To assess the pH dependence of singlet oxygenation of **2** ($pK_a = 8.2$ for the conjugate acid, **2H**$^+$) (*45*), LFP was used in place of steady-state photolysis to minimize interferences caused by the competing direct photolysis pathway. Rose Bengal was only sparingly soluble at high pD, and it interacted with **2H**$^+$ at low pD. Therefore, it was used as sensitizer only at pD 7.5. The sensitizer eosin Y was used as sensitizer in pD 6.4 and 9.8 buffered samples. These samples were analyzed in D_2O rather than H_2O due to the well-known solvent isotope effect on the lifetime of $^1O_2$ (*46*−*48*). The lifetime of $^1O_2$ is approximately 14 times longer in D_2O than H_2O (*48*).

The measured k_{tot} values and relative rate constants (k_{rel}) for model compounds of **1** and **2** are given in Tables 2 and 3 (see Supporting Information Sections S1 and S2, Figures S1−S14 for Stern−Volmer plots for **1**−**12**). The $^1O_2$ quenching

TABLE 1. Singlet Oxygen and Hydroxyl Radical Bimolecular Rate Constants and Direct Photolysis Quantum Yields for Cimetidine (1) and Ranitidine (2)[f]

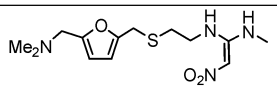


cimetidine (**1**)

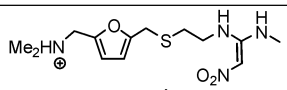


1H$^+$

pH	χ_1	χ_{1H^+}	$k_{rxn,{}^1O_2}$ [a,b]	$k_{rxn,\cdot OH}$ [a]	Φ_{direct} [c]
3	8×10^{-5}	> 0.999	†	650 ± 50	†
4.2	0.001	0.999	0.33 ± 0.03	†	†
6.9	0.387	0.613	9.2 ± 0.6	†	†
8.2	0.926	0.074	22 ± 2	†	†
10.2	0.999	8×10^{-4}	25 ± 2	†	†



ranitidine (**2**)



2H$^+$

pH	χ_2	χ_{2H^+}	$k_{tot,{}^1O_2}$ [a,d]	$k_{rxn,\cdot OH}$ [a]	Φ_{direct}
3	6×10^{-6}	> 0.999	†	1460 ± 240	†
6.0	0.006	0.994	†	†	0.0053 ± 0.0001
6.4 [e]	0.016	0.984	1.6 ± 0.2	†	†
7.5 [e]	0.166	0.834	2.65 ± 0.07	†	†
9.8 [e]	0.976	0.024	6.4 ± 0.4	†	†
10.0	0.984	0.016	†	†	0.0055 ± 0.0001

[a] 10^7 M^{-1} s^{-1}. [b] Measured by steady-state photolysis. [c] No direct photolysis observed for **1** or **1H**$^+$. [d] Measured by laser flash photolysis. [e] pD in D_2O. [f] Speciation at each pH value is calculated based on pK_a = 7.1 for **1H**$^+$ (*45*) and pK_a = 8.2 for **2H**$^+$ (*44*). † = not measured.

rate constant for FFA in D_2O was measured to be 8.3 ± 0.1 × 10^7 M^{-1} s^{-1}, which is in agreement with literature values (*48*).

Fenton Reaction: •OH k_{rxn} Measurements. The hydroxyl radical rate constant was determined using competition kinetics according to eq 7

$$k_{\cdot OH}^{S} = \frac{\ln([S_t]/[S_0])}{\ln([R_t]/[R_0])} k_{\cdot OH}^{R} \qquad (7)$$

where *S* is the substrate (**1H**$^+$ or **2H**$^+$) and *R* is the reference compound with a known rate constant for reaction with •OH (acetophenone, $k_{\bullet OH} = 5.9 \times 10^9$ M^{-1} s^{-1}) (*49*). A plot of ln([S_t]/[S_0]) versus ln([R_t]/[R_0]) including data for each time had a slope of 1.10 ± 0.09 for **1H**$^+$ and 2.5 ± 0.4 for **2H**$^+$ as shown in Figure 5. From Figure 5 and eq 7, it was determined that the •OH rate constants for reaction with the protonated forms of cimetidine, **1H**$^+$, and ranitidine, **2H**$^+$, are 6.5 ± 0.5 × 10^9 M^{-1} s^{-1} and 1.5 ± 0.2 × 10^{10} M^{-1} s^{-1}, respectively. The reported errors are based on the 95% confidence limits of the slopes as calculated by regression analysis using eq 7.

Discussion

Photolysis in Natural Water with Sunlight. The data obtained in Mississippi River water indicate that different photolysis pathways are likely to be responsible for the degradation of **1** and **2**. The DOM in natural water has been shown to produce $^1O_2$ as well as other reactive oxygen species upon irradiation. Laser flash and steady-state photolysis experiments have shown that both **1** and **2** react quickly with $^1O_2$,

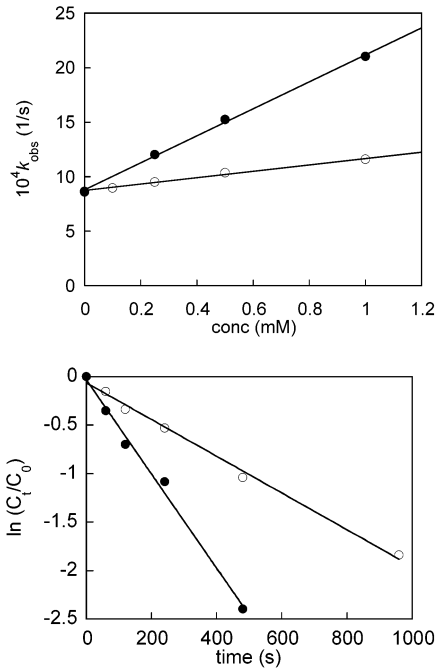
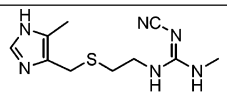
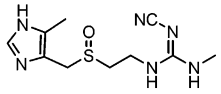


FIGURE 4. (Top panel) Comparison of k_{tot} for $3H^+$ (○) and 3 (●) in EtOH as determined by laser flash photolysis with Rose Bengal (40 μM) sensitizer. (Bottom panel) Comparison of k_{rxn} for 100 μM $3H^+$ (○) and 3 (●) in EtOH as determined by steady-state photolysis using Rose Bengal (40 μM) sensitizer under two 175 W Hg vapor lamps.

TABLE 2. Absolute and Relative Bimolecular Rate Constants in EtOH for the Interaction of Singlet Oxygen with Various Cimetidine Model Compounds Determined by Laser Flash Photolysis[a]

Compound	Structure	k_{tot} (10^8 $M^{-1}s^{-1}$)	k_{rel}
1		1.62 ± 0.02	1
10		1.93 ± 0.05	1.2
6		0.162 ± 0.002	0.10
8		<0.004	<0.002
9		0.75 ± 0.01	0.46

[a] Relative reaction rate constants (k_{rel}) are the total quenching rate constants for the substrates (S) relative to the parent compound **1** ($k_{rel} = k_{tot,S}/k_{tot,1}$).

and for cimetidine, singlet-oxygenation appears to be the dominant decay process in MRW. This is evidenced by the inhibited degradation of **1** by the $^1O_2$ quencher sodium azide in natural waters and the stability of **1** when photolyzed in DI water. Additional evidence for the involvement of $^1O_2$ is provided by the solvent isotope effect exhibited when the Mississippi River water solutions are diluted with either H_2O or D_2O. The magnitude of this isotope effect ($k_H/k_D = 0.52$) is in agreement with that calculated ($k_H/k_D = 0.55$) for **1** at pH 8. Without the sensitizers present in natural water, **1** does not decay upon irradiation, ruling out direct photolysis as a significant loss process. Hydroxyl radicals do not appear

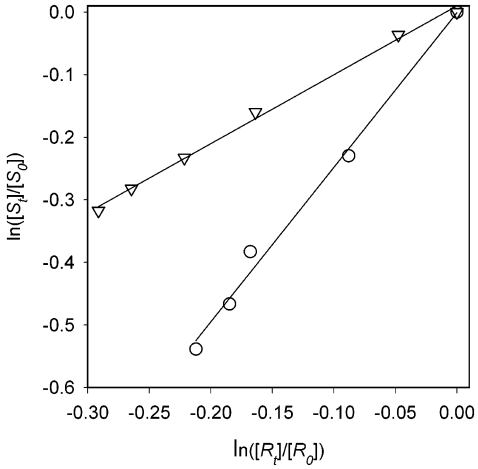
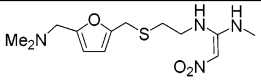
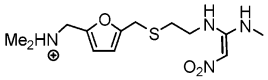
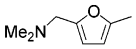
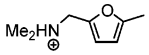


FIGURE 5. Competitive oxidation of substrates (S), ranitidine ($2H^+$, ○) and cimetidine ($1H^+$, ▽), versus acetophenone reference (R) by hydroxyl radicals generated using Fenton's reagent in pH 3 H_2O.

TABLE 3. Absolute and Relative Bimolecular Rate Constants in EtOH for the Interaction of Singlet Oxygen with Various Ranitidine Model Compounds Determined by Laser Flash Photolysis[a]

Compound	Structure	k_{tot} (10^7 $M^{-1}s^{-1}$)	k_{rel}
2		4.54 ± 0.04	1
$2H^+$		1.14 ± 0.02	0.25
3		12.4 ± 0.4	2.7
$3H^+$		3.14 ± 0.05	0.69
4		33 ± 2	7.3
5		4.06 ± 0.08	0.89
6		1.62 ± 0.02	0.36
7		<0.04	<0.01

[a] Relative reaction rate constants (k_{rel}) are the total quenching rate constants for the substrates (S) relative to the parent compound **2** ($k_{rel} = k_{tot,S}/k_{tot,2}$).

to be involved in the sensitized degradation of **1** in natural waters, as the radical scavenger 2-propanol does not alter the rate of decay.

Unlike cimetidine, ranitidine is subject to direct photolysis. In fact, the data from the experiments performed in natural waters indicate that direct photolysis is the major loss process for **2**. The degradation rate of **2** is 20% faster in natural water than in DI water and is suppressed to a rate equal to that in DI water by DABCO, a $^1O_2$ inhibitor. These data clearly implicate direct photolysis as the dominant photodegradation pathway for **2**, while reaction with $^1O_2$ is an additional loss process.

Direct Photolysis Degradation Rates. Cimetidine reacts negligibly under the sunlight irradiation conditions employed

in this study (summer sunlight in Minneapolis, MN, 45° latitude). Ranitidine is photodegraded much more quickly with a half-life of 35 min under noon summertime sunlight. The UV−vis spectra of **1** and **2** are markedly different (see Supporting Information, Figure S20), with **1** displaying an absorbance maximum at 218 nm and very little absorbance above 260 nm, while **2** has absorbance maxima at 226 and 315 nm. The photostability of **1** can be rationalized by the fact that it does not appreciably absorb in the wavelength region supplied by the solar spectrum. Likewise, the photolability of **2** can be rationalized in part by its efficient absorption of light in the lower wavelength region of the solar spectrum.

Study of models of the two chromophores in **2** indicated that the nitroacetamidine group, not the furan, is the important chromophore. The reaction rate constants of **2** and *N*,*N*′-dimethylnitroacetamidine (**7**) are similar and both contain absorbance maxima at 315 nm. The furfurylamine hydrochloride model compound $\mathbf{3H}^+$ degrades much more slowly under direct irradiation than does **2**. The UV−vis spectrum of $\mathbf{3H}^+$ displays a maximum at about 223 nm, which closely matches that of the first maximum of **2**, and minimal absorbance at environmentally important wavelengths ($\lambda >$ 300 nm).

Reaction of $^1O_2$ with Cimetidine and Ranitidine. Steady-state photolysis experiments show that both cimetidine and ranitidine react at high rates with $^1O_2$. The pH dependence of cimetidine reaction with $^1O_2$ has also been elucidated (Table 1). The range of reaction rate constants varies by a factor of 75 from pH 4.2, where cimetidine is present primarily as its conjugate acid form ($\mathbf{1H}^+$), to pH 10.2, where the speciation is dominated by **1** and very little of the conjugate acid is present. The fact that $^1O_2$ was involved in these oxidations is strongly supported by several lines of evidence. Results from laser flash photolysis experiments, in which [$^1O_2$] is monitored with time, agree quantitatively with the results from steady-state photolysis experiments, in which the concentration of the pharmaceutical is monitored with time. Additionally, when azide ion is added to the reaction mixture in the steady-state photolysis experiments, the reaction rate is depressed as predicted (see Supporting Information, Figures S16 and S17).

The steady-state photolysis and laser flash photolysis kinetic results indicate that, within experimental error, k_{rxn} is equal to k_{tot} for both pharmaceuticals in both EtOH and water. Thus, chemical reaction is the primary pathway by which ranitidine and cimetidine interact with $^1O_2$ and that the contribution from the physical quenching pathway is negligible. In determining the environmental fate of these compounds, it is not only important to quantify the rates of transformation but also to identify the reaction products. To that end, we have conducted a set of studies with model compounds that have allowed us to identify which functional groups are being oxidized in the reaction of $^1O_2$ with cimetidine and ranitidine.

Determination of the Site of Reaction with $^1O_2$ Using Cimetidine Model Compounds. To assess the site of reaction of $^1O_2$ with cimetidine, three model compounds, **6**, **8**, and **10**, that represent the functional groups present in cimetidine were examined by laser flash photolysis (Table 2). The data strongly implicate the dialkylimidazole ring as the most reactive group. The imidazole model compound **10** reacts 12 times faster than the sulfide model **6** and at least 500 times faster than the cyanoguanidine model **8**. Model compound **10** also reacted 20% faster than cimetidine itself, suggesting that tethering the sulfide group to the imidazole results in a slight depression of the rate of reaction with $^1O_2$. A similar effect was observed in the study of ranitidine model compounds.

Assignment of the imidazole as the reactive group is further supported by the study of cimetidine sulfoxide, **9**. Model **9** has essentially the same structure as **1**, but the sulfide functionality can be viewed as being blocked. This "knock-out" model displays a high reactivity toward $^1O_2$, quenching it at about half the rate of cimetidine. The decrease in reactivity of **9** relative to **1** is most likely due to the electron withdrawing effect of the sulfoxide group. The pH dependence of the singlet-oxygenation of **1** lends further credence to the imidazole being the reactive site. In going from pH 10 to pH 4, the imidazole ring becomes protonated, resulting in reduced electron density in the ring system. This electronic effect is expected to strongly manifest itself only in the heterocyclic moiety. Singlet oxygen is expected to react with the heterocycle of **1** to form an endoperoxide, as has been documented with other imidazole containing compounds (*50*−*52*). Further breakdown products arising from decomposition of the endoperoxides were reported by Kang and Foote (*51*, *52*).

Determination of the Site of Reaction with $^1O_2$ Using Ranitidine Model Compounds. Model compounds were studied to determine which functionalities in ranitidine were involved in the reaction with $^1O_2$. From the LFP data, it is apparent that the furan displays the highest reactivity toward $^1O_2$ (Table 3). This is consistent with other findings that have shown that substituted furans react at very high rates with $^1O_2$ (*48*). The range of quenching rates observed for the various furan substrates is interesting and can be understood by keeping in mind that $^1O_2$ is an electrophilic species. The furan containing the most electron-donating substituents is expected to react with the highest rate. Indeed **4**, which contains two electron-donating methyl groups, reacts fastest with $^1O_2$. As the electron-donating effect is reduced, the reaction with $^1O_2$ proceeds more slowly, as shown by **3**, **5**, and $\mathbf{3H}^+$. Because ranitidine reacts more slowly than dimethylfuran (**4**), we conclude that the thiomethyl and aminomethyl groups are deactivating. The notion that the amine functionality decreases the reactivity of the furan is further demonstrated by the effect of its protonation state on the reaction rate. Reactions of furans with $^1O_2$ have been well studied, with endoperoxide intermediacy being involved in the main reaction pathway (*53*−*58*). The endoperoxides generally are not isolable at ambient temperatures, and decomposition products including hydrolysis and cleavage products have been reported (*56*−*58*).

It is clear that the acetamidine portion of ranitidine is not involved in the interaction with $^1O_2$. With no observed quenching of the $^1O_2$ signal, **7** has a quenching rate constant $< 4 \times 10^5\ M^{-1}\ s^{-1}$. While olefins and amines have been shown to individually quench $^1O_2$ (*48*), these functional groups joined together as an acetamidine do not quench $^1O_2$ at a significant rate.

The sulfide functionality is also a potential site for singlet-oxygenation. For diethyl sulfide (**6**), k_{tot} has been measured to be $1.62 \times 10^7\ M^{-1}\ s^{-1}$. Although this value is similar to that seen for ranitidine, it is not believed that the sulfide competes with the furan for singlet-oxygenation. Sulfides are kinetically deactivated toward reaction with singlet oxygen by α-aryl substitution (e.g., dibenzyl sulfide has been reported to react with $^1O_2$ with a rate constant of $0.6 \times 10^7\ M^{-1}\ s^{-1}$) (*59*), and the α-furanyl substitution found in ranitidine is expected to act similarly. Also, the product of sulfur oxidation, the sulfoxide, was prepared independently, and it is not observed in the $^1O_2$ reactions by NMR or HPLC analysis.

Effect of pH on the Fate of Ranitidine. Experiments with **2** indicate that its direct photodegradation rate is insensitive to pH. The UV−vis spectrum and Φ_{direct} are unaltered across the pH range of 6−10. These pH limits correspond to values where ranitidine is primarily in its protonated form ($\mathbf{2H}^+$) and where the free base form (**2**) is the dominant species,

respectively.

Reaction of **2** with $^1O_2$ exhibits a pH dependence, with protonation of the dimethylamino group causing a decrease in the $^1O_2$ quenching rate constant, k_{tot}. This fact is evident from the laser flash photolysis studies of **2** in solutions buffered to various pD values. The more electron rich free base form reacts four times faster than the protonated form, which is consistent with the electrophilic nature of $^1O_2$.

There are two plausible explanations for the enhanced rate constant of the free amine. One explanation is that the free amine assists in quenching by acting as a physical quencher. This is a reasonable hypothesis since it is known that trialkylamines such as triethylamine ($k_{phys} \sim 10^7$ M^{-1} s^{-1}) are good physical quenchers (*48*). Upon protonation, this physical quenching component would be removed and a lower total quenching rate would be observed. A second explanation is that the protonated aminomethyl substituent found in $\mathbf{2H}^+$ withdraws electron density from the furan ring and, therefore, is a deactivating group. The two scenarios can be distinguished because upon protonation they predict a decrease in k_{phys} and k_{rxn}, respectively. Steady-state photolysis results for the ranitidine model compounds furfurylamine hydrochloride ($\mathbf{3H}^+$) and its free base, **3**, indicate that **3** chemically reacts almost three times faster than $\mathbf{3H}^+$ (Figure 4). These data suggests that for model compounds **3** and $\mathbf{3H}^+$, the majority (≥65%) of the difference in k_{tot} is due to changes in k_{rxn} between the free amine and protonated form. The fact that protonation of the dimethylamino group results in a 3−4-fold decrease in the reaction rate further supports the view that the furan, and not the sulfide, is the reactive group toward reaction with $^1O_2$ in ranitidine.

Reaction of •OH with Cimetidine and Ranitidine. Zbaida et al. (*40*) have previously isolated cimetidine sulfoxide, *N*-desmethylcimetidine, *N*-desmethylcimetidine sulfoxide, cimetidine guanylurea, and 5-hydroxymethylimidazole cimetidine sulfoxide as products in the reaction of cimetidine with Fenton's reagent, which is a testament to the nonspecific reactivity of the •OH. The bimolecular rate constants measured for the reactions of $\mathbf{1H}^+$ and $\mathbf{2H}^+$ with •OH are both approximately 10^{10} M^{-1} s^{-1}. Previous measurements by other groups have also found rate constants near 10^{10} M^{-1} s^{-1} for these processes, although these studies report the opposite reactivity order with cimetidine being found to be the more reactive toward •OH (*60*, *61*). While these rate constants are near the diffusion-controlled limit, reaction with •OH is not expected to be a significant decay process for either **1** or **2** due to the extremely low concentration of •OH in natural waters. It should be noted that the rate constant cannot be much larger for the unprotonated analogues, **1** and **2**, because the low pH rate constants approach the diffusion-controlled limit. Due to this fact and the low steady-state concentrations of •OH in natural waters (10^{-16} M in agriculturally impacted waters containing high nitrate levels to 10^{-18} M for pristine waters (*62*, *63*)), reaction with •OH is expected to be kinetically insignificant at all pHs in natural waters. The data for the photolyses of both **1** and **2** in natural waters with natural light in the presence of inhibitors verify this, as **1** was found to be degraded primarily by reaction with $^1O_2$, while **2** was degraded primarily by direct photolysis.

Environmental Significance. The experiments described in this work demonstrate that ranitidine and cimetidine are both photolabile in Mississippi River water (DOC = 16 mg/L, pH = 8.0), although they degrade by different mechanisms. Because ranitidine degrades primarily through a direct photolysis pathway with only a small contribution of a sensitized pathway involving singlet oxygen, its photochemical degradation rate in natural waters is relatively straightforward to predict. At 45 ° latitude in the summer, the direct photolysis half-life of ranitidine is 35 min in quartz test tubes and is expected to be approximately 70 min in surface water after correcting for the increase in rate caused by the lens effect of the curved test tubes (approximately a factor of 2) (*64*, *65*). In the winter, the half-life is expected to increase to 6 h based on the summer half-life and the differences in seasonal light intensity in the solar spectrum as compiled by Liefer (*66*). Similarly, the half-life of **2** at 30° latitude is calculated to be 65 min in the summer and 2.5 h in the winter based on latitudinal variations in the intensity of light in the solar spectrum (*66*). These half-lives represent only photochemical degradation and do not account for other processes, such as sorption. Furthermore, they correspond to maximum environmental photodegradation rates, and corrections should be applied for light absorption and scattering in the water column. Reaction of $^1O_2$ with **2** is expected to slightly decrease the half-lives calculated from the direct photolysis data.

For cimetidine the major photochemical degradation pathway is expected to be reaction with $^1O_2$ formed from the interaction of sunlight with DOC. For a pH 8 water body, using estimated surface concentrations of $^1O_2$ that range from 10^{-14} M in pristine waters to 10^{-12} M in highly colored waters (*28*, *67*), the expected half-life for **1** is calculated to range from 53 min to 90 h (or 7 d at 12 h sunlight per day). Under the same $^1O_2$ conditions, the half-lives are expected to increase to 2 and 200 h at pH 7 and 9 and 900 h in pH 6 water bodies.

Acknowledgments

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Supporting Information Available

Stern−Volmer plots for the quenching of singlet oxygen by **1**−**12** in ethanol and D_2O, plots of steady-state kinetic data for reactions of **1** and **2** with singlet oxygen, a representative transient decay curve from the laser flash photolysis experiments, UV−vis spectra of **1**−**4**, and characterization data for the Mississippi River water used in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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