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ARTICLE *in* ENVIRONMENTAL SCIENCE AND TECHNOLOGY · MARCH 2008

Impact Factor: 5.33 · DOI: 10.1021/es702245n · Source: PubMed

Environ. Sci. Technol. **2008,** *42,* 1256–1261

Free Radical Destruction of β-Blockers in Aqueous Solution

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Received September 6, 2007. Revised manuscript received November 13, 2007. Accepted November 23, 2007.

Many pharmaceutical compounds and metabolites are currently found in surface and ground waters which indicates their ineffective removal by conventional water treatment technologies. Advanced oxidation/reduction processes (AO/RPs) are alternatives to traditional water treatment, which utilize free radical reactions to directly degrade chemical contaminants. This study reports the absolute rate constants for reaction of three β-blockers (atenolol, metoprolol, and propranolol) with the two major AO/RP radicals; the hydroxyl radical (•OH) and hydrated electron (e^-_{aq}). The bimolecular reaction rate constants for •OH are $(7.05 \pm 0.27) \times 10^9$, $(8.39 \pm 0.06) \times 10^9$, and $(1.07 \pm 0.02) \times 10^{10}$, and for e^-_{aq} they are $(5.91 \pm 0.21) \times 10^8$, $(1.73 \pm 0.03) \times 10^8$, and $(1.26 \pm 0.02) \times 10^{10}$, respectively. Transient spectra were observed for the intermediate radicals produced by hydroxyl radical reactions. In addition, preliminary degradation mechanisms and major products were elucidated using ^{60}Co γ-irradiation and LC-MS. These data are required for both evaluating the potential use of AO/RPs for the destruction of these compounds and for studies of their fate and transport in surface waters where radical chemistry may be important in assessing their lifetime.

Introduction

The presence of active pharmaceutical ingredients (APIs) in surface waters is an emerging environmental issue and provides a new challenge to drinking water, wastewater, and water reuse treatment systems (*1*). Most of the APIs administered to patients are excreted either as metabolites or as the unchanged parent compounds (*2*). Another common practice is to dispose of outdated medicines "down the drain", but either way they end up in the wastewater treatment plants.

The presence of pharmaceuticals in the aquatic environment was reported as early as the beginning of the 1980s (*3*). Studies of various treatment technologies for the removal of APIs have been reported, including membrane filtration (*4*), activated carbon adsorption (*5*), and reverse osmosis (*6*). The effectiveness of these processes is also influenced by the amount and type of natural organic matter (NOM) present in the wastewater which results in higher treatment costs (*7*). Although partial removal of APIs can be achieved through these processes, recent studies have demonstrated that conventional water treatment processes are relatively inefficient in treating APIs (*8*). In addition, these technologies require the disposal of wastes such as membrane retentate and spent activated carbon generated during the treatment.

Advanced oxidation/reduction processes (AO/RPs) are alternatives to traditional treatment and have recently received considerable attention for API removal (*1*). AO/RPs typically involve the formation of hydroxyl radicals (•OH) as oxidizing species and either hydrated electrons (e^-_{aq}) or hydrogen atoms (H•) as reducing species, all of which can be utilized in the destruction of organic pollutants present in drinking or wastewater. AO/RPs are effective in the treatment of a variety of anthropogenic pollutants including APIs (*9–11*). However, to provide a fundamental understanding of the applicability of these processes to degrade APIs, it is necessary to determine the bimolecular reaction rate constants between the reactive species and the chemicals of interest.

Additionally, the environmental fate of APIs in natural waters is attracting increasing attention. In surface waters, while biodegradation may be important (*12*), it is likely that abiotic processes, such as phototransformation (*13–15*) and partitioning to sediments (*16, 17*) may actually have a greater impact on reducing aqueous concentrations of APIs. Hydroxyl radicals, especially in photosensitized oxidation, are also expected to play a key role during environmental degradation (*18*).

Beta-blockers belong to a group of cardiovascular APIs and are generally used in the treatment of disorders such as hypertension, angina, and arrhythmias. The activity of these compounds is to block the action of epinephrine and norepinephrine on the β-adrenergic receptors in the body, primarily in the heart (*19*). Among the β-blockers, atenolol, metoprolol, and propranolol have been in long-term use in Europe and North America, and they have also been detected in the aquatic environment (*16, 20–22*). Less than 10% of atenolol and metoprolol is removed by conventional wastewater treatment using activated sludge (*23*). Although there are some reports on the degradation of β-blockers by AO/RPs (*24–26*), there appears to be no reported aqueous kinetic data and only limited reporting of free-radical-based degradation byproducts (*27*).

The objective of this study was to determine the absolute rate constants for the reaction of the hydroxyl radical and hydrated electron with the three β-blocker pharmaceutical compounds: atenolol, propranolol, and metoprolol. In this work, transient free radical spectra produced by hydroxyl radical reaction with these three species were also recorded over the time period of 1–200 μs after irradiation to provide a better understanding of the nature of the intermediate radical species produced. Finally, detailed product studies of the free-radical-induced degradation pathways of these β-blockers using γ-irradiation in aerated solution were conducted to provide preliminary insight into the mechanisms that might occur under typical water treatment conditions.

Materials and Methods

Materials. The β-blocker pharmaceuticals: atenolol, propranolol hydrochloride, and (±)-metoprolol (+)-tartrate salt

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10.1021/es702245n CCC: $40.75
Published on Web 01/16/2008

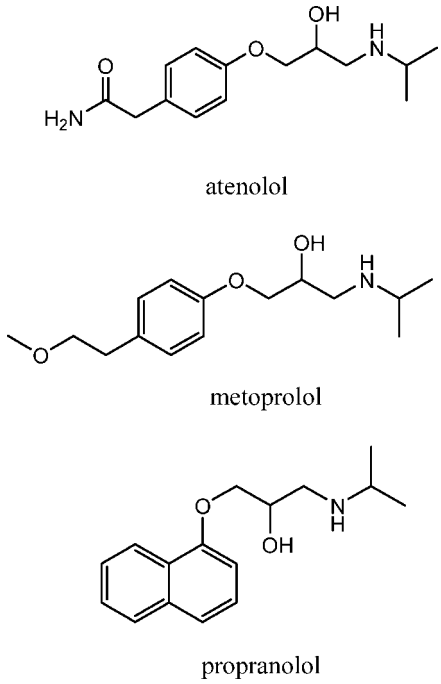


FIGURE 1. Chemical structures of the β-blockers.

were purchased from Sigma-Aldrich (≥99% purity). Their chemical structures are shown in Figure 1. Solutions were prepared using water filtered with a Millipore Milli-Q system, which includes constant illumination by a Xe arc lamp at 172 nm to keep total organic carbon concentrations below 13 μg L^{-1}. All kinetics solutions were buffered with 5.0 mM phosphate adjusted to pH 7.0, and sparged with high purity N_2O (for hydroxyl radical experiments) or N_2 (hydrated electron experiments) to remove dissolved oxygen.

Pulse Radiolysis and γ-Radiolysis. Electron pulse radiolysis experiments were performed at the Notre Dame Radiation Laboratory with the 8-MeV Titan Beta model TBS-8/16–1S linear accelerator. This irradiation and transient absorption detection system has been described in detail previously (*28*). Dosimetry (*29*) was performed using N_2O-saturated, 1.00×10^{-2} M KSCN solutions at $\lambda = 472$ nm, ($G\epsilon = 5.2 \times 10^{-4}$ m^2 J^{-1}) with average doses of 3–5 Gy per 2–3 ns pulse. Throughout this paper, the units of G are μmol J^{-1}, and ϵ is in units of M^{-1} cm^{-1}. All experimental data were determined by averaging 8−12 replicate pulses using the continuous flow mode of the instrument.

The radiolysis of water is described in eq 1.

$$H_2O \rightarrow (0.28)\cdot OH + (0.06)H\cdot + (0.27)e^-_{aq} + (0.05)H_2 + (0.07)H_2O_2 + (0.27)H^+ \quad (1)$$

where the numbers in parentheses are the G-values (yields) (*30, 31*). To study only the reactions of the hydroxyl radical, solutions were presaturated with nitrous oxide (N_2O), which quantitatively converts the hydrated electrons and hydrogen atoms to hydroxyl radicals via the following reactions (*30*):

$$e^- + N_2O + H_2O \rightarrow N_2 + HO^- + \cdot OH \; k_2 = 9.1 \times 10^9 M^{-1}s^{-1} \quad (2)$$

$$H\cdot + N_2O \rightarrow \cdot OH + N_2 \; k_3 = 2.1 \times 10^6 M^{-1}s^{-1} \quad (3)$$

To isolate hydrated electron reactions, solutions were presaturated with nitrogen in the presence of 0.10 M isopropanol to scavenge the hydroxyl radicals and hydrogen atoms, converting them into relatively inert isopropanol radicals (*30*):

$$(CH_3)_2CHOH + \cdot OH \rightarrow (CH_3)_2C\dot{O}H + H_2O \; k_4 = 1.9 \times 10^9 M^{-1}s^{-1} \quad (4)$$

$$(CH_3)_2CHOH + H\cdot \rightarrow (CH_3)_2C\dot{O}H + H_2 \; k_5 = 7.4 \times 10^7 M^{-1}s^{-1} \quad (5)$$

A Shepherd 109–86 Cobalt 60 source was used for steady-state γ radiolysis experiments with a dose rate of 0.0864 kGy min^{-1} as measured by Fricke dosimetry.

HPLC and LC-MS Analysis. The β-blocker pharmaceutical compounds and their reaction products were analyzed by HPLC under the following conditions: column, Phenomenex Gemini C_{18} 250 × 4.6 mm i.d.; the isocratic mobile phase consisted of 15% CH_3OH, 15% CH_3CN, and 70% 10 mM phosphate buffer solution (pH 3.0). The LC-MS system used in the study consisted of an Agilent 1100 HPLC pump and a Waters LCT Classic mass spectrometer with electrospray ionization source. A sample volume of 10 μL was applied to a Phenomenex Luna C_{18} (2) HPLC column (2.0 × 150 mm). The mobile phase was (A) 98% H_2O + 2% CH_3CN + 0.2% formic acid and (B) CH_3CN + 0.2% formic acid. Gradient elution was 2% of B for 1 min followed by a linear increase to 95% B at 50 min, and then held constant for an additional 7 min. The mass spectral data were obtained in the positive ion mode between m/z 100−350.

Results and Discussion

•OH Transient Spectra. For all three β-blockers, the reaction with the hydroxyl radical generated the transient absorption spectra shown in Figure 2. The peak absorptions in the range 300–350 nm are characteristic of reaction with the aromatic rings in these compounds to form hydroxycyclohexadienyl radicals (*32, 33*). Peak absorption coefficient values were calculated using a hydroxyl radical initial G-value of 0.59 μmol J^{-1} under these conditions, based upon the intraspur scavenging model calculations of LaVerne and Pimblott (*35*). The spectra obtained for the transients from the reaction of atenolol and metoprolol with the hydroxyl radical were generally similar; however, the spectra of propranolol showed less absorbance in the region 260–280 nm and exhibited a peak at 330 nm and a small shoulder around 380 nm. The λ_{max} for all three intermediates was red-shifted by 20–50 nm compared to the λ_{max} of the parent compounds. Such a shift suggests that the •OH had added to the aromatic ring resulting in extended conjugation in these systems as noted previously in studies of •OH reactions with other substituted benzene species (*36*).

Kinetic Measurements. The bimolecular rate constants for hydroxyl radical reaction were determined from the rate of absorption change with concentration at the λ_{max}. Typical

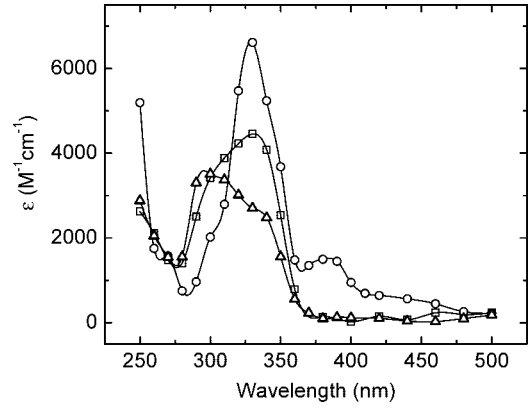


FIGURE 2. Initial transient spectrum obtained upon the hydroxyl radical oxidation of atenolol (□), metoprolol (Δ) and propranolol (O) in N_2O-saturated pH 7.0 water at room temperature.

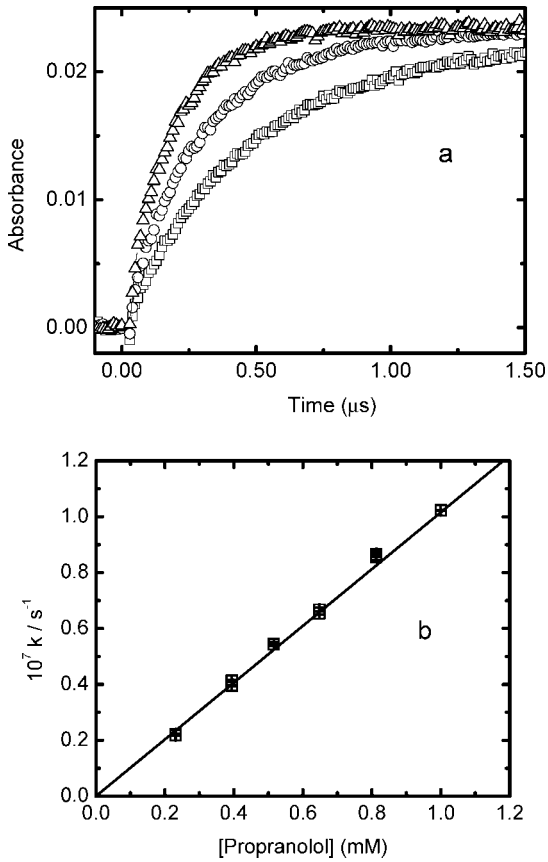


FIGURE 3. (a): Growth kinetics observed for the hydroxyl radical oxidation at 330 nm for 0.23 (□), 0.39 (○), and 0.65 (Δ) mM propranolol at pH 7.0 and room temperature. (b): Second-order rate constant determination for the reaction of hydroxyl radicals with propranolol. The straight line is the weighted linear plot, with a slope of 1.07 ± 0.02.

TABLE 1. Measured Rate Constants (M^{-1} s^{-1}) and Spectral Parameters for Hydroxyl Radical and Hydrated Electron Reaction with β-Blockers

compound	atenolol	metoprolol	propranolol
·OH λ_{max}/nm	330	300	330
$\epsilon_{max}/M^{-1}cm^{-1}$	4460	3510	6600
10^{-9} k ·OH /$M^{-1}s^{-1}$	7.05 ± 0.27	8.39 ± 0.06	10.7 ± 0.2
10^{-8} $k_{e^-aq}/M^{-1}s^{-1}$	5.91 ± 0.21	1.73 ± 0.03	126 ± 2

kinetic data for propranolol are given in Figure 3a, and these were processed using the procedures outlined by Mezyk et al. (*37*). In brief, the absolute hydroxyl radical rate constants were obtained by fitting exponential curves to the pseudo first-order growth kinetics (Figure 3a) and plotting these values as a function of the concentrations of the β-blocker (Figure 3b) to obtain the rate constants summarized in Table 1.

The range (7–10 × 10^9 $M^{-1}s^{-1}$) of the rate constants for hydroxyl radical reaction with the three β-blockers is comparable to previous rate constants measurements for aqueous hydroxyl radical reaction with benzene (7.5–7.8 × 10^9 M^{-1} s^{-1}) and naphthalene (9−12 × 10^9 M^{-1} s^{-1}) (*30*) further supporting our assignment of the initial formation of hydroxycyclohexadienyl radicals. The measured value for atenolol, (7.05 ± 0.27) × 10^9 M^{-1} s^{-1}), is consistent with the hydroxyl radical reaction being predominantly at the ring moiety, with only minimal contribution from the electron withdrawing NH_2COCH_2− side chain. The slight increase for metoprolol ((8.39 ± 0.06) × 10^9 M^{-1} s^{-1}) is consistent with

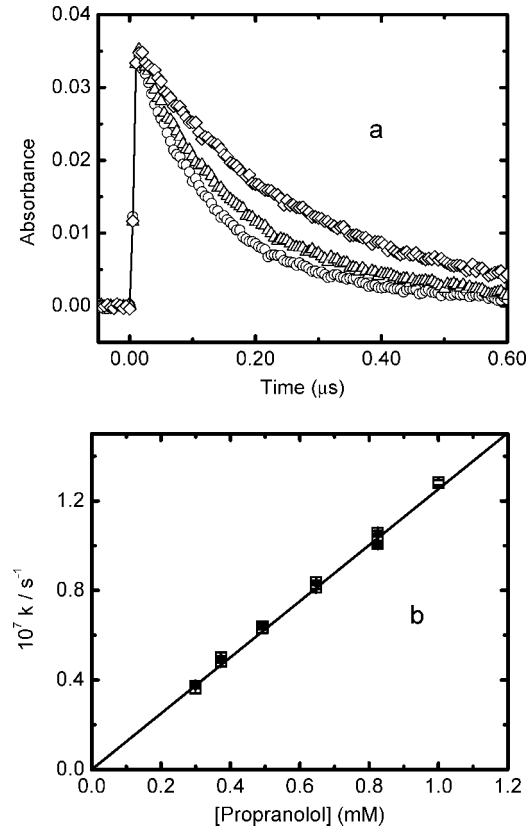


FIGURE 4. (a): Typical decay kinetics for hydrated electron reduction at 700 nm for 0.65 (○), 0.50 (Δ), and 0.30 (◇) mM propranolol at pH 7.0 and room temperature. (b): Second-order rate constant determination for the reaction of the hydrated electron with propranolol. The straight line is the weighted linear plot, with a slope of 1.26 ± 0.02.

the weaker electron-withdrawing $CH_3OCH_2CH_2$− side chain group, as noted previously for other aromatic compounds (e.g. ref *38*.). The higher value for propranolol ((1.07 ± 0.02) × 10^{10} M^{-1} s^{-1}) reflects the fact that the naphthalene group has both a higher electron density and more potential sites for hydroxyl radical reaction.

The rate constants for hydrated electron reaction with the three β-blockers were measured by directly monitoring the change the absorption of e^-_{aq} at 700 nm in nitrogen-saturated solutions at pH 7.0. The analysis steps are outlined by Mezyk et al. (*37*) and illustrated in Figure 4 for propranolol. The decay curves (Figure 4a) were fitted to pseudo first-order exponential kinetics, from which the second-order linear plot shown in Figure 4b was obtained. The slope of such a plot is the second-order rate constant for e^-_{aq} reduction of propranolol.

These reduction rate constants are summarized in Table 1. The hydrated electron rate constant for propranolol ((1.26 ± 0.02) × 10^{10} M^{-1} s^{-1} is ∼100 times faster than for atenolol ((5.91 ± 0.21 × 10^8 M^{-1} s^{-1}) and metoprolol ((1.73 ± 0.03) × 10^8 M^{-1} s^{-1}), again attributed to the extended conjugate system of the naphthalene group. The same difference of 2 orders of magnitude has also been reported for the analogous reduction rate constants for benzene (0.7–1.3 × 10^7 M^{-1} s^{-1}) and naphthalene (5.0–6.3 × 10^9 M^{-1} s^{-1}) (*30*). However, the absolute magnitude of these three β-blocker reduction rate constants being considerably higher than for the two simple aromatic systems indicates that some hydrated electron reactions must also be occurring on the side-chains.

Transformation Pathways for the Reaction of β-Blockers with •OH. In addition to the reaction kinetics for these two radicals with the three β-blockers, we also investigated the

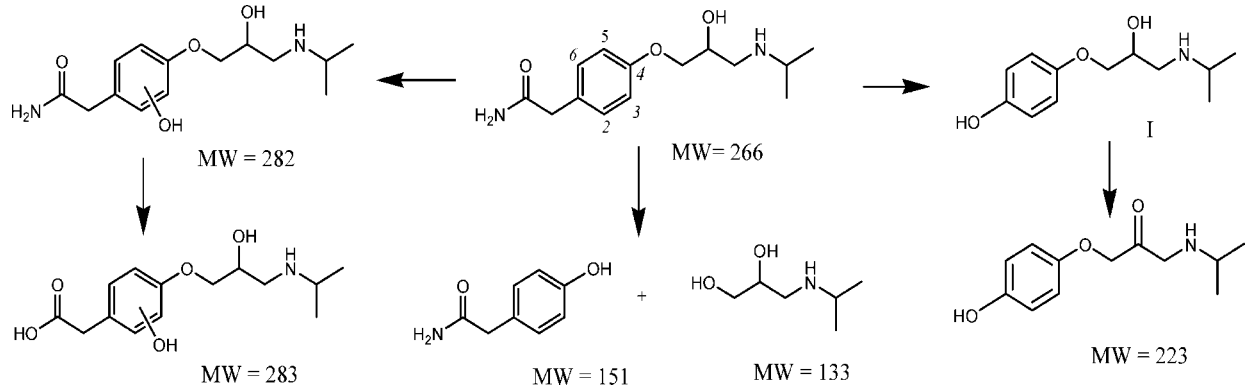
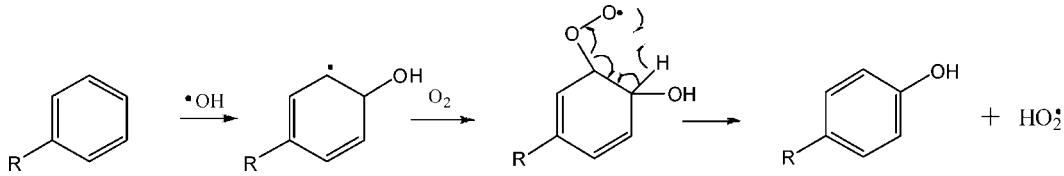


FIGURE 5. Degradation products and proposed reaction pathways for •OH oxidation of atenolol.

SCHEME 1



stable products formed in these reactions. These experiments were performed using ^{60}Co steady-state radiolysis, with products assigned using LC-MS. The experiments were conducted using air-saturated 1.0 mM solutions of the parent compounds buffered at pH 7.0. In the presence of air, the hydrated electrons and hydrogen atoms produced in the radiolysis are expected to mostly react with dissolved oxygen to produce the relatively inert superoxide anion (*30*).

Therefore under these conditions, the chemistry is mostly dominated by the hydroxyl radical reactions. All three compounds were rapidly degraded by γ-irradiation, and at an absorbed dose of 3.0 kGy, less than 50% of the initial concentrations remained (Supporting Information Figure 1S). The degradation profiles of the three β-blockers were fitted using exponential decay kinetics, to give half-life doses of 2.25 ± 0.02, 1.84 ± 0.03, and 1.69 ± 0.03 kGy for atenolol, metoprolol, and propranolol respectively. These values are consistent with the increasing trend observed for the hydroxyl radical rate constants.

Analyses by LC-MS at multiple irradiation doses revealed six atenolol decomposition products at detectable levels. Our structural assignments of the breakdown products of β-blockers during γ-irradiation were based on the analysis of the total ion chromatogram (TIC) and the corresponding mass spectra. The masses of the different products were determined from the peaks corresponding to the protonated molecule, $[M + H]^+$. For the purpose of this paper, we will refer to the products by molecular weight (MW).

The major degradation products produced in the steady-state irradiation of atenolol are summarized in Figure 5. Two separate products with MW of 282 were observed, corresponding to the addition of 16 mass units to the parent peak. This is consistent with hydroxylation of the aromatic ring. The addition of the electrophilic hydroxyl radical to the aromatic ring forms a resonance-stabilized carbon-centered radical with subsequent addition of oxygen and elimination of a hydroperoxyl radical, yielding the phenolic product as shown in Scheme SCHEME 1 (*34*).

The product with MW 151 is attributed to hydroxyl radical reaction at the ipso position of atenolol, labeled 4, in the molecular structure given for atenolol in Figure 5. This leads to the formation of the corresponding phenol, while the product with MW 133 (also identified in the γ irradiation of metoprolol and propranolol), is assigned to an amino-diol formed from •OH induced cleavage of the side chain. The product with MW 283 corresponds to the •OH radical oxidation of the primary amide group in the main side chain to form the acid. Oxidation of the −OH group yields a product with MW 223 which we propose is a ketone. The intermediate product (I) was not observed, possibly due to its fast rate of reaction with •OH.

The product assignments arising from γ irradiation of metoprolol (Figure 6) are similar to those for atenolol. The product with MW 283 (addition of 16 mass units to the parent MW) is observed, and similarly, we propose it arises from •OH radical addition to the benzene ring. The product with MW 133 was again identified; however, the product (MW 152) that would arise from ipso attack at position 4 was not observed due to the lack of response under ESI conditions.

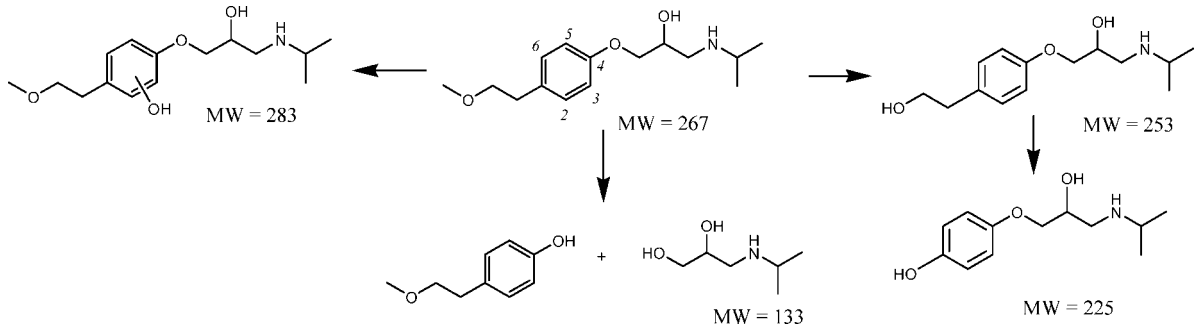


FIGURE 6. Degradation products and proposed reaction pathways for •OH oxidation of metoprolol.

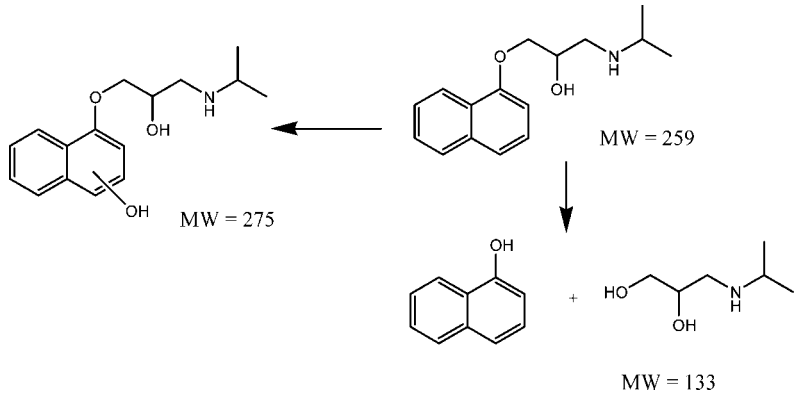


FIGURE 7. Degradation products and proposed reaction pathways for •OH oxidation of propranolol.

Product analysis of the γ-irradiation of propranolol revealed six major peaks at MW 275 (Supporting Information Figure 2S), as expected given the increased number of available sites on the naphthalene ring for hydroxyl radical addition (Figure 7). Since the specificity of electrophilic aromatic substitution is typically governed by the nature of the substituents, reactions involving •OH radicals are susceptible to substituent effects which may account for the different amount of MW 275 products. The ipso-directed oxidation resulting in the production of the MW 133 species was again observed.

The dependence of the relative amounts of β-blocker degradation products on γ radiation dose is summarized in Supporting Information Table 1S. Since the products have similar structures, we assume that their response factors (peak intensity/molecule) are similar; hence, the peak intensities are indicative of the relative yields. The ipso-adducted side chain product with MW 133 and phenolic product with MW + 16 are the major products during γ-irradiation of the β-blockers. Phenolic products with MW +16 are important products which reach maximum levels at approximately 3–5 kGy. The product with MW 133 reaches a maximum concentration after 7.78 kGy irradiation and then declines presumably due to further reaction of this product with radicals. The early appearance of peaks assigned to the phenolic and ipso-adducted side chain product is consistent with the relative reaction rates for the hydroxyl radical reactions leading to these products compared to the other reaction pathways.

Comparative ecotoxicological hazards have been reported (*39*) for β-blockers and their human metabolites but only for two of the degradation products observed in the present study. All of the present degradation products showed an initial increase in relative concentration with irradiation dose and then a decline (Supporting Information Table 1S). This result suggests that any issues related to the ecotoxicological properties of such products would not be significant for an appropriate extended irradiation dose. The ultimate aim is to facilitate the degradation of these compounds to the point where effluents are nontoxic.

Implications. The data presented above provides fundamental information necessary to apply AO/RPs to treatment of aqueous waste streams. It appears that both oxidative and reductive processes could result in the effective removal or assistance in the removal of these compounds. Although a full kinetic model is beyond the scope of this study, as this would require quantitative evaluation of all of the intermediates formed, as well as their radical reaction rate constants, these kinetic and mechanistic data do provide a quantitative foundation for the initial evaluation of AO/RPs efficiency in removing β-blockers from real-world waters which can contain high levels of dissolved natural organic matter (NOM) and other hydroxyl radical scavengers. For example, in an aerated wastewater containing 7 mg L^{-1} NOM (580 μM NOM assuming 12 g C per mole C), and 10 μg L^{-1} atenolol (37.6 nM) at pH 8.0 and a typical alkalinity of 100 mg L^{-1} (as $CaCO_3$, corresponding to ~1.0 mM HCO_3^-), the hydrated electrons produced will be quantitatively scavenged by dissolved oxygen, and the hydroxyl radical reaction will be partitioned according to the following equations (eq 6 from ref *40* and eq 8 from ref *30*):

$$\cdot OH + NOM \rightarrow H_2O + NOM^{\cdot} \; k_{NOM} = 2.25 \times 10^8 M^{-1}s^{-1} \quad (6)$$

$$\cdot OH + \text{atenolol} \rightarrow \text{intermediate} \; k_{\text{atenolol}} = 7.05 \times 10^9 M^{-1}s^{-1} \quad (7)$$

$$\cdot OH + HCO_3 \rightarrow OH^- + CO_3 \; k_{HCO_3^-} = 8.5 \times 10^6 M^{-1}s^{-1} \quad (8)$$

Based on the relative rates of these three reactions under these conditions, the fraction of hydroxyl radical available to degrade the atenolol (reaction 7) is calculated to be only 0.19%. The corresponding values for metoprolol and propranolol are 0.23 and 0.30%, respectively. Although these calculated reaction efficiencies are low, they would be expected to remain relatively constant under AO/RPs conditions, and thus provide an estimate for the extent of treatment that would be required to achieve any significant improvement over the 10% removal that has been reported for these compounds using conventional activated sludge wastewater treatment (*23*).

Acknowledgments

This work was performed at the Radiation Laboratory, University of Notre Dame, which is supported by the Office of Basic Energy Sciences, U.S. Department of Energy. Financial support is also acknowledged from the WateReuse Foundation Grant number is WRF 04-017. This is contribution 19 from the University of California, Irvine, Urban Water Research Center.

Supporting Information Available

Two figures showing γ-irradiation of three β-blockers; LC/MS analysis data for the m/z 276 decomposition products of propranolol and one table for the LC-MS peak areas for the β-blocker degradation products. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) Ikehata, K.; Naghashkar, N. J.; Gamal El-Din, M. Degradation of aqueous pharmaceuticals by ozonation and advanced oxidation processes: A review. *Ozone: Sci. Eng.* **2006**, *28*, 353–414.

(2) Kummerer, K. In *Pharmaceuticals in the Environment*; Kummerer, K., Ed.; Springer, 2004.

(3) Richardson, M. L.; Bowron, J. M. The fate of pharmaceutical chemicals in the aquatic environment: A review. *J. Pharm. Pharmacol* **1985**, *37*, 1–12.
(4) Nghiem, L. D.; Schafer, A. I.; Elimelech, M. Pharmaceutical retention mechanisms by nanofiltration membranes. *Environ. Sci. Technol.* **2005**, *39*, 7698–7705.
(5) Heberer, T. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: A review of recent research data. *Toxicol. Lett.* **2002**, *131*, 5–17.
(6) Hartig, C.; Ernst, M.; Jekel, M. Membrane filtration of two sulphonamides in tertiary effluents and subsequent adsorption on activated carbon. *Water Res.* **2001**, *35*, 3998–4003.
(7) Larsen, T. A.; Lienert, J.; Joss, A.; Siegrist, H. How to avoid pharmaceuticals in the aquatic environment. *J. Biotechnol.* **2004**, *113*, 295–304.
(8) Westerhoff, P.; Yoon, Y.; Snyder, S. A.; Wert, E. Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. *Environ. Sci. Technol.* **2005**, *39*, 6649–6663.
(9) Huber, M. M.; Canonica, S.; Park, G.-Y.; von Gunten, U. Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. *Environ. Sci. Technol.* **2003**, *37*, 1016–1024.
(10) Ohko, Y.; Iuchi, K.-i.; Niwa, C.; Tatsuma, T.; Nakashima, T.; Iguchi, T.; Kubota, Y.; Fujishima, A. 17b-Estradiol degradation by TiO_2 photocatalysis as a means of reducing estrogenic activity. *Environ. Sci. Technol.* **2002**, *36*, 4175–4181.
(11) Perez-Estrada, L. A.; Malato, S.; Gernjak, W.; Agueera, A.; Thurman, E. M.; Ferrer, I.; Fernandez-Alba, A. R. Photo-fenton degradation of diclofenac: identification of main intermediates and degradation Pathway. *Environ. Sci. Technol.* **2005**, *39*, 8300–8306.
(12) Lam, M. W.; Young, C. J.; Brain, R. A.; Johnson, D. J.; Hanson, M. A.; Wilson, C. J.; Richards, S. M.; Solomon, K. R.; Mabury, S. A. Aquatic persistence of eight pharmaceuticals in a microcosm study. *Environ. Toxicol. Chem.* **2004**, *23*, 1431–1440.
(13) Boreen, A. L.; Arnold, W. A.; McNeill, K. Photochemical fate of sulfa drugs in the aquatic environment: Sulfa drugs containing five-membered heterocyclic groups. *Environ. Sci. Technol.* **2004**, *38*, 3933–3940.
(14) Latch, D. E.; Stender, B. L.; Packer, J. L.; Arnold, W. A.; McNeill, K. Photochemical fate of pharmaceuticals in the environment: Cimetidine and ranitidine. *Environ. Sci. Technol.* **2003**, *37*, 3342–3350.
(15) Boreen, A. L.; Arnold, W. A.; McNeill, K. Triplet-sensitized photodegradation of sulfa drugs containing six-membered heterocyclic groups: Identification of an SO_2 extrusion photoproduct. *Environ. Sci. Technol.* **2005**, *39*, 3630–3638.
(16) Ternes, T. A. Occurrence of drugs in German sewage treatment plants and rivers. *Water Res.* **1998**, *32*, 3245–3260.
(17) Ternes, T. A.; Hirsch, R. Occurrence and behavior of X-ray contrast media in sewage facilities and the aquatic environment. *Environ. Sci. Technol.* **2000**, *34*, 2741–2748.
(18) Cooper, W. J.; Zika, R. G.; Petasne, R. G.; Fischer, A. M. In *Aquatic Humic Substances: Influence on Fate and Treatment of Pollutanbts*; Suffet, I. H., MacCarthy, P., Eds.; American Chemical Society: Washington, DC, 1989.
(19) Borchard, U. Pharmacological properties of beta-adrenoceptor blocking drugs. *J. Clin. Basic Cardiol.* **1998**, 1–5.
(20) Huggett, D. B.; Khan, I. A.; Foran, C. M.; Schlenk, D. Determination of beta-adrenergic receptor blocking pharmaceuticals in United States wastewater effluent. *Environ. Pollut.* **2003**, *121*, 199–205.
(21) Liu, Q.; Williams, H. E. Kinetic and degradation products for direct photolysis of beta-blockers in water. *Environ. Sci. Technol.* **2007**, *41*, 803–810.
(22) Lee, H.-B.; Sarafin, K.; Peart, T. E. Determination of beta-blockers and beta 2-agonists in sewage by solid-phase extraction and liquid chromatography tandem mass spectrometry. *J. Chromatogr., A.* **2007**, *1148*, 158–167.
(23) Paxeus, N. Removal of selected non-steroidal anti-inflammatory drugs (NSAIDs), gemfibrozil, carbamazepine, beta blockers, trimethoprim and triclosan in conventional wastewater treatment plants in five EU countries and their discharge to the aquatic environment. *Water Sci. Technol.* **2004**, *50*, 253–260.
(24) Andreozzi, R.; Campanela, L.; Fraysse, B.; Garric, J.; Gonnella, A.; Lo Giudice, R.; Marotta, R.; Pinto, G.; Pollio, A. Effects of advanced oxidation processes (AOPs) on the toxicity of a mixture of pharmaceuticals. *Water Sci. Technol.* **2004**, *50*, 23–28.
(25) Ternes, T. A.; Stuber, J.; Herrmann, N.; McDowell, D.; Ried, A.; Kampmann, M.; Teiser, B. Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater. *Water Res.* **2003**, *37*, 1976–1982.
(26) Ternes, T. A.; Meisenheimer, M.; McDowell, D.; Sacher, F.; Brauch, H.-J.; Haist-Gulde, B.; Preuss, G.; Wilme, U.; Zulei-Seibert, N. Removal of pharmaceuticals during drinking water treatment. *Environ. Sci. Technol.* **2002**, *36*, 3855–3863.
(27) Mulla, R. M.; Kulkarni, R. M.; Nandibewoor, S. T. Kinetic and mechanistic investigation of oxidative degradation and deamination of atenolol by diperiodatonickelate(IV) in aqueous alkaline medium. *J. Chem. Res. (S)* **2003**, *6*, 315–316.
(28) Whitham, K.; Lyons, S.; Miller, R.; Nett, D.; Treas, P.; Zante, A.; Fessenden, R. W.; Thomas, M. D.; Wang, Y. *IEEE Proceedings Particle Accelerator Conference and International Conference on High Energy Accelerators* EEE Operations Center; Laurie Gennari Publishers: Dallas, TX, 1996; p. 131.
(29) Buxton, G. V.; Stuart, C. R. Re-evaluation of the thiocyanate dosimeter for pulse radiolysis. *J. Chem. Soc. Faraday, Trans.* **1995**, *91*, 279–281.
(30) Buxton, G. V.; Greenstock, C. L.; Helman, W. P.; Ross, A. B. Critical review of rate constants for reactions of hydrated electrons, hydrogen atom and hydroxyl radicals (OH/O) in aqueous solutions. *J. Phys. Chem. Ref. Data* **1988**, *17*, 513–886.
(31) Spinks, J. W. T.; Woods, R. J. In *An Introduction to Radiation Chemistry*; John Wiley & Sons: NY, 1964.
(32) Merga, G.; Schuchmann, H. P.; Rao, B. S. M.; Von Conntag, C. OH radical-induced oxidation of chlorobenzene in aqueous solution in the absence and presence of oxygen. *J. Chem. Soc. Faraday Trans. 2* **1996**, *6*, 1097–1103.
(33) Merga, G.; Rao, B. S. M.; Mohan, H.; Mittal, J. P. Reactions of OH and $SO_4^{\bullet-}$ with some halobenzenes and halotoluenes: A radiation chemical study. *J. Phy. Chem.* **1994**, *98*, 9158–9164.
(34) Kurata, T.; Watanabe, Y.; Katoh, M.; Sawaki, Y. Mechanism of aromatic hydroxylation in the Fenton and related reactions. One-electron oxidation and the NIH shift. *J. Am. Chem. Soc.* **1988**, *110*, 7472–7478.
(35) LaVerne, J. A.; Pimblott, S. M. Yields of hydroxyl radical and hydrated electron scavenging reactions in aqueous solutions of biological interest. *Radiat. Res.* **1993**, *135*, 16–23.
(36) Sharma, S. B.; Mudaliar, M.; Rao, B. S. M. Radiation chemical oxidation of benzaldehyde, acetophenone, and benzophenone. *J. Phy. Chem. A* **1997**, *101*, 8402–8408.
(37) Mezyk, S. P.; Neubauer, T. J.; Cooper, W. J.; Peller, J. R. Free-radical-induced oxidative and reductive degradation of sulfa drugs in water: Absolute kinetics and efficiencies of hydroxyl radical and hydrated electron reactions. *J. Phys. Chem. A* **2007**, *111*, 9019–9024.
(38) Haag, W. R.; Yao, C. C. D. Rate constants for reaction of hydroxyl radicals with several drinking water contaminants. *Environ. Sci. Technol.* **1992**, *26*, 1005–1013.
(39) Escher, B. I.; Bramaz, N. M., R.; Lienert, J. Comparative ecotoxicological hazard assessment of beta-blockers and their human metabolites using a mode-of-action-based test battery and a QSAR approach. *Environ. Sci. Technol.* **2006**, *40*, 7402–7408.
(40) Westerhoff, P.; Mezyk, S. P.; Cooper, W. J.; Minakata, D. Electron pulse radiolysis determination of hydroxyl radical rate constants with Suwannee River fulvic acid and other dissolved organic matter isolates. *Environ. Sci. Technol.* **2007**, *41*, 4640–4646.

ES702245N