Free-Radical Destruction of β-Lactam Antibiotics in Aqueous Solution

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Many pharmaceutical compounds and metabolites are being found in surface and ground waters, indicating their ineffective removal by conventional wastewater treatment technologies. Advanced oxidation/reduction processes (AO/RPs), which utilize free-radical reactions to directly degrade chemical contaminants, are alternatives to traditional water treatment. This study reports the absolute rate constants for reaction of three β-lactam antibiotics (penicillin G, penicillin V, amoxicillin) and a model compound (+)-6-aminopenicillanic acid with the two major AO/RP reactive species: hydroxyl radical (•OH) and hydrated electron (e^-_{aq}). The bimolecular reaction rate constants (M^{-1} s^{-1}) for penicillin G, penicillin V, amoxicillin, and (+)-6-aminopenicillanic acid for •OH were $(7.97 \pm 0.11) \times 10^9$, $(8.76 \pm 0.28) \times 10^9$, $(6.94 \pm 0.44) \times 10^9$, and $(2.40 \pm 0.05) \times 10^9$ and for e^-_{aq} were $(3.92 \pm 0.10) \times 10^9$, $(5.76 \pm 0.24) \times 10^9$, $(3.47 \pm 0.07) \times 10^9$, and $(3.35 \pm 0.06) \times 10^9$, respectively. To provide a better understanding of the decomposition of the intermediate radicals produced by hydroxyl radical reactions, transient absorption spectra were observed from 1 to 100 μs. In addition, preliminary degradation mechanisms and major products were elucidated using ^{137}Cs 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 studies of their fate and transport in surface waters where radical chemistry may be important in assessing their lifetime.

Introduction

Incomplete removal of pharmaceutical compounds and personal care products (PPCPs) during the wastewater treatment process has led to the detection of PPCPs in a variety of surface and ground waters throughout the world. These compounds are therefore receiving an increased amount of attention as an emerging class of environmental pollutants. PPCPs may pose an environmental threat because they are designed to have a specific physiological effect on humans or animals.

Studies concerning PPCPs in aquatic environments have clearly shown that their removal by municipal wastewater treatment plants is often incomplete.[1] In drinking water treatment, removal of PPCPs by activated carbon can be an effective process; however, depending on the water quality, relatively high carbon loading may be necessary. For example, activated carbon systems may experience rapid breakthrough and therefore reduced efficiency due to the presence of natural organic matter.[2] Ozonation can destroy some PPCPs in raw and/or clarified water; unfortunately, the competition between PPCPs and organic material in the raw water may lead to rapid depletion of ozone, resulting in incomplete oxidation of PPCPs.[3]

Advanced oxidation/reduction processes (AO/RPs) are alternatives to traditional treatment and have recently received considerable attention for PPCPs removal.[4] AO/RPs typically involve formation of hydroxyl radicals (•OH) as oxidizing species and 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 water or wastewater. AO/RPs are effective in the treatment of a variety of anthropogenic pollutants including PPCPs.[5–7] However, to provide a fundamental understanding of the applicability of these processes in the degradation of PPCPs, it is necessary to determine the bimolecular reaction rate constants between the reactive species and the chemicals of interest.

Degradation rates and free-radical processes are also relevant in the natural environment where the fate of PPCPs in waters has attracted increasing attention. While biodegradation may be important in surface water,[8] it is likely that abiotic processes, such as phototransformation[9–11] and partitioning to sediments,[12,13] may actually have a greater impact on reducing aqueous concentrations of PPCPs. Hydroxyl radicals, especially in photosensitized oxidation, may be important and lead to environmental degradation.[14]

β-Lactam antibiotics have been chosen as the subject of this study because of their large sales volume in Europe and the United States.[15] Several studies have indicated that these antibiotics are practically nonbiodegradable and have the potential to survive wastewater treatment. These properties can be expected to lead to the persistence of these compounds in the environment and potential for bioaccumulation.[16–18]

The objective of this study was to determine the absolute rate constants for the reaction of the •OH and e^-_{aq} with the three β-lactam antibiotics: penicillin G, penicillin V, and amoxicillin. All three compounds have an identical core structure, (+)-6-aminopenicillanic acid (APA). Therefore, APA was also studied to provide additional insights into the degradation pathways. In this research, transient free-radical spectra produced by the hydroxyl radical reaction with these three compounds were recorded over a time period of 1−100 μs after irradiation to provide a better understanding of the nature of the intermediate radical species produced. Finally, product studies of the free-radical-induced degradation of these β-lactam antibiotics result-

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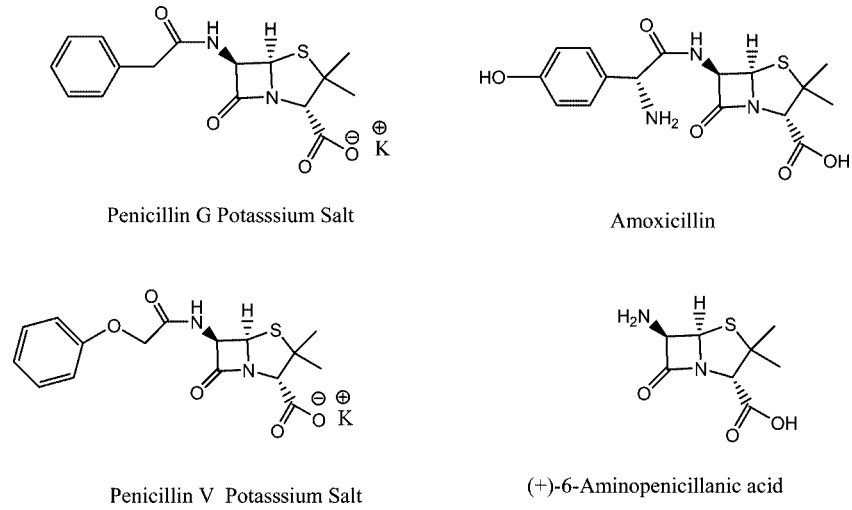

Figure 1. Structures of the β-lactam antibiotics and the model compound.

SCHEME 1

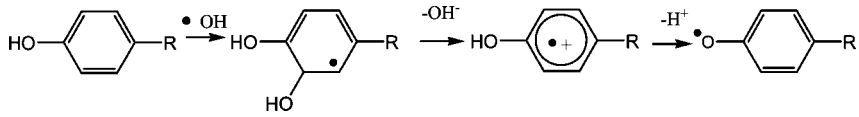

TABLE 1: Measured Rate Constants (M^{-1} s^{-1}) and Spectral Parameters for Hydroxyl Radical and Hydrated Electron Reaction with β-Lactam Antibiotics and a Model Compound

	penicillin G	penicillin V	amoxicillin	(+)-6-aminopenicillanic acid
$^{\bullet}OH$ λ_{max} (nm)	320	320	350	no transient absorbance
ϵ_{max} ($M^{-1}cm^{-1}$)	3300	3350	3200	
$k_{^{\bullet}OH}$ (10^9 $M^{-1}s^{-1}$)	7.97 ± 0.11	8.76 ± 0.28	6.94 ± 0.44	2.40 ± 0.05
$k_{e^-_{aq}}$ (10^9 $M^{-1}s^{-1}$)	3.92 ± 0.10	5.76 ± 0.24	3.47 ± 0.07	3.35 ± 0.06

ing from γ irradiation in aerated solutions were conducted to provide preliminary insight into the mechanisms that might occur under typical water treatment conditions.

Methods and Materials

Materials. The β-lactam antibiotic pharmaceuticals penicillin G, penicillin V, and amoxicillin and the model compound (+)-6-aminopenicillanic acid (APA) were purchased from Sigma-Aldrich (≥99% purity). Their chemical structures are shown in Figure 1. Solutions were prepared using water filtered through a Millipore Milli-Q system that includes constant illumination with a Xe arc lamp at 172 nm to keep total organic carbon concentrations below 13 μg L^{-1}. All kinetic 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 (for 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.[19] Dosimetry[20] 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 8−15 replicate pulses using the continuous flow mode of the instrument.

The radiolysis of water is described in eq 1

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

where the numbers in parentheses are the G values (μmol J^{-1}).[21,22] To study only the reactions of the hydroxyl radical, solutions were presaturated with nitrous oxide (N_2O), which quantitatively converts the e^-_{aq} and hydrogen atoms ($H^{\bullet}$) to $^{\bullet}OH$ via the reactions[21]

$$e^-_{aq} + N_2O + H_2O \rightarrow N_2 + HO^- + {}^{\bullet}OH \quad k_1 = 9.1 \times 10^9\ M^{-1}\ s^{-1} \quad (2)$$

$$H^{\bullet} + N_2O \rightarrow {}^{\bullet}OH + N_2 \quad k_2 = 2.1 \times 10^6\ M^{-1}\ s^{-1} \quad (3)$$

To isolate e^-_{aq}, 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[21]

$$(CH_3)_2CHOH + {}^{\bullet}OH \rightarrow (CH_3)_2C^{\bullet}OH + H_2O \quad k_3 = 1.9 \times 10^9\ M^{-1}\ s^{-1} \quad (4)$$

$$(CH_3)_2CHOH + H^{\bullet} \rightarrow (CH_3)_2C^{\bullet}OH + H_2 \quad k_4 = 7.4 \times 10^7\ M^{-1}\ s^{-1} \quad (5)$$

^{137}Cs gamma-ray irradiations (662 kV radiation) were performed using a J. L. Shepherd Mark I model A68 Irradiator which has a fixed central rod source in a 30 cm diameter × 33

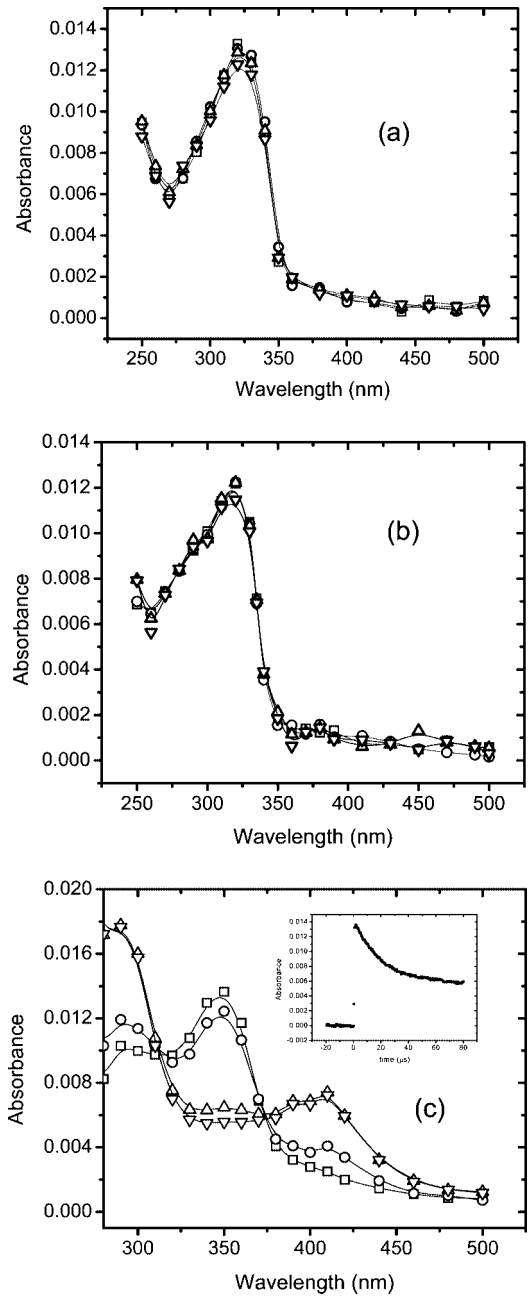

Figure 2. Transient absorption spectra obtained from electron pulse radiolysis of N_2O-saturated solutions of penicillin G (a), penicillin V (b), and amoxicillin (c): 1 (□), 5 (○), 50 (Δ), and 100 μs (∇). The insert on c shows the decay trace of the intermediate of amoxicillin observed at 350 nm.

cm high cavity. Samples could be placed reproducibly in glass test tubes in a rack at varying distances from the source guide tube to provide dose rates varying from 4.2×10^3 (0.42) to 5×10^2 Gy/h (0.05 Mrad/h).

HPLC and LC−MS Analysis. The β-lactam antibiotics 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 60% CH_3OH and 40% 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 an electrospray ionization source. A sample volume of 10 μL was injected onto 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% acetic acid and (B) CH_3CN + 0.2% acetic acid.

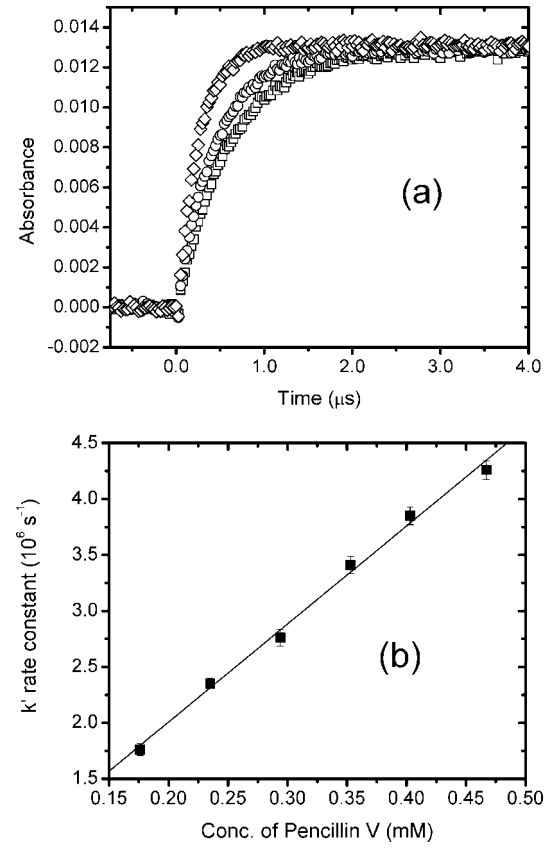

Figure 3. (a) Typical growth kinetics of transient absorption at 320 nm in a pulse-irradiated solution at pH 7.0 and room temperature for 0.467 (◇), 0.235 (○), and 0.176 (□) mM pencillin V. (b) Second-order rate constant determination for the reaction of hydroxyl radicals with penicillin V at 320 nm (■). Solid line corresponds to the value of the overall rate constant $k = (8.76 \pm 0.28) \times 10^9$ M^{-1} s^{-1}.

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. Mass spectra (*m*/*z* 100−350) were obtained in negative-ion mode.

Results and Discussion

•OH Transient Spectra. All of the three β-lactam antibiotics reacted with the •OH to give transient absorption spectra (Figure 2), but no transient absorption spectrum was observed for APA. The hydroxyl radical was apparently reacting rapidly with the aromatic ring in the side chain of penicillin V, penicillin G, and amoxicillin. The reaction process usually adds onto the aromatic ring to form hydroxycyclohexadienyl radical that displays strong absorption in the 300−350 nm range.[23,24] The spectra obtained for the transients from reaction of penicillin G and penicillin V with the hydroxyl radical were generally similar; both intermediates were relatively stable on the 100 μs time scale.

The transient absorption spectra of amoxicillin (Figure 2c) exhibited a peak at 350 nm, which decayed following first- order kinetics, with a rate of 5×10^4 s^{-1} (Figure 2c, insert). The isosbestic point at 375 nm suggests that a second intermediate was produced with a λ_{max} at 410 nm. It is possible that the initial formation of dihydroxyl benzene radical for amoxicillin is less stable than addition to the nonhydroxyl-substituted ring as in the other two penicillin compounds. Similar results have been observed in the •OH oxidation of phenol.[25,26] It is believed that hydroxycyclohexadienyl phenol follows, eliminating H_2O, forming oxygen radical via the pathway shown in Scheme 1.

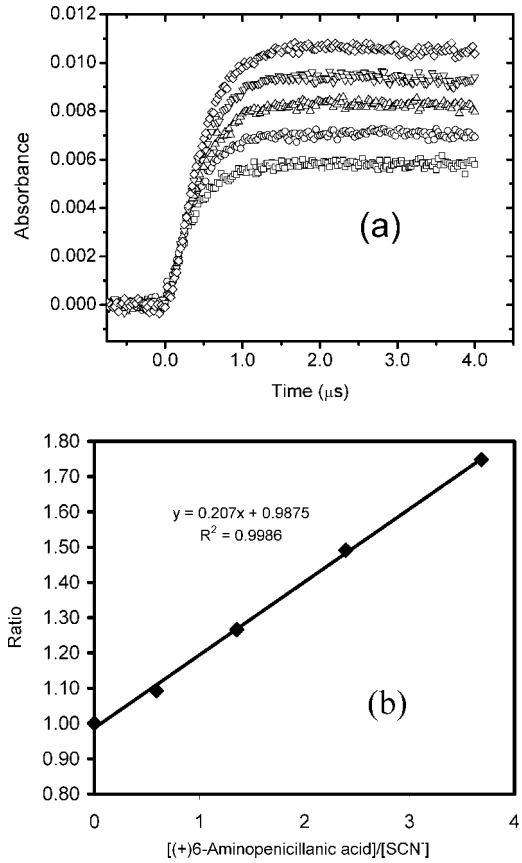

Figure 4. (a). Kinetics of $(SCN)_2^{\bullet -}$ formation at 472 nm for N_2O-saturated 2.92×10^{-4} M KSCN solution containing 0 (◊), 0.17 (▽), 0.39 (Δ), 0.69 (○), and 1.0 (□) mM (+)-6-aminopenicillanic acid at pH 7.0 and room temperature. (b) Competition kinetics plot for hydroxyl radical reaction with 6-aminopenicillanic acid using SCN^- as a standard. Solid line is a weighted linear fit with a slope of 0.207 ± 0.004. This gives a second-order rate constant for 6-aminopenicillanic acid reaction as $(2.40 \pm 0.05) \times 10^9$.

λ_{max} for all three intermediates including the initial intermediate formed by amoxicillin was red shifted by 30−50 nm compared to the λ_{max} of the parent compounds. Such a shift suggests that the •OH has added into the aromatic ring, resulting in extended conjugation in these systems as noted previously in studies of •OH reactions with other substituted benzene species.[27] Peak absorption coefficient values are given in Table 1. They were calculated using a hydroxyl radical initial *G* value of 0.59 μmol J^{-1}, a value based upon the intraspur scavenging model calculations of LaVerne and Pimblott.[28]

Kinetic Measurements. The bimolecular reaction rate constants for •OH reaction with the three β-lactam antibiotics have been determined from the rate of absorption change with concentration at the λ_{max}. Typical kinetic data for penicillin V are given in Figure 3a. These were processed using the procedures outlined by Mezyk et al.[29] 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-lactam antibiotics (Figure 3b) to obtain the rate constants summarized in Table 1.

The range $(6.9-8.7 \times 10^9\ M^{-1}\ s^{-1})$ of the rate constants for hydroxyl radical reaction with the penicillins and amoxicillin was comparable to previous rate constant measurements for hydroxyl radical reaction with benzene $(7.5-7.8 \times 10^9\ M^{-1}\ s^{-1})$ and phenol $(6.6 \times 10^9\ M^{-1}\ s^{-1})$.[21] Kinetic modeling and degradation mechanisms for benzene and phenol have been

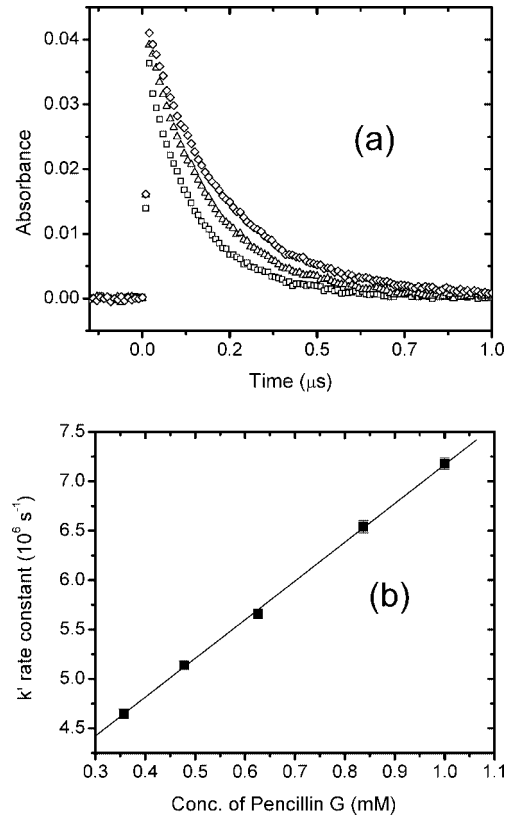

Figure 5. (a) Typical decay kinetics for hydrated electron reduction (measured at 700 nm) for 1.00 (□), 0.626 (Δ), and 0.357 (◊) mM penicillin G at pH = 7.0 and room temperature. (b) Second-order rate constant determination for reaction of the hydrated electron with penicillin G. The straight line is the weighted linear plot with a slope of 3.92 ± 0.10.

reported.[25,26] This further supports our assignment of the initial reaction being formation of hydroxycyclohexadienyl radicals. The rate constant of amoxicillin is the slowest of the three β-lactam antibiotics, reflecting to the influence of −OH, as noted above for phenol. The slight increase from penicillin G ((7.97 ± 0.11) × 10^9 M^{-1} s^{-1}) to penicillin V ((8.76 ± 0.28) × 10^9 M^{-1} s^{-1}) is consistent with the more electron-donating RO— side chain group, as noted previously for other aromatic compounds.[30]

To further explore the role of •OH and its reactivity with different functional groups, APA was selected as a model compound that is the core of the β-lactam antibiotics. Reaction of hydroxyl radical with APA did not generate any significant intermediate absorption spectra, and therefore, the rate constant was determined using SCN^- competition kinetics based on monitoring the $(SCN)_2^{\bullet -}$ absorption at 472 nm. Equations 6 and 7 show the respective reaction of APA and SCN^- with OH radical

$$^{\bullet}OH + APA \xrightarrow{K_5} H_2O + \text{intermediate} \quad (6)$$

$$^{\bullet}OH + SCN^- (+SCN^-) \xrightarrow{K_6} OH^- + (SCN)_2^{\bullet -} \quad (7)$$

This competition can be analyzed to give the expression

$$\frac{[(SCN)_2^{\bullet -}]_0}{[(SCN)_2^{\bullet -}]} = 1 + \frac{K_5[APA]}{K_6[SCN^-]} \quad (8)$$

where $[(SCN)_2^{\bullet -}]_0$ is the absorbance of this transient at 472 nm when only SCN^- is present and $[(SCN)_2^{\bullet -}]$ is the reduced yield

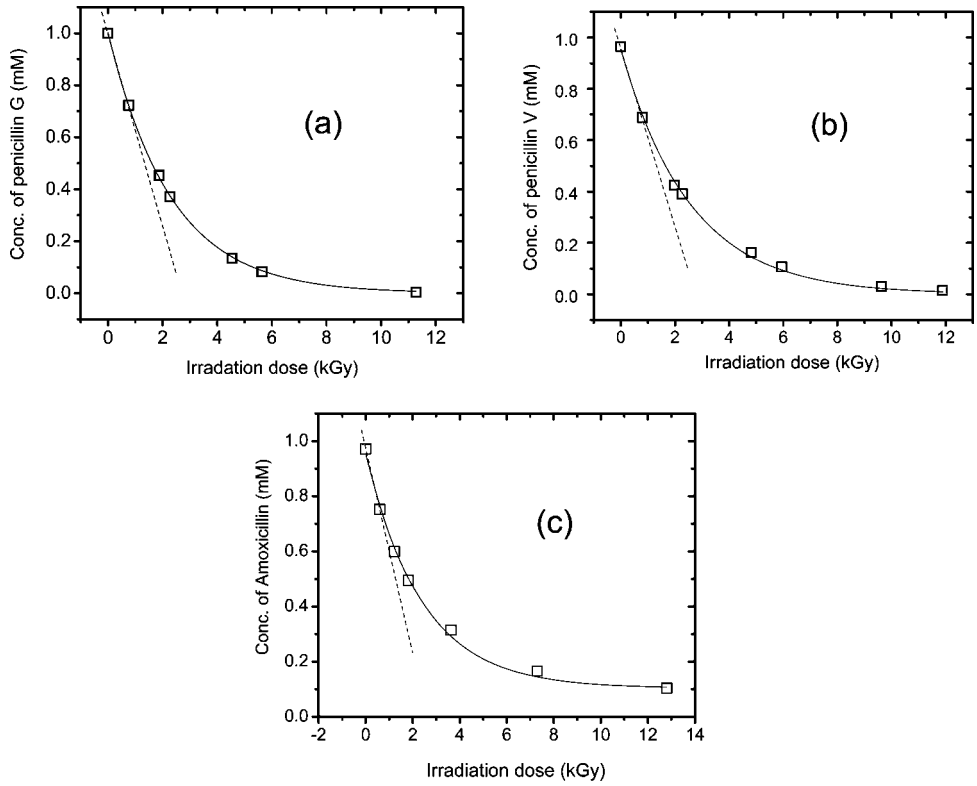

Figure 6. Measured loss of penicillin G (a), penicillin V (b), and amoxicillin (c) in aerated aqueous solutions using ^{137}Cs γ irradiation. Curves correspond to fitted exponential loss, while dashed straight lines are the estimated initial slope values of $k = -3.69 \times 10^{-4}$, -3.47×10^{-4}, and -3.71×10^{-4} M kGy^{-1} for penicillin G, penicillin V, and amoxicillin, respectively.

of this transient when the APA is present. Therefore, a plot of $[(SCN)_2^{\bullet-}]_0/[(SCN)_2^{\bullet-}]$ against the ratio [APA]/[SCN$^-$] should give a straight line of slope k_5/k_6. On the basis of the established rate constant for hydroxyl radical reaction with SCN$^-$, $k_6 = 1.05 \times 10^{10}$ M^{-1} s^{-1}, the rate constant (k_5) for APA can be calculated.

Kinetic data obtained at 472 nm are shown in Figure 4, and as expected, a decrease in the maximum $(SCN)_2^{\bullet-}$ absorption intensity was observed when increasing amounts of APA were added. The transformed plot shown in Figure 4b gives a weighted linear fit corresponding to a reaction rate constant of $k_5 = (2.40 \pm 0.05) \times 10^9$ M^{-1} s^{-1}.

The hydroxyl radical rate constant of APA is significantly lower than that of the β-lactam antibiotics, which suggests that reaction of the APA moiety of the antibiotics was only a minor component of the overall $^{\bullet}$OH oxidation. On the basis of the rate constants of the APA core and the three antibiotics, only 30% (2.40/7.97), 25% (2.40/8.76), and 35% (2.40/6.94) of the $^{\bullet}$OH are capable of reacting with the APA core of the penicillin G, penicillin V, and amoxicillin, respectively.

The rate constants for hydrated electron reaction with the three β-lactam antibiotics and APA were measured by directly monitoring the change in the absorption of e^-_{aq} at 700 nm in nitrogen-saturated solutions at pH 7.0,[29] as shown in Figure 5 for penicillin G. The decay curves (Figure 5a) were fitted to pseudo-first-order exponential kinetics, giving the second-order linear plot shown in Figure 5b. The slope of such a plot is the second-order rate constant for e^-_{aq} reduction of penicillin G.

The bimolecular reaction rate constants are summarized in Table 1. The hydrated electron rate constants for β-lactam antibiotics are ~100 times faster than for benzene ($0.7-1.3 \times 10^7$ M^{-1} s^{-1}). The difference of 2 orders of magnitude and the similarity to the rate of the model-APA suggest that most of the hydrated electron reactions must be occurring with that core

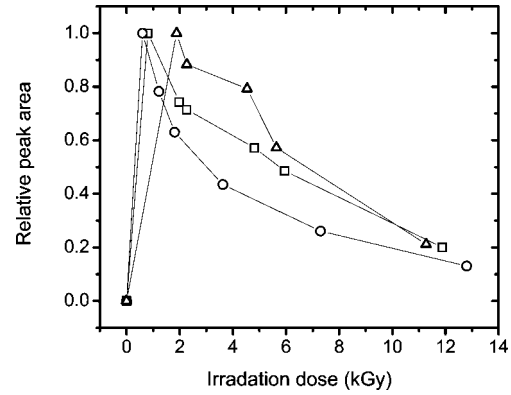

Figure 7. LC-MS relative peak areas for phenolic products (M + 16) of β-lactam antibiotics with respect to γ-radiation dose: penicillin G (Δ), penicillin V (□), and amoxicillin (○).

part of the antibiotics. A comparison of the rate constants of the APA and the three β-lactam antibiotics shows 85% (3.35/3.92), 58% (3.35/5.76), and 97% (3.35/3.47) of the e^-_{aq} reacting with the APA moiety present in penicillin G, penicillin V, and amoxicillin, respectively.

Steady-State Irradiation and Reaction Product Information. In addition to the reaction kinetics for the two reactive species with the three β-lactam antibiotics, steady-state experiments were performed using ^{137}Cs radiolysis to determine the efficiency of these radicals in the degradation of the β-lactam antibiotics. Steady-state irradiation of these antibiotics in aerated aqueous solutions resulted in decreases in concentration as the doses were increased (Figure 6). The curvature of the plots was consistent with previously reported irradiation studies for other contaminants in water.[31–33] The curves indicate competition for the reactive species ($^{\bullet}$OH and e^-_{aq}) between the parent β-lactam antibiotics and the reaction

products generated as the dose increased. The degradation profiles of the three β-lactam antibiotics were fitted using exponential decay kinetics, giving the dose for 50% removal, 2.30 ± 0.02, 2.41 ± 0.11, 2.56 ± 0.06 kGy for penicillin V, penicillin G, and amoxicillin, respectively. These values are consistent with the increasing trend observed for the hydroxyl radical rate constants.

Using the lowest dose measurements, it is possible to obtain an estimate of the initial slope for the individual antibiotics as illustrated by the straight lines in Figure 6. These lines correspond to removal of the individual β-lactam antibiotics, assuming that no interference from stable products occurred. At the early doses of the experiments all hydroxyl radicals will react with the antibiotics, while the hydrated electron will react with both the antibiotic and the dissolved oxygen present

$$e_{aq}^- + O_2 \rightarrow O_2^{\bullet -} \quad k_7 = 1.9 \times 10^{10}\ M^{-1}\ s^{-1} \qquad (9)$$

On the basis of the reaction rate constants and the known concentrations of the antibiotics and O_2 (assumed 2.5×10^{-4} M), it can be calculated that 55%, 45%, and 41% of the initial e^-_{aq} will react with the penicillin V, penicillin G, and amoxicillin, respectively. From the $^{\bullet}OH$ and e^-_{aq} yield G values (see eq 1), theoretical initial degradation rates of -4.3×10^{-4}, -4.0×10^{-4}, and -3.9×10^{-4} M kGy^{-1} can be calculated for penicillin V, penicillin G, and amoxicillin, respectively. In combination with the experimentally measured slopes (figure 6), we concluded that combination of the $^{\bullet}OH$ and e^-_{aq} reactions with penicillin V, penicillin G, and amoxicillin occur with 81%, 92%, and 95% efficiency, respectively.

Product Analysis. LC-MS analyses of the irradiation products for various γ-irradiation doses revealed several decomposition products at detectable concentrations. The rates of reaction of $^{\bullet}OH$ with the different reaction sites present in β-lactam antibiotics are expected to vary significantly; however, addition to the aromatic side chain predominates.[21] Three main products (separated by HPLC) with the same MW of 350 were observed from the reaction of $^{\bullet}OH$ with penicillin G (MW = 334), and these were assigned as isomeric monohydroxyl derivatives, consistent with hydroxylation of the aromatic ring. 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 to give the phenolic products.[34] Similarly for penicillin V, three monohydroxyl degradation products were observed, while one dihydroxyl product was formed for amoxicillin. The relative amounts of phenolic products of β-lactam antibiotics with respect to γ-radiation dose are shown in Figure 7. The phenolic products (MW + 16) are the main products which reach their maximum concentrations at approximately 1−2 kGy, after that they decline presumably because of continued reaction of these products with radicals. This result suggests that with increasing irradiation dose, continued degradation of products will occur and issues related to their toxicity should not be significant, but this will be further evaluated as these product species are identified.

Implications. The absolute bimolecular reaction rate constants for reaction of two major AO/RP reactive species with penicillin V, penicillin G, and amoxicillin have been measured: for $^{\bullet}OH$ were $(8.76 \pm 0.28) \times 10^9$, $(7.97 \pm 0.11) \times 10^9$, and $(6.94 \pm 0.44) \times 10^9$ and for e^-_{aq} were $(5.76 \pm 0.24) \times 10^9$, $(3.92 \pm 0.10) \times 10^9$, and $(3.47 \pm 0.07) \times 10^9$, respectively. The measured rate constants are consistent with hydroxyl radical reaction predominantly at the aromatic ring moiety, while solvated electron reactions occur at the APA core moiety.

The major degradation pathway arising from γ irradiation of β-lactam antibiotics appears to involve hydroxyl radical addition to the benzene ring to form mixtures of phenolic compounds. These results indicate that advanced oxidation processes involving production of $^{\bullet}OH$ radicals are attractive treatment methods for degradation of β-lactam antibiotics in aqueous solution. However, it would be necessary to undertake a careful evaluation of the toxicity of the degradation products and their related intermediate species before any practical implementation of such a treatment method.

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