ABSTRACT

JONES, KIMBERLY GREENWOOD. Applications of Radiation Chemistry to Understand the Fate and Transport of Emerging Pollutants of Concern in Coastal Waters. (Under the direction of William J. Cooper and Daniel L. Kamykowski.)

Absolute rate constants for hydroxyl radical, $^{\cdot}OH$, and hydrated electron, e^{-}_{aq}, reactions with environmental pollutants of concern, EPOCs, in water at room temperature were measured using the techniques of electron pulse radiolysis and transient absorption spectroscopy. Twenty bimolecular $^{\cdot}OH$ rate constants, k ($M^{-1}s^{-1}$), were obtained, with many first reported, such as the algal toxins; domoic acid $(9.45\pm0.035) \times 10^9$ and kainic acid $(2.46\pm0.029) \times 10^9$, pharmaceuticals; nadolol $(3.38\pm0.46) \times 10^8$, tylosin $(8.64\pm0.78) \times 10^9$, and trimethoprim $(1.13\pm0.02) \times 10^{10}$, $(8.13\pm0.12) \times 10^9$. Hydrated electron reaction rate constants for seven EPOCs; chloramphenicol, diclofenac, ibuprofen, ketoprofen, naproxen, trimethoprim and vanillin were determined via pulse radiolysis.

The hydroxyl radical oxidatively decomposes pollutants, while the hydrated electron is a powerful reducing agent, particularly breaking down halogenated pollutants. Domoic acid model compounds were analyzed and compared for their reaction rates with the hydroxyl radical. Domoic acid was found to have a relatively rapid $^{\cdot}OH$ rate constant that should lead to high removal efficiency in advanced oxidative processes. The chemical kinetics of the free-radical-induced degradation were used to determine potential persistence in natural water systems. Using the bimolecular rate constants generated in this study, as well as those being compiled in databases, it is possible to calculate the relative importance of the three primary products of water radiolysis on the removal of some organic compounds of interest.

APPLICATIONS OF RADIATION CHEMISTRY TO UNDERSTAND THE FATE AND TRANSPORT OF EMERGING POLLUTANTS OF CONCERN IN COASTAL WATERS

by
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DEDICATION

To my husband, Scott, for the immense patience, support, love, and encouragement throughout my many years of studies; and to my father, William Roland “Bud” Greenwood, for giving me a touch of his incredible courage, and for taking such pride in my accomplishments.

BIOGRAPHY

Kimberly Jean Greenwood was born in Fort Benning, Georgia, on 19 May 1965, to William Roland and Shirley Grace Brown Greenwood. She married Scott Lewis Jones on 4 August 1984. In 1987, Kimberly Jones graduated from the University of North Carolina at Wilmington with a Bachelor of Arts degree in Chemistry and Biology. While pursuing the BAs, she represented UNCW on its Division I volleyball team. Her work experience includes a researcher in the Biology Lab at Carolina Power & Light Nuclear Plant, Southport, North Carolina. The Jones family was blessed with a baby girl, Calley Grace, on 9 June 1988. Hobbies included playing on the semi-pro beach doubles volleyball circuit, and stained glass. In 1989, Mrs. Jones entered the masters program in Chemistry at the University of North Carolina at Wilmington. On 27 November 1991, the family was again blessed with a baby boy, Robert Lewis. Additional work experiences came in the form of teaching assistantships at the university. Kim completed thesis work on bioactive marine natural products, and graduated with a MS in Chemistry in July 1993. In 1994, work began in the Cooperative PhD Program with UNC-Wilmington and North Carolina State University in Marine Science. Again the family was blessed with a baby boy, William Scott, on 11 May 1996. Work at Brunswick Community College (BCC) began part time in the fall of 1998, and progressed to full time chemistry instructor in 1999, Chair of the Sciences in 2001, Director of College Transfer & Developmental Programs in 2003, and Grants Development Director in 2007. Kimberly, Scott, and their three children happily reside in Southport, North Carolina.

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Chapter 1 Introduction

In the face of conflicting demands of today's society, water quality is the most essential environmental concern of the 21st century. A global priority must be the protection of both our fresh and salt water resources. Environmental water quality, and drinking water availability and quality are the focus of intense research. A key aspect of drinking water safety is ensuring that sources of drinking water, such as rivers, aquifers, and even the ocean, are protected from contamination. The class of compounds, known as the persistent organic pollutants (POPs), has received a great deal of attention, and many issues have been addressed through regulation. Recent reports have indicated that a surprisingly wide variety of pharmaceuticals and personal care products are entering the aquatic environment. Their bioactivity has been shown to be very potent at very low concentrations. Determining the extent and persistence of these compounds, emerging pollutants of concern (EPOCs), has been a recent growth area in environmental chemistry.

The growing group of compounds that are referred to as emerging pollutants of concern (EPOCs) may be produced biologically in situ, such as toxins produced from algal blooms; or be anthropogenic in nature, such as pharmaceuticals and pesticides. Mass prescription and mass consumption, with conventional medicine and pharmaceutical companies encouraging millions upon millions of people to take drugs, make the environmental impact of pharmaceuticals quite large. Most of these drugs are synthetically produced and highly potent to biological systems. A pharmaceutical

example of an EPOC, used for both human medicinal practice and as an animal feedstock additive, would be tetracycline. Tetracyclines are called "broad-spectrum" antibiotics, because they can be used to treat a wide variety of infections. Physicians may prescribe these drugs to treat eye infections, acne, pneumonia, Gonorrhea, Rocky Mountain spotted fever, urinary tract infections, and other infections caused by bacteria. Bioavailability studies of tetracycline hydrochloride given to adult males show that on average, more than 50% is excreted in the urine for each 250 mg tablet consumed [1]. Animals also excrete more than half of what is added to their feed, with hogs representing the largest fraction, nearly 70%, given the antibiotic supplements. In 2005, Environmental Defense reported that two states, North Carolina and Iowa, are each estimated to use three million pounds of antibiotics as feed additives annually; the same quantity estimated to be used for human medical treatment ***nationwide*** [2]. Use of antibiotic feed additives is highly concentrated in a few counties; indeed, the highest-use county in the U.S. (Duplin County, NC) is estimated to use more antibiotics as feed additives than 35 states. The environment is seeing a deluge of EPOCs from many sources, and tetracycline is but one example.

Many such compounds pass through waste water treatment plants or are from non-point sources, and flush into natural bodies of water. Three areas of research related to EPOCs are their:

- characterization
- quantification
- **fate and transport**

Many of these compounds tend to have high transformation and removal rates, but many do not need to be persistent in the environment to cause negative effects. These compounds tend to have **high bioactivity with low concentrations**, and are being continuously introduced into the environment. Measuring persistence in the environment may need to begin with redefining whether persistence is how long a chemical stays in a medium and/or if it is continually put into the medium and therefore, is a persistent risk. Multi-variate or Multimedia modeling is a new approach to credibly measuring persistence. Persistence is a key parameter for registering new chemicals, performing risk assessment on existing chemicals, and identifying chemicals of particular concern within international accords, such as the Stockholm Convention on Persistent Organic Pollutants (POPs) [3] and the UN Economic Commission for Europe Convention on Long-Range Transboundary Air Pollution [4]. The following figure, Figure 1.1, demonstrates possible sources and pathways of EPOCs in aquatic systems.

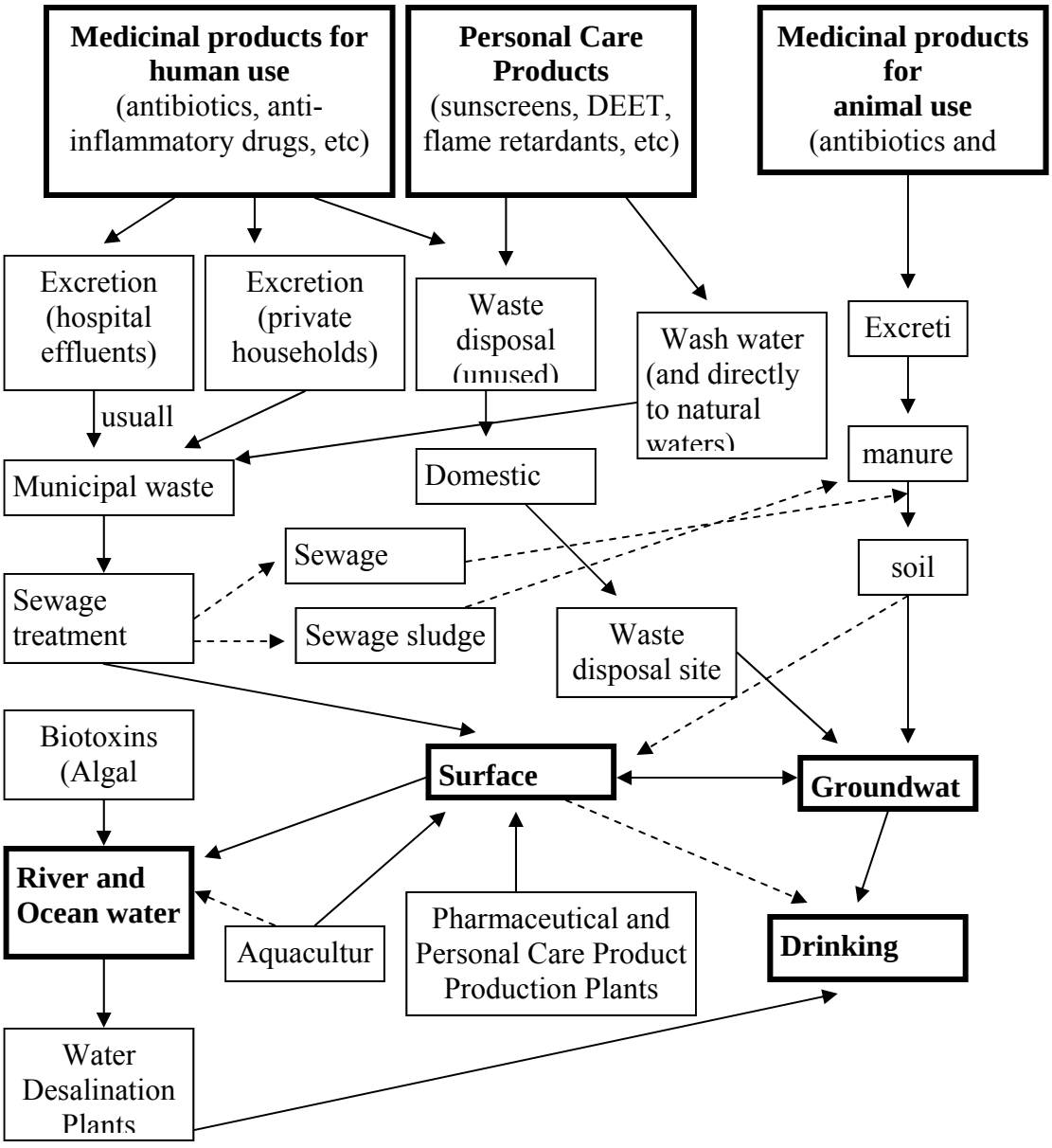


Figure 1.1. Scheme showing possible sources and pathways for the occurrence of pharmaceutical, personal care product, and biotoxin residues in the aquatic environment, as adapted from
Heberer, 2002 [5].

When we look at **fate and transport** in the environment, there are three distinct processes: biological, chemical, and physical. The biological processes focus on microorganisms and nutrient uptake. The physical processes focus on such concerns as particle adsorption, transport, and mixing. The chemical processes focus on equilibrium, solubilities, and redox and surface water reactions (i.e. sunlight mediated photolysis). As advances in analytical methods find the presence of many trace organic contaminants, the ecotoxicity and persistence of these pollutants must be analyzed. Although found in trace quantities in natural systems, these compounds are **extremely bioactive**, and the ecological effects have yet to be determined. The purpose of this investigation is to examine the water-based, free-radical chemistry that mediates the environmental fate of an ever-increasing number of EPOCs.

The increasing analytical ability to detect low concentrations of biologically active, organic compounds in aquatic environments has produced startling evidence of many contaminants, both in the environment and in drinking water [6-9]. The occurrence and fate of these contaminants is an emerging international issue in environmental chemistry. In some investigations carried out in Austria, Brazil, Canada, Croatia, England, Germany, Greece, Italy, Spain, Switzerland, The Netherlands, and the U.S., more than 80 compounds, pharmaceuticals and several drug metabolites, have been detected in the aquatic environment [5]. In a national reconnaissance of contaminants in 2000, 80% of 139 streams sampled throughout the United States were found to contain low concentrations of pharmaceuticals, hormones, and other organic wastewater contaminants [10]. As advances in analytical methods document the

presence of many trace organic contaminants, the ecotoxicity and persistence of these pollutants must be assessed.

It is thought that radical chemistry is important in the fate and transport of many contaminants. Radiation chemistry makes it is possible to isolate reactions of various radicals with the chemicals of interest. Using reaction rates and steady state radical concentrations, pollutant lifetimes in aquatic systems can be estimated [11, 12]. Advanced oxidation processes use free radicals, principally hydroxyl radicals (˙OH), which attack and decompose pollutants. For stable compounds, the free radical processes may be the principle pathway for degradation. An understanding of the kinetics involved and mechanistic details of the hydroxyl radical attack on organic compounds will aid in designing strategies for abating problematic environmental contaminants. "Irradiation of some systems gives rise not only to the degradation of pollutants, but also changes in the physico-chemical properties of the systems. For example, the radiolytic aggregation of fine-disperse particles leads to the formation of precipitates that capture pollutants and act as a removal mechanism" [12]. Reactive intermediates come in many oxidative forms as shown in the following Figure 1.2.

"Indirect"(or "Sensitized") Processes:
A solute (S) other than R absorbs the photon that causes R to be degraded, and the reaction involves a reactive intermediate.

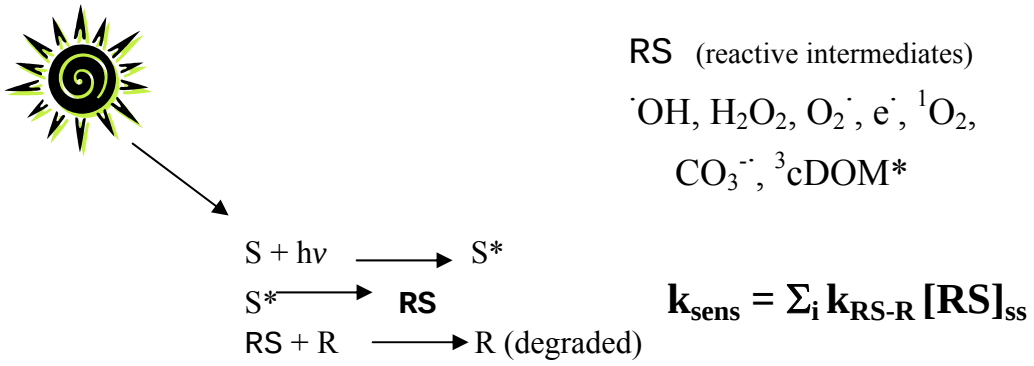


Figure 1.2. Photochemistry of Natural Waters

An additional major concern in any advanced oxidation process is the formation of undesirable chemicals as reaction intermediates [13]. It is not unusual to observe several intermediates with toxicity greater than the parent compound itself.

Pharmaceuticals, and other synthetically produced compounds, are not the only sources of concern [6]. Another area of interest in a growing number of coastal environments is harmful algal bloom toxins. The toxins represent both an ecosystem and human health effect. Another issue that arises for both algal bloom toxins and EPOCs relates to water supply. As one alternative to water supply, desalination is becoming a more widely used alternative to the more tradition sources such as aquifers and lakes. Therefore, if water that is being used as source water is experiencing a bloom, it is possible that these toxins may either be passed to the treated water or concentrated in the untreated water. Key water purification technologies include a wide range of reverse osmosis (RO) and electrodialysis reversal (EDR) systems. Water

would be pulled from the local coastal aquatic environment, seawater and brackish, where there is the possibility of domoic or other EPOCs in the water column. Worldwide, in the late 1990s, there were more than 12,500 desalination plants in operation, generating more than six billion gallons of fresh water per day and accounting for about one percent of the world's daily production of drinking water [14]. Coastal areas make up the majority of these facilities, due to greater efficiency and easier concentrate disposal. If all contaminates that are classified as EPOCs are captured in the concentrate, then what fate does the concentrate have? The majority of coastal desalination plants use surface water discharge, where coastal water can be used to dilute the concentrate, providing an inexpensive and supposedly environmentally benign disposal option. Membrane-based wastewater reclamation is another process by which modeling and understanding the fate of microconstituents is crucial. As the technologies advance, such as high recovery/high pressure membranes for brine conversion in reverse osmosis systems, so will the issues surrounding brine disposal, and the fate of the microconstituents within. Investigating the fate of these compounds is a daunting challenge given the large number of variables in a natural system.

The frequency and intensity of harmful algal blooms has increased, leading to an increased incidence of poisoning of shell fish, large fish kills, and deaths of livestock and wildlife, as well as illness and death in humans exposed [15]. Algal toxins that impact human health are generally categorized as neurotoxins or hepatotoxins that are produced by dinoflagellates, diatoms, and cyanobacteria (blue-green algae). Dinoflagellate and diatom toxins impact humans primarily through the consumption of seafood; cyanobacterial toxins can impact humans through drinking-water

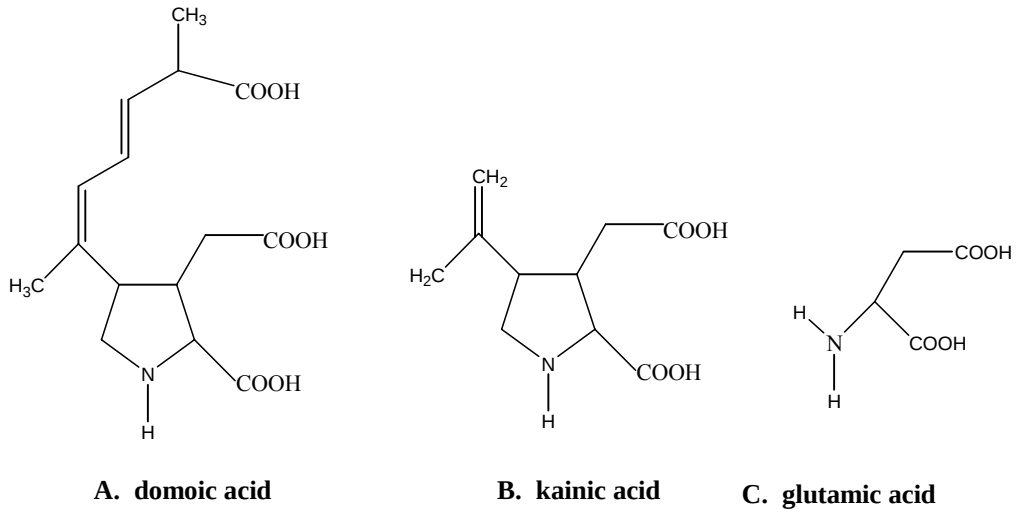
contamination. The presence of specific algal toxins in finished drinking water had not been proved analytically until a recent discovery of cyanobacterial toxins in finished drinking waters in Florida [16] and in a survey of US and Canadian drinking waters sponsored by the American Water Works Association Research Foundation [17]. In the report to the Florida Department of Health, 75 of the 167 Florida surface water bodies sampled contained toxic cyanobacteria blooms, and microcystins, anatoxin-a, and cylindrospermopsin were found and quantified in finished drinking waters at level that exceed proposed human health guidelines [16]. Cylindrospermopsin, from a bloom, was found in a drinking-water reservoir in Australia, following a poisoning episode involving 138 children and 10 adults. The US and Canadian survey (conducted from 1996-1998) reported source and finished drinking waters with 80% of the 677 utility source water samples collected testing positive for microcystins, and 4.3% exceeded WHO drinking-water concentration standards [17]. However, only two of the finished drinking-water samples exceeded the WHO guideline. These recent studies clearly show the need for a better mechanistic understanding as to the fate of these chemical toxins. The focus of this dissertation is using radiation chemistry to study on the oxidation processes that will aide in mechanistic studies for emerging pollutants of concern (EPOCs) and the model of an in situ, biologically produced toxin, domoic acid.

A. Domoic Acid and Its Model Compounds

Domoic acid is a naturally occurring excitatory amino acid, first isolated and identified in the macro red algae *Chondria armata* [18]. At least nine species of the marine diatom genus *Pseudo-nitzschia* are now known to produce domoic acid [19]. Domoic acid was identified as the causative agent in an episode of fatal human poisoning in Prince Edward Island, Canada in 1987 [20]. Following the consumption of mussels, *Mytilus edilus*, more than 100 people were hospitalized with at least four fatalities. Many patients exhibited short-term memory impairment, which prompted the naming of this toxic syndrome as Amnesic Shellfish Poisoning (ASP) [21]. When the algae is consumed, the domoic acid becomes concentrated in the visceral hepatopancreas or gill structures of animals such as oysters, mussels, sardines, scallops, clams, crabs, and anchovies [22], which often act as seafood for other larger animals. Thus, like humans, when loons, grebes, dolphins, sea lions, pelicans, or cormorants [23, 24] then consume this concentrated domoic acid, they may become disoriented and the result is often death. Recent front page articles, July and August 2006, in the Los Angeles Times chronicle humans and marine life alike that are exhibiting classic symptoms of domoic acid poisoning. The articles cite that more than 14,000 seals, sea lions and dolphins have landed sick or dead along the California shoreline in the last decade [25].

Domoic acid is a water soluble member of the Kainoids, a group of neurologically active amino acids that includes another marine metabolite, kainic acid [26]. Much interest has been generated in the kainoids due to all of their potent

biological effects, such as insecticidal [27], anthelmintic, [8, 28] and neuroexcitatory properties [29]. The mechanism of domoic acid toxicity is explained by its structural similarity with the excitatory neurotransmitter glutamic acid and its analogues, see Figure 3, but with a much stronger receptor affinity [30]. Domoic acid is three times more potent than its analogue kainic acid and up to 100 times more potent than glutamic acid itself [31].



A. domoic acid **B. kainic acid** **C. glutamic acid**

Figure 3. Domoic acid and kainic acid are structurally analogous to the excitatory neurotransmitter glutamic acid.

In Asia, *Digenea simplex* is a red alga that has been used as a folk remedy for the treatment of roundworm disease (ascariasis) for many centuries [32]. Domoic acid, first isolated from *Chondria armata*, the same family as *Digenea simplex* (Rhodomelaceae) was also noted as being used for anthelmintic folk medicine and an insecticidal against flies. The active constituent of the *Digenea simplex*, α-kainic acid, has been developed into an anthelmintic drug, and has later been found to have both neurotoxic and neuroexcitatory properties. Today, with other kainoid amino acids, such

as domoic acid, kainic acid is more important as a research reagent in neurophysiology than as a human medicine.

The neurotoxins, domoic acid and kainic acid, have been chosen as *in situ* biologically-formed, organic microconstituents of environmental concern. The purpose of this investigation is to examine the water-based, free-radical chemistry that mediates the fate of domoic acid in the aquatic environment. Extracellular concentrations of domoic acid during a bloom can reach >100 nmol L^{-1}, with cell concentrations of $>10^6$ cells L^{-1} [33]. Studies have shown the transfer of domoic acid from exposed rat mothers to the young through milk [34]. Since neonatals have been shown to be a particularly susceptible population [35], biomonitoring and following the degradation of toxin from a bloom, as it effects mammal and human populations, is crucial. Understanding the environmental fate of domoic acid and its analogs can only be determined using kinetic and mechanistic data, which will enable the development of models to describe the details of the free-radical-based Advanced Oxidation Processes.

A recent study published in Limnology and Oceanography, examines the photodegradation of domoic acid in natural water matrices [36]. The study shows that domoic acid is most likely photodegraded via a direct photochemical pathway. Indications are that sunlight-mediated reactions are an important, yet previously unrecognized, sink of dissolved domoic acid, since it is degraded by sunlight in seawater on a time scale of days. Research indicated that trace-metal chelates did not enhance photodegradation. However, indirect photolysis kinetic mechanisms have not been studied. Other sinks, such as bacterial consumption, adsorption to particles, and dilution will also need to be quantified in field conditions. Another recent study uses a

multivariate approach to the removal of domoic acid from natural waters [37]. This model indicated that Fe(III) and dissolved organic matter (DOM) together are significant promoters of domoic acid photooxidation, and contrastingly, the interaction of PO_4^{-3} and/or Fe(III) to inhibit photooxidation. Nitrates and phosphates independently had no statistically significant impact. This multifactor modeling approach is a unique way to consider the many water quality parameters that effect photochemical processes. Incorporating as many kinetic considerations, such as direct and indirect, photolysis will only aide such model in better prediction of environmental impact.

In order to look at how photooxidation may occur with domoic acid, kainic acid, and its degradation products, several model compounds, as represented in Figure 4, were chosen in order to better analyze free radical processes. Many of these compounds are pharmaceutically, amino acid agonists. The kinetic and mechanistic information for these compounds will be used to develop a kinetic model for the aqueous radiation chemistry of these compounds, particularly domoic acid and kainic acid.

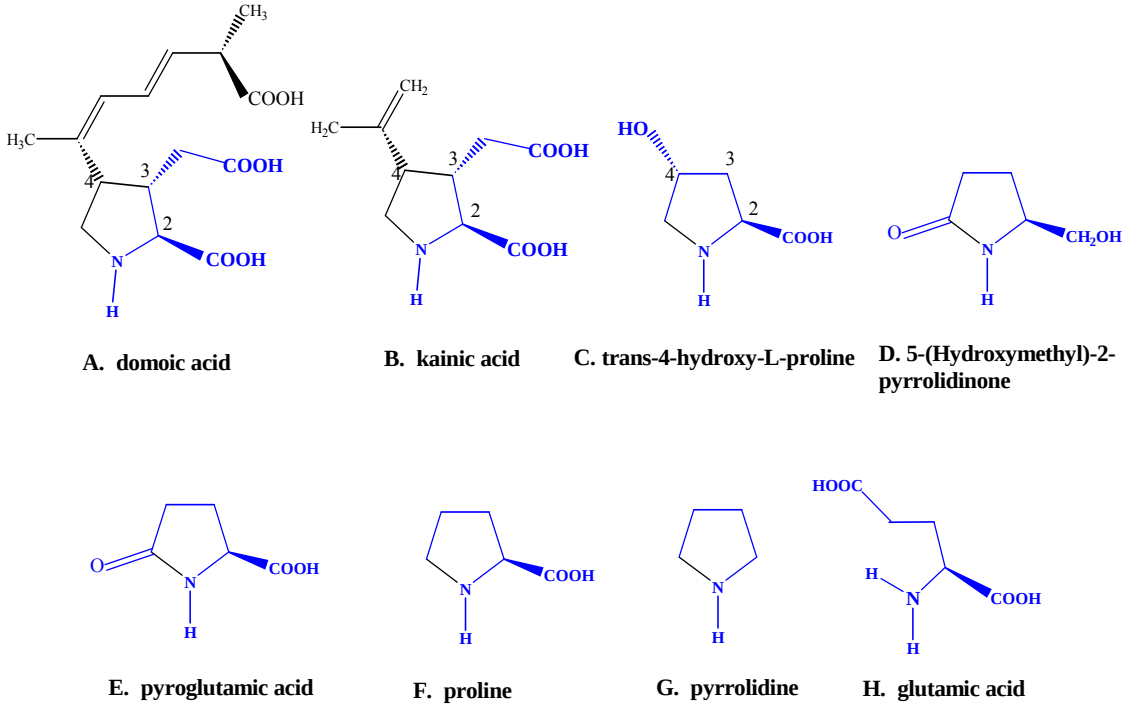


Figure 4. Domoic acid, kainic acid, and the model compounds analyzed for free radical kinetics.

B. Pharmaceuticals as EPOCs

Pharmaceuticals/EPOCs and their bioactive metabolites can be continually introduced to the aquatic environment as complex mixtures via a number of routes but primarily by both untreated and treated sewage. Aquatic pollution is particularly troublesome because aquatic organisms are captive to continual life-cycle, multigenerational exposure. The possibility for continual but undetectable or unnoticed effects on aquatic organisms is particularly worrisome, because effects could accumulate so slowly that major change goes undetected until the cumulative level of these effects finally cascades to irreversible change, changes that would otherwise be attributed to natural adaptation or ecologic succession. As opposed to the conventional, persistent priority pollutants, EPOCs need not be persistent if they are continually introduced to surface waters, even at low parts-per-trillion/parts-per-billion concentrations (ng-mu g/L) [38]. The following table is measured concentrations of target EPOCs (ng/L) sorted by therapeutic class in influent and effluent grab samples collected from the Back River wastewater treatment plant (BRWWTP), Baltimore, MD [39].

Table 1. Concentrations of target EPOCs (ng/L) sorted by therapeutic class

Target EPOCs	Therapeutic class	Wastewater influent concentration (ng/L)	Wastewater effluent concentration (ng/L)	Removal efficiency (%)
Ibuprofen	NSAID	1900	250	87
Acetaminophen	NSAID	960	ND	>99
Naproxen	NSAID	3200	380	88
Ketoprofen	NSAID	1200	280	77
Diclofenac	NSAID	110	90	18

Relative standard deviations (R.S.D.) values were calculated using quadruplicate wastewater influent and effluent samples. Removal efficiency was calculated using the average influent and effluent EPOC concentrations [40].

Americans spend over $18 billion a year on over the counter products. Another example of a pharmaceutical chosen for study, and of a drug that is produced and consumed in mass is ibuprofen. Ibuprofen is a phenylpropionic acid, non-steroidal anti-inflammatory drug (NSAID) introduced into the United States in 1974 as a prescription product intended to treat arthritic conditions at daily doses of up to 2400 mg. It was subsequently approved for daily doses of up to 3200 mg/day, and then as a prescription drug to treat mild to moderate pain in 1978. Since it became available to consumers in 1984, over 100 billion 200 mg tablets of ibuprofen have been sold over the counter (OTC) in the United States alone. Today, consumption of OTC ibuprofen accounts for approximately one third of the market for OTC analgesics [40].

Environmental regulation of such chemicals is based on reports from pharmaceutical companies to the FDA [41]. Data to support environmental risk assessments are generated to support registration of products in the United States. In

the US, formal assessments are supplied to the FDA for any new drug with projected use that could result in a surface water concentration above one part-per-billion. The FDA uses two factors to determine the no effect concentrations to humans. First, safe exposure levels for the pharmaceuticals are normally directly related to therapeutic dose. Second, because many pharmaceuticals or their metabolites are ionic compounds, bioconcentration in fish tissue is not generally an important exposure pathway for human consumption [42]. The pharmaceutical industry in the US continues to investigate potential effects on the environment of trace levels of EPOCs in surface waters. Through the Pharmaceutical Research and Manufacturers of America (PhRMA), the industry has developed an environmental fate and effects model (PhATE) to predict concentrations of EPOCs in surface and drinking water to support risk assessment activities [43].

Another concentration model is reported by M.M. Huber. His study is investigating the oxidation of pharmaceuticals during conventional ozonation and advanced oxidation processes (AOPs) applied in drinking water treatment, reported hydroxyl radical rate constants for two of the pharmaceutical in this study [44]. Ibuprofen's second order rate constant with $^{\cdot}OH$ was determined by UV/H_2O_2 method as $7.4 \pm 1.2 \times 10^9$ $M^{-1}s^{-1}$, and diclofenac was determined by γ radiolysis as $7.5 \pm 1.5 \times 10^9$ $M^{-1}s^{-1}$. Huber's study and a subsequent pilot study, model reactions of selected pharmaceuticals with ozone (k_{O3}) and OH radicals (k_{OH}) to show that the second order rate constants determined in pure aqueous solution could be applied to predict the behavior of pharmaceuticals dissolved in natural waters. Overall the studies concluded that ozonation and AOPs are efficient removal processes of pharmaceuticals in drinking

waters. Other various studies have also reported hydroxyl radical rate constants of pharmaceuticals in this study. Pulse radiolysis is the method used in this study and described in detail later, and it is an **absolute value measured directly**. Other methods represented in Table 2 are relative values measured by steady state. The following table is a compilation from both a literature search and the Notre Dame Radiation Lab's Data Center (refer to references listed with the Center, www.rcdc.nd.edu, accessed March 2007):

Table 2. Hydroxy radical rate constants for pharmaceuticals of interest (from literature)

Pharmaceutical	**second order hydroxyl radical rate constant**	**Experimental Method**
naproxen	$9.6 \pm 0.05 \times 10^9$ $M^{-1}s^{-1}$ 2.4×10^{10} $M^{-1}s^{-1}$	Fenton's reaction[45] Fenton's reaction
ibuprofen	$7.4 \pm 1.2 \times 10^9$ $M^{-1}s^{-1}$	UV/H_2O_2
diclofenac	$7.5 \pm 1.5 \times 10^9$ $M^{-1}s^{-1}$	γ radiolysis
ketoprofen	1.6×10^{10} $M^{-1}s^{-1}$	Fenton's reaction
glutamic acid	1.6×10^8 $M^{-1}s^{-1}$	γ radiolysis
chloramphenicol	5.8×10^9 $M^{-1}s^{-1}$	Pulse radiolysis
indole-3-acetic acid	9.5×10^9 $M^{-1}s^{-1}$	γ radiolysis
indole	3.2×10^{10} $M^{-1}s^{-1}$	Pulse radiolysis
Tetracycline, conj. acid	4.3×10^8 $M^{-1}s^{-1}$	γ radiolysis
L-proline	3.1×10^8 $M^{-1}s^{-1}$ 6.5×10^8 $M^{-1}s^{-1}$	X-radiolysis γ radiolysis

Pharmaceuticals of various actions with representative structures and complexities were chosen for this study. The following table lists the EPOCs analyzed in this study and its pharmacological effect and chemical structure:

Table 3. Environmental pollutants of concern (EPOCs) analyzed

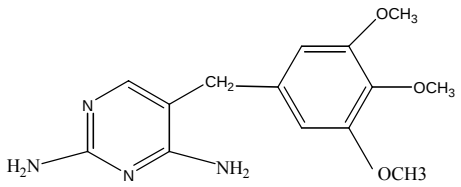
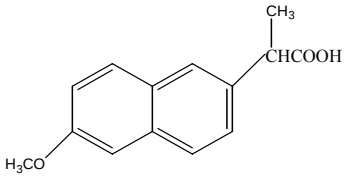
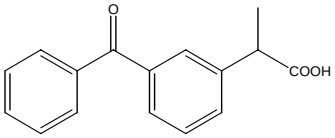
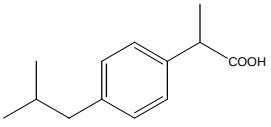
Environmental Pollutants of Concern (EPOCs) Analyzed		
	EPOC Name Pharmacological Effect	Structure
1	Trimethoprim Anti-Infective Agents, Urinary Antimalarials Folic Acid Antagonists	
2	(-)-Naproxen sodium salt NSAID Anti-Inflammatory Agents, Non-Steroidal Gout Suppressants Cyclooxygenase Inhibitors	
3	(S)-(+)-Ketoprofen NSAID Anti-Inflammatory Agents, Non-Steroidal Cyclooxygenase Inhibitors	
4	Ibuprofen sodium salt NSAID Anti-Inflammatory Agents, Non-Steroidal Cyclooxygenase Inhibitors Analgesics, Non-Narcotic	

Table 3 (continued)

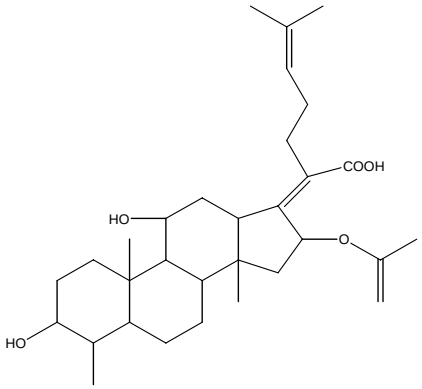
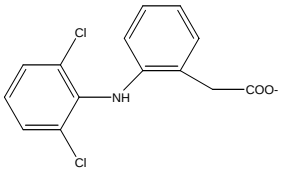
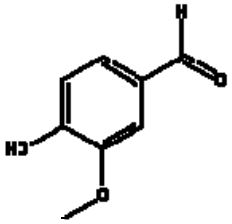
Environmental Pollutants of Concern (EPOCs) Analyzed		
	EPOC Name Pharmacological Effect	Structure
5	Fusidic acid sodium salt Anti-Bacterial Agents Protein Synthesis Inhibitors	
6	Diclofenac sodium salt NSAID Anti-Inflammatory Agents, Non-Steroidal Cyclooxygenase Inhibitors	
7	Vanillin Anticonvulsants Antioxidants Antimutagenic Agents	

Table 3 (continued)

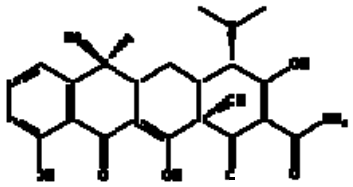
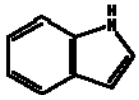
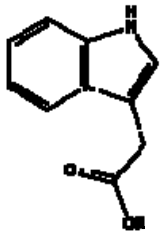
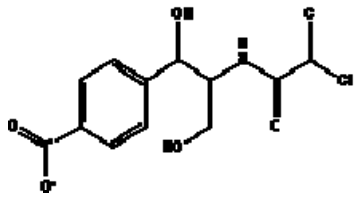
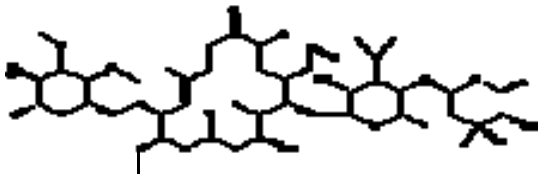
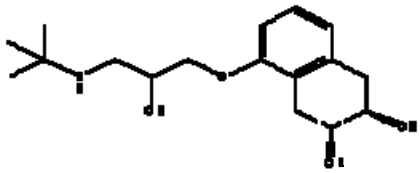
Environmental Pollutants of Concern (EPOCs) Analyzed		
	EPOC Name Pharmacological Effect	Structure
8	Tetracycline Anti-Bacterial Agents Protein Synthesis Inhibitors	
9	Indole Anticancer	
10	Indole-3-acetic acid Plant Growth Regulators	
11	Chloramphenicol Anti-Bacterial Agents Protein Synthesis Inhibitors	

Table 3 (continued)

Environmental Pollutants of Concern (EPOCs) Analyzed		
	EPOC Name Pharmacological Effect	Structure
12	Tylosin Anti-Bacterial Agents	
13	Nadolol Adrenergic beta-Antagonists Anti-Arrhythmia Agents Antihypertensive Agents Sympatholytics	

C. Radiation Chemistry and Advanced Oxidative Processes

Sunlight-induced photochemical processes that occur in natural surface water have been shown to play an important role in the redox chemistry of these waters [46-50]. Natural water photochemistry is highly reactive in nature, and is difficult to directly observe due to the complexity of the solutions. Direct and indirect photoprocesses have important ramifications with respect to modifications of pollutants,

regulation of the redox properties of natural waters, and the decomposition of humic substances. Studies show that photochemically mediated processes affect the chemistry of pollutants in natural waters [5, 12, 38, 42, 51, 52]. The hydroxyl radical is one of the most powerful oxidants known (E^o = 2.73 V). Hydroxyl radicals are generated in natural waters by the photolysis of nitrite and nitrate; and in waters containing sufficiently high metal ion concentrations, through ligand-to-metal charge-transfer reactions; through photo-Fenton chemistry, and due to direct photolysis of colored dissolved organic matter (CDOM) [53]. The following figures outline the mechanisms of nitrite and nitrate photolysis, photo-Fenton chemistry, and photolysis of DOM:

Nitrite and Nitrate Photolysis

$$NO_2^- + h\nu \rightarrow NO + O^- \quad [1]$$

$$NO_3^- + h\nu \rightarrow NO_2 + O^- \quad [2]$$

$$O^- + H_2O \rightarrow {}^{\cdot}OH + OH^- \quad [3]$$

Photo-Fenton hydroxyl radical formation[54]

$$Fe(III)L_n + h\nu \rightarrow Fe(II) \quad [4]$$

$$Fe(II) + H_2O_2 \rightarrow {}^{\cdot}OH + Fe(III) \quad [5]$$

Water oxidation by photoexcited DOM

$$DOM + h\nu \rightarrow DOM^* \quad [6]$$

$$DOM^* + H_2O \rightarrow DOM\text{-}H^{\cdot} + {}^{\cdot}OH \quad [7]$$

Sunlight induced photochemical reactions are probably the most important abiotic processes determining the aquatic fate of organic compounds in natural waters [55]. Two photoinduced alteration processes are commonly met in the surface layers of aquatic systems: direct and indirect photolysis. In direct photolysis, the organic compounds absorb UV light a procedure that either enables them to react with the constituents of water or induce self-decomposition. Indirect photolysis involves the photodegradation of organic compounds caused by photosensitizers like oxygen and hydroxyl or peroxy radicals produced by the photolysis of humic and inorganic substances [56]. Although both processes can occur simultaneously, indirect photolysis plays the most important role in the behavior and environmental half-life of organic contaminants. That is because natural waters contain a variety of substances (dissolved organic matter (DOM), bicarbonates, nitrates, chloride) that may either inhibit [57] or enhance [58] the photo-alteration of organic compounds, by scavenging or generating photo-oxidant agents comprised of both reactive oxygen species and other non-reactive oxygen species transient [50, 59]. Thus, irrespectively of the effect of direct photolysis, indirect pathways are ubiquitous. The ability and contribution of each reactive transient on the systematic removal of organic compounds is concentration depended, and is determined by the steady-state concentration of the reactants as a result of the mass balance between their production and consumption rates.

Advanced oxidation processes (AOPs) are defined as those processes that generate the reactive hydroxyl radical, ·OH, [60] to destroy contaminant organic chemicals in water. More recently, it has been recognized that other reactive species may also be present in some processes, thus the chemical basis for these processes has

been expanded to include other oxidizing species such as "holes" in heterogeneous TiO_2, and also reducing species such as the hydrogen atom ($^{\cdot}H$), the solvated or aqueous electron ($\mathbf{e^-_{aq}}$), and for heterogeneous catalysis involving metal oxides, reducing conduction band electrons. Technically, these could be generally referred to as advanced oxidation/reduction processes (AORPs). Strictly speaking, the holes and e^-_{aq} are not free radicals, and therefore we refer to all these entities as "reactive species" and not free radicals. However, in most cases the first products of reactions between holes or e^-_{aq} and organic compounds are free radicals, and therefore free radical chemistry is the basis for understanding, applying, and eventually determining the environmental fate in its broadest sense.

In this study, the radiolysis of organic solutes (EPOCs) in aqueous solution involves the use of short pulses of high-energy electrons (from a linear accelerator or LINAC). The initial high energy irradiation causes ionization of the water molecule, to give free electrons that subsequently become hydrated, e^-_{aq}, and H_20^+ which decomposes to give hydroxyl radicals, $^{\cdot}OH$, and H^+. The subsequent reactions of these initially formed species include formation of H_2O_2 (from combination of two $^{\cdot}OH$ radicals), $^{\cdot}H$ (from e^-_{aq} and H^+) and H_2 (from reaction of two $^{\cdot}H$ atoms). These techniques have been used for over 30 years in the field of radiation chemistry and it has been shown that the species produced in the irradiation of water (pH 3-11) is constant. The irradiation of water produces hydroxyl radicals, hydrated electrons and hydrogen atoms, along with several other species, where the numbers preceding each species are their G-values (the numbers of species produced per 100 eV of energy absorbed) [61] according to:

$$H_2O \text{-}\!\!\wwvy\!\!\rightarrow\ 2.7\ {}^{\cdot}OH + 2.6\ e^{-} + 0.6\ {}^{\cdot}H + 0.45\ H_2 + 0.7\ H_2O_2 + 2.6\ H^{+} \quad [8]$$

The major advantage of using this technique is the simultaneous, quantitative, generation of three reactive species found in AOPs with concentrations in the nM to μM range. The H_2 and H^+ produced are not reactive and H_2O_2 is only reactive at much longer times. The great advantage of the radiolysis method over other methods for generating reactive intermediates lies in the fact that the amount of energy absorbed by any component of the system is proportional to its electron fraction. This means that in moderately dilute (<0.1 M) aqueous solution, essentially all the energy is absorbed by the water so that the yields of the primary radicals, e^-_{aq}, $H^{\cdot}$ and ${}^{\cdot}OH$ are always well known [62].

The isolation of one reactive species is easily accomplished by the addition of simple chemicals. To realize totally oxidative conditions, with only hydroxyl radicals present, one can saturate the solution with nitrous oxide gas (N_2O) which converts hydrated electrons and hydrogen atoms to hydroxyl radicals by the following fast reactions:

$$e^-_{aq} + N_2O + H_2O \rightarrow N_2 + OH^- + {}^{\cdot}OH \quad [9]$$

$$k_9 = 9.1 \times 10^8\ M^{-1}s^{-1}$$

$$H^{\cdot} + N_2O \rightarrow N_2 + {}^{\cdot}OH \quad [10]$$

$$k_{10} = 2.1 \times 10^6\ M^{-1}s^{-1}$$

This chemistry effectively doubles the yield of hydroxyl radicals in the system.

To isolate the reducing hydrated electron in aqueous solution, typically an inert alcohol (such as tert-butyl alcohol, R-OH) is added at high concentrations, which preferentially reacts with the formed hydroxyl radicals and hydrogen atoms:

$$^{\cdot}OH + R\text{-}OH \rightarrow H_2O + {}^{\cdot}R\text{-}OH \quad [11]$$

$$k_{11} = 6.6 \times 10^{8}\ M^{-1}s^{-1}$$

$$^{\cdot}H + R\text{-}OH \rightarrow H_2 + {}^{\cdot}R\text{-}OH \quad [12]$$

$$k_{12} = 1.7 \times 10^{5}\ M^{-1}s^{-1}$$

The product alcohol radical, .R-OH, is relatively inert, and will not usually interfere with the reductive chemistry of interest.

Radiation chemistry is concerned with all processes which occur following the absorption of ionizing radiation into the aqueous medium until all products have been formed and all the absorbed energy from the radioactive particle has been thermalized. This occurs at an approximate timescale of 10^{-17} seconds after the ionization event [63].

On a nuclear particle time scale, the study of radiation chemistry includes the period of time from the moment of the interaction of the ionizing particle (electron) to a time when the particle is thermalized [64]. The overall time period is subdivided into three distinct stages and each stage correlates to significant events exhibited by the particle in each stage. The stages are categorized into the physical, physiochemical, or chemical. Each stage and significant event is marked to the time in seconds after the interaction of an atomic particle with water medium. Several timescales describing the interaction of an electron with water have been proposed by those identified in Table 4. Each author

identified a unique time within each stage along with a description of their respective significant events. A collective summary of these stage timescales along with their respective events was prepared and presented in Table 4.

Table 4. Events occurring after excitation of an electron in water[64]

Event	Time (Sec.)	Stage	Reference
Earliest discernable time based on Uncertainty Principle.	10^{-17}	Physical Stage	(Mozumder, 1969)[65]
Ionization Event, Excitation e^- $H_2O\bullet$ ←\/\/\/\/ H_2O \/\/\/\/→ $H_2O^+ + e^-$	10^{-16}		(Buxton ,2004)[66]
H_2O	10^{-15}		(Buxton, 2004)[66]
$\bullet OH + H_3O$	10^{-14}		(Buxton, 2004)[66]
$H\bullet + \bullet OH$ $H2 + O\bullet$	10^{-13}	Physiochemical Stage	(Buxton, 2004)[66]
Electron thermalized and hydrated "picosecond barrier". e^-_{aq}	10^{-12}		(Buxton, 2004,[66]; Mozumder and Magee, 1975)[67]
	10^{-11}		
Minimum time for diffusion controlled reactions in the bulk of the liquid.	10^{-10}		(Spinks and Woods, 1964)[68]
Spur reaction complete.	10^{-9}	Chemical Stage	(Magee and Chatterjee, 1987)[69]
Track end (blob, short track) reactions complete.	10^{-8}		(Magee and Chatterjee, 1987)
Formation of molecular products complete e^-_{aq}, $H\bullet$, $\bullet OH$, H_2, H_2O_2, H_3O^+.	10^{-7}		(Buxton, 2004)[66]
	10^{-6}		
Reaction time for radical with solute in molar concentration.	10^{-5}		(Spinks and Woods, 1964)[68]
Radical Reactions with scavenger at micromolar concentration.	10^{-4}		(Magee and Chatterjee, 1987)[69]
Radiative lifetime of triplet excited state.	10^{-3}		(Spinks and Woods, 1964)[68]
	10^{-2}		
	10^{-1}		
Chemical Reactions Complete.	0		(Spinks and Woods, 1964)[68]

The radiation chemistry of interest is the study of domoic acid and kainic acid representing toxins formed in situ by biological organisms. Additional environmental pollutants of concern (EPOCs) representing other sources were analyzed for their hydroxyl radical reaction rate constants, such as the anti-inflammatory drugs of ibuprofen, ketoprofen, and naproxen; antibiotics of trimethoprim and fusidic acid; and vanillin. Solvated electron rate constants were analyzed for four of the EPOCs. The hydroxyl radical and solvated electron rate constants generated will assist in modeling the mechanisms for environmental fate of EPOCs in coastal aquatic environments.

D. Environmental Fate

Natural waters are open and dynamic systems with the ultimate source of the energy flow coming from the sun's radiation. Aquatic chemistry is of practical importance due to the necessity of water as a resource. The quantity of water as a substance is abundant. Our concern must lie with the quality of water and its distribution. Simplified and manageable models may be used to illustrate the principal regulatory factors that control the chemical composition of natural waters. To be useful, a model need not be realistic as long as it produces pertinent generalizations and valuable insight into the nature of aquatic chemical processes and improves our ability to describe and to measure natural water systems [70]. Environmental fate models require very crude simplifications of the environmental system to provide a manageable framework for studying and predicting the fate of chemicals, in which the basic

environmental compartments, such as air, soil, and sediment, are treated uniformly. Although this approach may severely limit accuracy, the resolution is still sufficient for the output to be useful. Understanding chemical fate in natural processes is seriously hampered by a lack of kinetic information on reactions typically encountered in natural waters, not to mention those created and influenced by human input.

The long-term goal of research of this nature is to provide the data necessary to develop kinetic models that describe the underlying chemistry for insight into natural aquatic processes and for process applications, such as wastewater and desalination concentrate treatment. The persistence of a chemical in the environment is widely accepted as dependent on its dynamic partitioning between the various environmental compartments as well as its degradation rate within each compartment [71]. Considerable advances have been made in developing models for expressing the theoretical overall persistence of chemicals, and various endpoints have been suggested, such as residence time, joint persistence, and persistence in a temporal remote state [72]. Techniques for measuring the physicochemical properties of chemicals have improved, and more sophisticated methods for describing their partitioning processes exist. However, the lack of accurate compartmental degradation rates remains a key weakness for all modeled predictions of persistence [73]. In Chapter 4, an estimate of sunlight half-lives of EPOCs for their reaction with $^{\cdot}OH$ will be presented. Also, evaluation of a model for predicting the best use of advanced oxidative processes for degradation of pollutants will be examined. In extrapolating from laboratory experiments to natural environments, it is necessary to account for many variables. A review of such variables as the chemical processes of direct and indirect photolysis, biological properties, and physical distribution will also

be discussed in Chapter 4.

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Chapter 2 Hydroxyl Radical Rate Constant Determination for Domoic Acid and Kainic Acid, and a Study of Hydroxyl Radical Mediated Reaction Pathways

Chapter 2 is formatted for potential publication in *Environmental Science and Technology*.

ABSTRACT

Absolute rate constants for the free-radical-induced degradation of domoic acid, kainic acid, and their model compounds were determined using electron pulse radiolysis and transient absorption spectroscopy. Rate constants for hydroxyl radical, •OH, reactions of domoic acid and kainic acid were (9.45±0.035) x 10^9 M^{-1} s^{-1} and (2.46±0.029) x 10^9 M^{-1} s^{-1}, respectively. Studies give evidence that the conjugated double bond of the C4 substituent of both domoic acid and kainic acid is the preferential initial site of ·OH attack, destroying the conjugation and molecular conformation. Comparing the reaction rates of compounds without the conjugated substituent to those with, would seem to substantiate the importance of this site for initial hydroxyl radical attack.

The chemical kinetics of the free-radical-induced degradation were used to determine potential persistence in natural water systems as a result of indirect photolysis. The half life ($t_{½}$) for domoic acid with exposure to constant June, midday sunlight was determined to be approximately 34 days in a natural water system. Given the real life time that 34 days of continual, maximum sunlight might represent and the rapid scavenging in surface waters, significant photodegradation via ·OH mechanisms is

unlikely. Reaction rates are rapid, but also, probably negligible in surface waters because of the low steady-state concentrations of ·OH.

The reaction rate constants and mechanisms studied in this work, may be applicable within many subsequent investigations and touch on a wide variety of fields. Hydroxyl radical rate constants for biotoxins, such as domoic acid, will assist in modeling its environmental fate. The neurological importance of kainic acid and the kainate receptors may utilize the hydroxyl radical rate constants of kainic acid, pyrrolidine, and the pyrrolidine-like compounds to analyze intracellular radical scavenging. As potent antioxidants or radioprotective compounds, stable nitroxide radicals are being studied not only for their direct reactivity with hydroxyl radicals, but also for their ability to detoxify hydroxyl radical-derived secondary radicals. Environmental concerns in relation to the increase in water desalination plants world-wide, has increased the study of the brine concentrate formed by the process. Concentrate discharge could possibly contain significant concentrations of biotoxins, such as domoic acid, that are brought in from areas experiencing an active algal bloom. Advanced oxidative processes may be a possibility for remediation prior to discharge, given the rapid reaction rate of domoic acid with hydroxyl radicals, and the subsequent change caused in molecular conformation.

INTRODUCTION

In the 1950s, both (-)-kainic acid and (-)-domoic acid were isolated from the red marine algae of the same family (Rhodomelaceae), *Digenea simplex* and *Chondria armata*, respectively [1, 2]. These algae, possessing the compounds known as kainoids, have been used in anthelmintic (roundworm disease) folk medicine in Japan for centuries [3]. The toxins have more recently received notoriety as the potent neurotoxins and excitatory amino acids responsible for the shellfish poisonings known as Amnesic Shellfish Poisoning (ASP). Domoic acid, produced by the pinnate diatoms, *Pseudonitzschia* spp. and sequestered by filter-feeding shellfish, surfaced as the causative toxin in a deadly seafood poisoning incident in Canada in 1987 [4].

Prior to the incident, research was already focused on the use of kainic acid as a neuroexcitatory amino acid. Excitatory amino acid receptors have been shown to play an important role in vision and locomotor control, and in learning, memory and brain development [5]. Therefore, agents acting on excitatory amino acid receptors are expected to be therapeutically useful in treating neurological disorders, including ischemia, epilepsy, schizophrenia, pain, anxiety and amyotropic lateral sclerosis, as well as for treating various chronic neurodegenerative diseases, such as Alzheimer's, Huntington's and Parkinson's diseases and neuronal damage resulting from cerebral ischemia [6, 7]. On a medicinal vein, the hydroxyl radical reaction rate of kainic acid may assist in giving more insight into the mechanisms of oxidative stress. It has been proposed that the production of hydroxyl radicals may contribute to the pathophysiology of the previously mentioned conditions [8].

Domoic acid and kainic acid are water soluble members of the Kainoids, a group of neurologically active amino acids. The mechanism of domoic acid toxicity and kainic acid's neuroexcitatory properties is explained by its structural similarity with the excitatory neurotransmitter glutamic acid, see Figure 2.1, but with a much stronger receptor affinity [9]. Domoic acid is three times more potent than its analogue kainic acid and up to 100 times more potent than glutamic acid itself [10]. The strength of binding at the kainate receptor, one of three types of the ionotropic (ion channel) class of glutamate receptors, determines the potency of neuroexcitation [11]. It has been determined that C4 stereochemistry, C4 substituent and molecular conformation strongly influence the binding. The nature of the C4 substituent is particularly critical. The Z-configuration of a C1' alkene is more active than the E-configuration, and compounds bearing sp^2 substituents have an activity more than 1000-fold that of a compound with an analogous saturated substituent. In order to better understand the relationship of structure, activity and fate, this study evaluated the hydroxyl radical rate constants of a series of structurally similar chemicals.

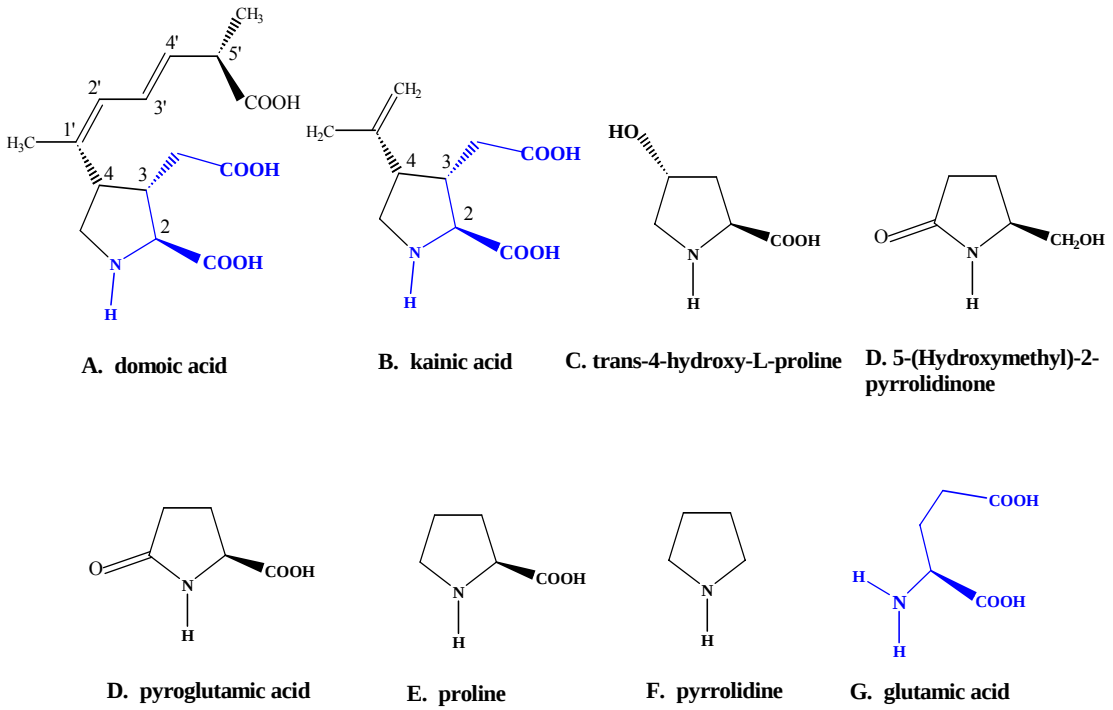


FIGURE 2.1. Domoic acid, kainic acid and the model compounds analyzed for free radical kinetics.

The potency of domoic acid has become an issue of serious concern, as the incidents of *Pseudonitzschia* spp. blooms have increased in recent times. When the algae is consumed, the domoic acid becomes concentrated in the visceral hepatopancreas or gill structures of animals such as oysters, mussels, sardines, scallops, clams, crabs, and anchovies, which often act as seafood for other larger animals [12]. Thus, like humans, when loons, grebes, dolphins, sea lions, pelicans, or cormorants then consume this concentrated domoic acid, they may become disoriented and the result is often death [13, 14]. As in other recent summers, front page articles in the Los Angeles Times chronicle humans and marine life alike that are exhibiting classic symptoms of domoic acid poisoning. The articles cite that more than 14,000 seals, sea lions and dolphins have landed sick or dead along the California shoreline in the last decade [15].

The environmental fate of domoic acid is poorly understood. Many toxic organic compounds have been shown to undergo rapid, extracellular microbial degradation in natural systems [16, 17]. Studies of the biodegradation of domoic acid by a variety of bacteria isolated from the marine environment indicate that the ability to grow on or degrade domoic acid was rare. In fact, domoic acid was inhibitory to resting cells or growing cultures of most of these bacteria [18, 19]. Hagstrom, et al, recently reported the dissolved toxin to be stable in the presence of the bacteria studied for at least 20 days [19]. Another study suggested that photodegradation seemed to be the pathway to degradation, rather than bacterial degradation [20]. It was also noted in a follow up experiment, that there was essentially no decrease in concentration for the first 6 days of the observation of domoic acid degradation, with added bacteria in the light. After 12 days, the domoic acid concentrations of flasks kept in the light showed a 68% decline from their initial mean domoic acid concentration, versus, those maintained in darkness displayed only a 17% decline. Those flasks with bacteria added and maintained in the light had an intermediate decline in concentration of 40%. Bates, et al speculated that the bacteria may even protect the domoic acid by scavenging any superoxide produced by the incident light [20].

Direct and indirect, sensitized, photochemical degradation pathways are a potentially important sink of domoic acid in seawater. Preliminary studies on direct photolysis have indicated that domoic acid in seawater is rapidly degraded upon exposure to simulated sunlight [21]. Exposure to full-spectrum light for 22 h resulted in domoic acid degradation in all three water types in the absence of added iron: 36% for deionized water, 44% for artificial seawater and 41% for natural seawater, relative to the

time zero value. A recent study by Bouillon et al. reported similar results, with domoic acid concentrations decreasing exponentially as a function of irradiation time (10 hour incubation, 84 to 18 nmol L^{-1}), with no loss observed in dark controls [22]. Using a multivariate, microscale, high-throughput experimental approach, Fisher et al. determined that Fe(III) and DOM are significant promoters of domoic acid photooxidation. In contrast, PO_4^{3-} interacts with Fe(III) to inhibit the photooxidation of domoic acid, but PO_4^{3-} alone does not act to slow or accelerate domoic acid photodegradation [23]. Domoic acid in these matrices had half-lives ranging over 12-36 hours. Domoic acid is most likely, initially, degraded by direct photochemical pathways. In order to get a more complete picture of photodegradation rates for domoic acid, this paper will investigate the indirect, or sensitized, photochemical degradation pathways through the use of radiation chemistry. The chemical kinetics of the free-radical-induced degradation were used to determine potential persistence in natural water systems as a result of indirect photolysis.

EXPERIMENTAL SECTION

All chemicals in this study were used as received from the chemical distributor. Domoic acid (Fluka, 2 mg, Lot No. 1279749, >97%; Biomedicals, Inc., 5 mg, Lot. No. 2253J, >98%) and (-)-(a)-kainic acid (hydrate) (Cayman Chem., 50 mg, cat.#78050, >98%) were available in small quantities. All solutions were made using deionized, Millipore-quality water (18 MΩ resistance, 120 μg L-1 TOC), and were prepared immediately before irradiation. Other model compounds; trans-4-hydroxy-L-proline, 5-(hydroxymethyl)-2-pyrrolininone, L-pyroglutamic acid, proline, pyrrolidine, and

glutamic acid were obtained at the highest purity available. The dosimetry [24] was based on the oxidation of 0.01M thiocyanate anions (SCN^-) to $(SCN)_2^{\cdot -}$ in aqueous, N_2O-saturated solutions at pH 7.5, phosphate buffered.

Kinetic measurements on these solutions were performed using the linear accelerator/absorption spectroscopy system at the Department of Energy Radiation Laboratory, University of Notre Dame [25]. The model TB-8/16-1S linear electron accelerator, providing 5-50 ns pulses of 8 MeV electrons and generating radical concentrations of 1-3 μM per pulse in all investigated systems, was used for the pulse radiolysis experiments. The basic details of the equipment and data analysis have been given elsewhere [25, 26].

Direct measurements of the growth kinetics were measured where possible. Pyrrolidine was the only compound to give a significant intermediate absorption in the UV-visible range of 260-800 nm. Pyrrolidine was measured by the direct transient method of pulse radiolysis at 472 nm. All of the other compounds evaluated exhibited very weak transient intensity, which was too small to allow accurate direct measurements of the growth kinetics of their intermediates. Therefore, the hydroxyl radical rate constants for those compounds were determined using SCN- competition kinetics, monitoring the change of absorption intensity of the produced $(SCN)_2^{\cdot -}$ transient at 475 nm. The experimental data were obtained by either direct transient or competition kinetics, and the confidence limit for each rate constant was calculated. The data for the ratio of [EPOC]/[SCN^-] and the ratio of intensity were input into a linear curve fitting program (ORIGIN 7.5^{TM}) for plotting with the confidence limits identified as one

standard deviation (S_X). The hydroxyl radical decay data are presented with the linear plotting data derived from the curve fitting program.

RESULTS AND DISCUSSION

Kinetic Measurements. The radiolysis of water gives a distribution of transient and stable products according to the equation [27, 28]:

$$H_2O \text{ -}\!\!\wwvv\!\!\rightarrow [0.28]\ {}^{\bullet}OH + [0.06]\ H^{\bullet} + [0.27]e_{aq}^{-} + [0.05]H_2 + [0.07]H_2O_2 + [0.27]H_3O^{+} \quad [1]$$

where the numbers in brackets are the G-values (yields) in μmol J^{-1}. Absolute dosimetry for kinetics measurements was based on the transient absorbance produced in N_2O-saturated 1.0 x 10^{-2} M KSCN solution at $\lambda = 475$ nm ($G\varepsilon = 5.2 \times 10^{-4}$ m^2 J^{-1}) with doses of 3-5 Gy per 2-3 ns pulse [29].

Pyrrolidine was the only compound that had its hydroxyl radical rate constant determined by direct transient pulse radiolysis. One reactive radical was observed at 472 nm for pyrrolidine, as a result of a series of different doses and solute concentrations. The product exhibited a sufficiently high extinction coefficient, ensuring that pseudo-first order kinetics were applicable. The hydroxyl radical rate constant for pyrrolidine was determined by direct transient pulse radiolysis to be (2.43$\pm$ 0.05) x 10^9 $M^{-1}s^{-1}$, see Figure 2.2.

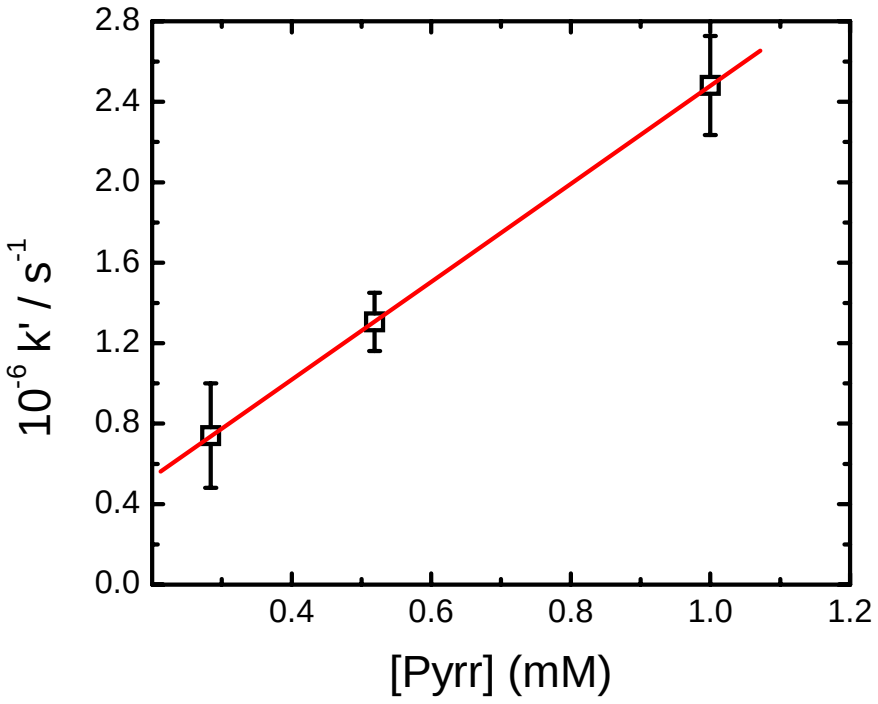


FIGURE 2.2. Transient spectra kinetics plot for ˙OH reaction with pyrrolidine at the wavelength of 472 nm. The solid line is a weighted linear fit, corresponding to a pseudo first-order rate constant for pyrrolidine radical, where $k_1 = (2.43 \pm 0.05) \times 10^9$ $M^{-1}s^{-1}$.

The domoic acid, kainic acid and remaining model compounds' oxidation by reaction with the hydroxyl radical gave no significant transient absorbance over the range 260-800 nm. The radical rate constant determination, therefore, was performed using SCN^- competition kinetics, by monitoring the changes in absorption of the $(SCN)_2^{\bullet -}$ transient at 475 nm in the competition [27]:

$$^{\bullet}OH + \text{Domoic Acid (DA)} \rightarrow \text{products} \qquad [2]$$

$$^{\bullet}OH + SCN^- (+ SCN^-) \rightarrow OH^- + (SCN)_2^{\bullet -} \qquad [3]$$

This competition can be analyzed to give the expression:

$$\frac{[(SCN)_2^{\bullet -}]_o}{[(SCN)_2^{\bullet -}]} = 1 + \frac{k_2[DA]}{k_3[SCN^-]} \qquad [4]$$

where a plot of $[(SCN)_2^{\bullet -}]_o/[(SCN)_2^{\bullet -}]$ against the concentration ratio $[DA]/[SCN^-]$ gives a straight line of slope k_2/k_3. Based on the rate constant for hydroxyl radical reaction with SCN^-, $k_3 = 1.1 \times 10^{10}\ M^{-1}\ s^{-1}$ [27], the k_2 rate constant is readily determined [26].

To isolate the reaction of $^{\bullet}OH$ with the kainoid-like compounds, solutions were pre-saturated with N_2O, which quantitatively converts hydrated electrons, e_{aq}^-, and hydrogen atom, $^{\bullet}H$, to $^{\bullet}OH$ [27]:

$$e_{aq}^- + N_2O + H_2O \rightarrow N_2 + OH^- + {}^{\bullet}OH \qquad k_5 = 9.1 \times 10^9\ M^{-1}\ s^{-1} \qquad [5]$$

$$^{\bullet}H + N_2O \rightarrow {}^{\bullet}OH + N_2 \qquad k_6 = 2.1 \times 10^6\ M^{-1}\ s^{-1} \qquad [6]$$

The hydroxyl radical kinetic data were obtained using absorption spectroscopy at 475 nm for domoic acid, kainic acid, and the remaining model compounds, minus pyrrolidine and glutamic acid. Glutamic acid is listed from reference at the Notre Dame Radiation Data Center [30], and is presented for modeling purposes. A typical kinetic plot of $(SCN)_2^{\bullet -}$ formation for the domoic acid reaction with $^{\bullet}OH$ is graphically presented in Figure 2.3. The transformed kinetic data for the hydroxyl radical of domoic acid and kainic acid are graphically presented in Figures 2.4 and 2.6, representing hydroxyl radical rate constants of $(9.45 \pm 0.035) \times 10^9\ M^{-1}s^{-1}$ and $(2.46 \pm 0.029) \times 10^9\ M^{-1}s^{-1}$, respectively. Figure 2.5 graphically represents a typical kinetic plot of $(SCN)_2^{\bullet -}$ formation for the kainic acid reaction with $^{\bullet}OH$ at 475 nm. Table 2.1 presents all of the calculated hydroxyl radical rate constants for domoic acid and its model compounds.

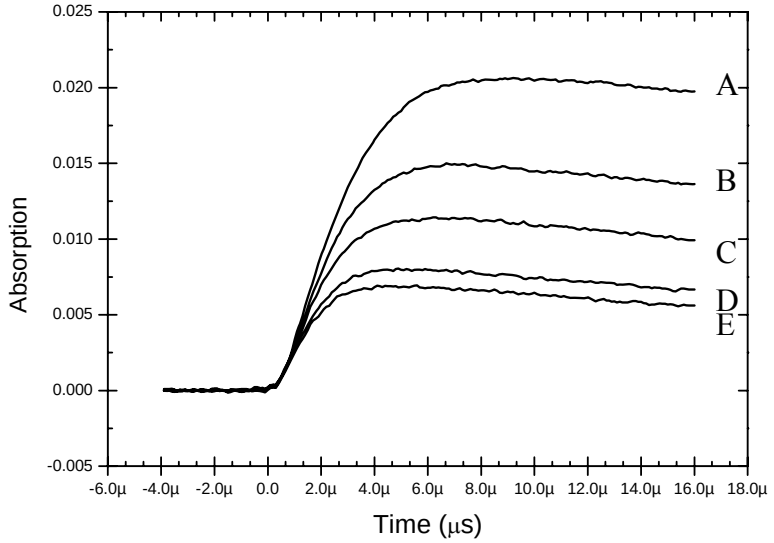


FIGURE 2.3. Typical kinetic plot of $(SCN)_2^{\cdot -}$ formation for domoic acid reaction with $^{\cdot}OH$. Plot for 475 nm and N_2O^- saturated 6.15 x 10^{-5} M KSCN solution containing zero (A), 3.57 x 10^{-5} M (B), 6.74 x 10^{-5} M (C), 1.13 x 10^{-4} M (D), and 1.41 x 10^{-4} M domoic acid at 7.5 pH and 21°C. Kinetic traces shown were obtained from an average of 20 pulses.

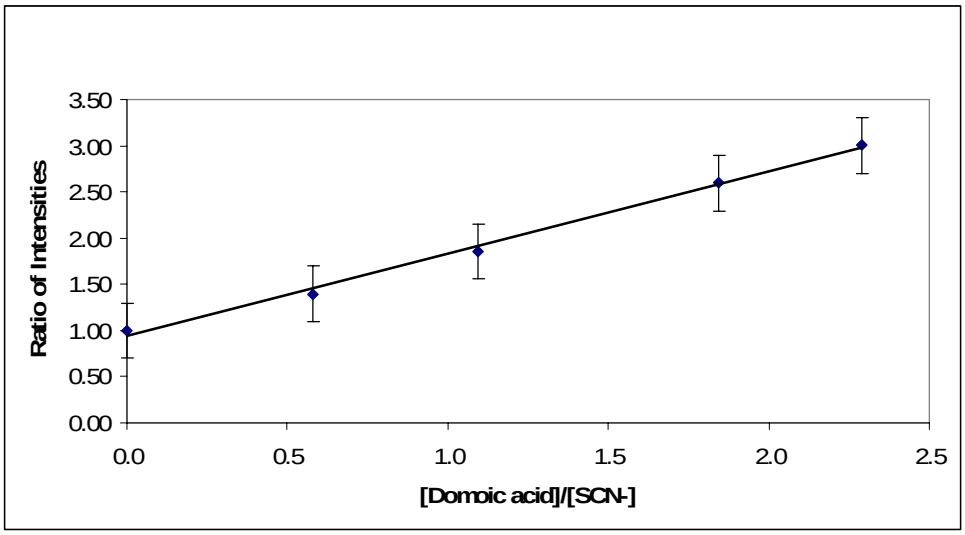


FIGURE 2.4. Competition kinetics plot for $^{\cdot}OH$ reaction with domoic acid using SCN^- as a standard. The solid line is a weighted linear fit, corresponding to a slope of 8.91 $\pm$ 0.33 x 10^{-1}. A pseudo first-order rate constant for domoic acid reaction was derived where, $k_1 = (9.45 \pm 0.35) \times 10^9$ $M^{-1}s^{-1}$.

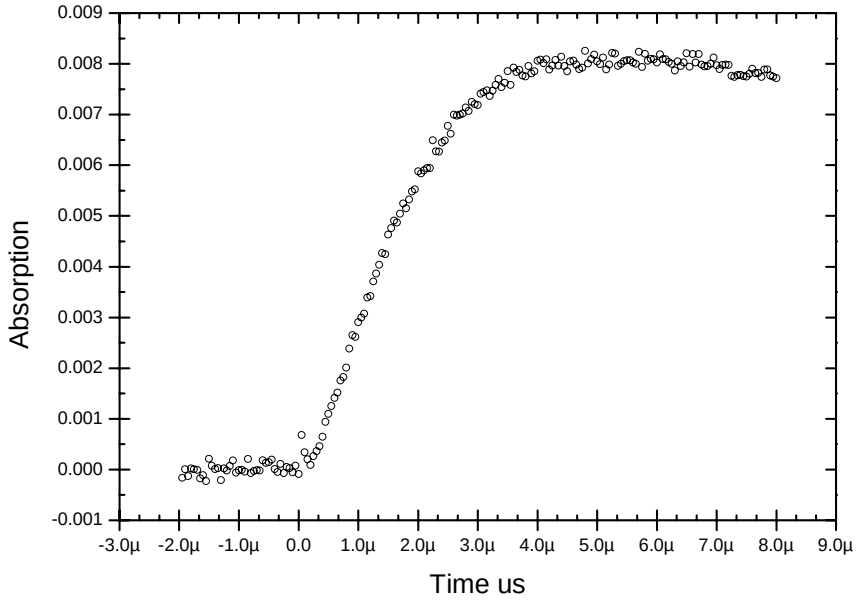


FIGURE 2.5. Typical kinetic plot of $(SCN)_2^{\cdot-}$ formation for kainic acid reaction with $^{\cdot}OH$. Plot for 475 nm and N_2O^- saturated 6.15 x 10^{-5} M KSCN containing 3.01 x 10^{-4} M kainic acid at 7.5 pH and 21^{o}C.

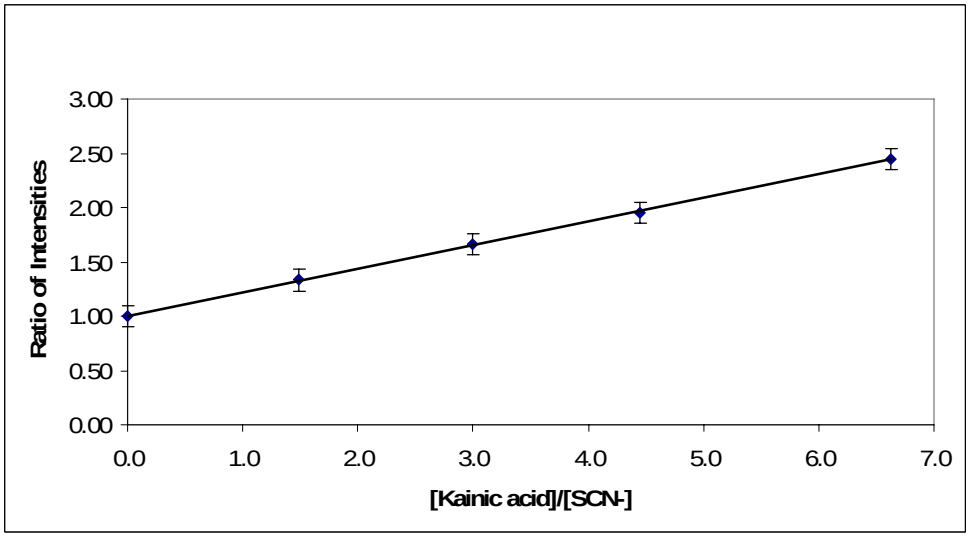


FIGURE 6. Competition kinetics plot for $^{\cdot}OH$ reaction with kainic acid using SCN^- as a standard The solid line is a weighted linear fit, corresponding to a slope of 2.17 $\pm$ 0.03 x 10^{-1}. A pseudo first-order rate constant for kainic acid reaction was derived where, k_1 = (2.46$\pm$0.03) x 10^9 $M^{-1}s^{-1}$.

TABLE 2.1. Hydroxyl radical rate constants ($M^{-1}s^{-1}$) of domoic acid and its model compounds

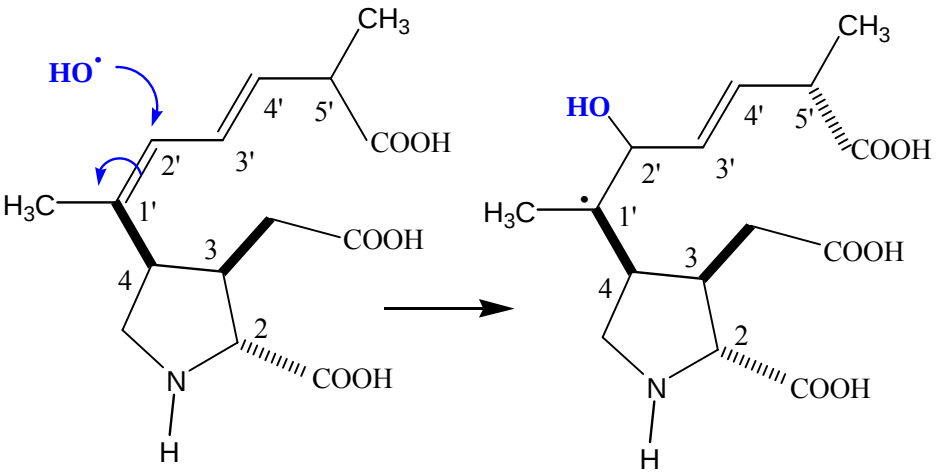
Compounds of Interest	**$^{\cdot}$OH Rate Constant ($M^{-1}s^{-1}$)**
domoic acid	$(9.45 \pm 0.04) \times 10^9$
kainic acid	$(2.46 \pm 0.03) \times 10^9$
trans-4-hydroxy-L-proline	$(4.40 \pm 0.07) \times 10^8$
5-(hydroxymethyl)-2-pyrrolininone	$(1.93 \pm 0.04) \times 10^9$
L-pyroglutamic acid	$(1.05 \pm 0.01) \times 10^9$
proline	$(2.78 \pm 0.07) \times 10^8$
pyrrolidine	$(2.43 \pm 0.05) \times 10^9$
glutamic acid	$k_{reference} = 6.4 \times 10^9$ pH ~2 (NDRL)

Oxidative Degradation. The most common pathway for the oxidation of amino acids, such as glutamic acid involves the hydroxyl radical-mediated abstraction of a hydrogen atom to form a carbon-centered radical at the α-position of the nitrogen function [31]. Addition of O_2 to the carbon-centered radicals leads to formation of peroxy radical derivatives, which upon decomposition leads to production of NH_3 and α-ketoacids, or to production of NH_3, CO_2, and aldehydes or carboxylic acids [32]. Radical formation is facilitated and stabilized by the complementary electron-donating and electron-withdrawing effects of the substituents, to delocalize charge and unpaired

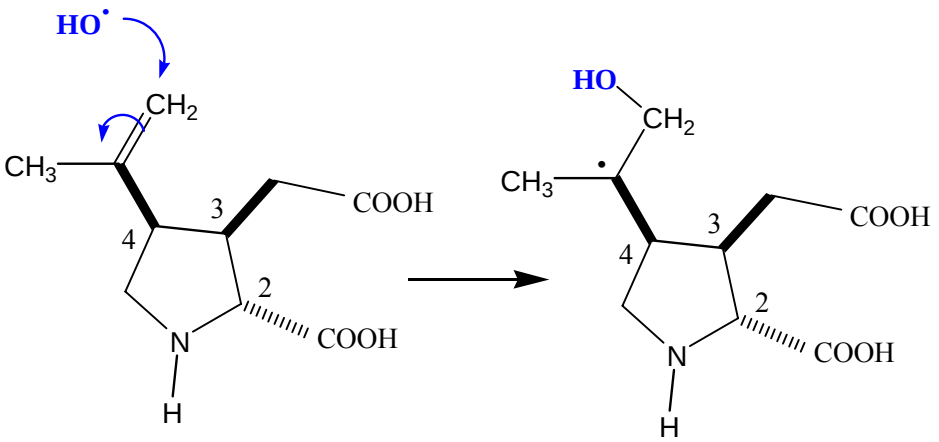
spin density that develop in reaction transition states [33, 34]. This facilitation may explain the comparatively rapid hydroxyl radical reaction rate.

It has been shown that binding of the kainoids at the kainate receptor is influenced strongly by the C4 stereochemistry, its substituent, and the molecular conformation [11, 35-37]. Kainate structure/activity research indicates the depolarizing activity and kainate e-type selectivity strongly depends on the nature of the ~-electron group attached to C4 and its orientation in the molecule [36]. All of the amino acids analyzed in the study showed very weak activities compared with those of kainic acid. These weak activities are probably due to the fixed double bond plane of the isopropenyl group in nearly same plane as the pyrrolidine ring. This arrangement must be inconvenient for the substrate to interact with the receptor. The double bond plane of the C4-substituent should be diagonal to the pyrrolidine ring to demonstrate the potent depolarizing activity [38]. "The C 1'-C2' double bond confers a planar 'knifeblade' shape to this part of the side chain that appears to be necessary for high affinity binding…When the first double bond is reduced...the planar shape is replaced by a nonplanar 'umbrella' shape that occupies much more volume, thus interfering with binding..." [37].

Studies give evidence that the conjugated double bond is the preferential initial site of $^{\cdot}OH$ attack, destroying the conjugation and molecular conformation, resulting in free rotation around the carbons of the C4 substituent [39-41], as presented in Figure 2.7. The reaction rate is rapid. It would be considered essentially a diffusion rate at $< 10^{10}$ $M^{-1}s^{-1}$, so the hydroxyl reaction rate for domoic acid reflects a reaction limited by the concentration of the hydroxyl radical.



A. domoic acid



B. kainic acid

FIGURE 2.7. Initial hydroxyl radical attack occurs at the C1' alkene, which causes immediate interference at the binding site

Photodegradation Estimation for Domoic acid in Natural Waters.

Foundational to all of reactions studied in this project, is that in the course of the chemical reaction, concentrations will change with time as reactants become products. Experimental chemical kinetics includes the development of techniques that allow for

the study of chemical reactions including the measurement and analysis of chemical reaction dynamics. Sunlight-induced photochemical processes, as previously mentioned, have been determined to be a primary degradation mechanism for the in situ, biologically produced amnesic shellfish poison (ASP), domoic acid [20, 22, 23]. The redox chemistry in surface waters has been linked to humic substances as initiators of photoreactions, and some of those reactions are considered secondary products. Photochemically mediated processes, both primary and secondary, have important ramifications with respect to modifications of pollutants, regulation of the redox properties of natural waters, and the decomposition of humic substances [42-44].

Direct sunlight photolysis of hydrogen peroxide is one possible mechanism for the formation of ·OH in surface waters, but it is not considered as a primary mechanism [45-47]. Significant sources of ·OH may come from secondary (indirect or sensitized) Photo-Fenton reactions, the oxidation of Cu(I) and Fe(II) by H_2O_2 and/or by nitrate ion photolysis [48-51]. Considering the photochemical reaction of DA with ·OH to produce a product, a second order rate law would apply. However, if the initial concentration of the reactant ·OH is much larger than the concentration of DA, the concentration of ·OH will not change appreciably during the course of the reaction. The concentration of the reactant in excess, [·OH], will remain almost constant. This may be a large assumption given the low steady-state concentrations of ·OH in surface, but it is useful in modeling to determine relative half-lives of environmental pollutants of concern.

The steady-state concentration of the relatively short-lived photoreactant [·OH] was experimentally determined in a way that produced a simple second-order rate law.

The rate of transformation of domoic acid (DA) was first order in concentration of both DA and ·OH, giving a second order overall.

$$\frac{d[DA]}{dt} = k_{DA,OH}[{}^{\cdot}OH]_{SS}[DA] \quad [7]$$

$k\ {}^{\cdot}OH\ DA = 9.45 \times 10^{9}\ M^{-1}s^{-1}$

${}^{\cdot}OH_{SS} = 2.5 \times 10^{-17}$ M (Midday, June, sunlight 1 kW/m^2 with DOM [51])

$$\frac{d[DA]}{dt} = (9.45 \times 10^{9}\ M^{-1}s^{-1})(2.5 \times 10^{-17}\ M)[DA] \quad [8]$$

$$\frac{d[DA]}{dt} = (2.4 \times 10^{-7})[DA] \quad [9]$$

First order half life of Domoic Acid

$$t_{1/2}\ DA = \frac{-\ln 1/2}{k} = \frac{0.693}{k} = \frac{0.693}{2.4 \times 10^{-7}} = \frac{2.9 \times 10^{6} s}{s^{-1}} \frac{(1\ min)(1\ hr)(1\ day)}{(60\ s)(60\ min)(24\ hrs)} = \mathbf{34\ days} \quad [10]$$

So, the half life ($t_{½}$) for domoic acid with exposure to constant June, midday sunlight, using this model, is 34 days in a natural water system. Given the real life time that 34 days of continual, maximum sunlight might represent, significant photodegradation via ·OH mechanisms is unlikely. Reaction rates are rapid, but also, probably negligible in surface waters because of the low steady-state concentrations of ·OH.

Implications. The applications of hydroxyl radical rate constants with the compounds analyzed are quite broad-ranging. The hydroxyl radical is highly reactive, and oxidizes most organic compounds at almost diffusion controlled rates [52]. Kinetic data known for reactions of hydroxyl radicals with various solutes tabulated in extensive lists can now form the basis for prediction of reactions of different solutes present in

aqueous solution in competition for the oxidizing species [53-55]. Because the reaction rate constants for reactions of hydroxyl radicals with organic molecules are fairly insensitive to parameters such as pH and salt concentrations, the values listed in the literature can easily be applied without further corrections.

Due to the hydroxyl radical's high reactivity, it is indiscriminate, reacting with the first substrate available. It is unlikely, given the low steady state concentration of ·OH in marine waters, that significant destruction of these kainoid-like compounds would occur. However, given the high reaction rate of ·OH with both domoic acid and kainic acid, it is possible to have a reaction occur, particularly with secondary radical reaction products, that would decrease or alter their biological activity in surface waters. The rapid reaction rate determined for kainic acid may be of particular importance to understanding the intracellular oxidative processes associated with many of the neurological diseases mentioned in the introduction.

The focus of the series of compounds chosen was primarily to review the mechanism of hydroxyl radical attack of kainoid-like compounds. Another use of the hydroxyl radical rate constants for the heterocyclic, pyrrolidine-like compounds would be in the analysis of intracellular radical scavenging by cyclic nitroxides and formation of such compounds as peroxynitrite. In studies of the involvement of radicals in diverse pathological processes, research is focusing on efficient antioxidants that will diminish radical-induced damage. Biological injury is primarily attributed to highly reactive ·OH radicals [56]. Cyclic nitroxides are cell permeable stable radicals of diverse size, charge, and lipophilicity, which effectively protect cells, tissues, organs, and whole animals from radical-induced damage [57-60]. As potent antioxidants or radioprotective compounds,

stable nitroxide radicals are being studied not only for their direct reactivity with hydroxyl radicals, but also for their ability to detoxify hydroxyl radical-derived secondary radicals [61].

As hydroxyl radicals are considered to be one of the main oxidizing species in the advanced oxidation processes (AOPs). Free radical AOPs have been well studied for degradation of many environmental pollutants [62-65]. Models of the fate of environmental pollutants, such as algal bloom toxins, pharmaceuticals, pesticides, and personal care products, in natural waters are complicated by the extremely variable composition, and in most cases relatively complex systems [66]. The chemical species that are most common are dissolved organic matter and a number of ions, such as chloride, nitrate, sulfate, carbonates and sodium. In attempting to model natural waters using the $^{\cdot}OH$ rate constants within a system, the consideration of initial solute concentrations and of $^{\cdot}OH$ scavenging in relation to pH becomes very important. Models have been considered with single solute systems [67-70], with natural chemical species [23, 71, 72], with the photochemical degradation[22, 73], with the microbial degradation[18], and even with mixtures of the microconstituents [71], and each meets with a level of success. However, they are each interdependent and only pieces of the natural system that is extremely dynamic. Every rate constant, concentration value, absorption, degradation mechanism, relationship, etc. brings conceptual models one step closer to agreement between empirical and modeled results.

With increased water demand and stresses on fresh water sources, desalination plants are being installed on a global basis [74]. The high salt concentration in the brine and several chemical products used in the desalination process are most often returned to

the sea [75]. Most impacts on the marine environment arise as a consequence of this brine discharge. High environmental quality plants are reviewing the content and impact of concentrate discharge [76]. One area of concern has arisen from the increase in coastal harmful algal blooms. If a bloom should occur near water intake, then biotoxins, such as domoic acid could be significant in the concentrate. Advanced oxidative processes, such as ozonation and/or irradiation, could possibly be used to remediate concentrate before disposal, thus reducing environmental impact.

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Chapter 3 Hydroxyl Radical Rate Constant Determination of Selected Pharmaceuticals as Environmental Pollutants of Concern (EPOCs)

Chapter 3 is formatted for potential publication in *The Journal of Physical Chemistry*.

ABSTRACT

Absolute rate constants for the reaction of twelve pharmaceutical compounds with the hydroxyl radical in water have been determined using electron pulse radiolysis and absorption spectroscopy. The absolute rate constants for seven of those compounds with the hydrated electron in water have also been determined using electron pulse radiolysis and absorption spectroscopy. Pharmaceuticals/EPOCs and their bioactive metabolites can be continually introduced to the aquatic environment as complex mixtures via a number of routes, but primarily by both untreated and treated sewage. There is evidence that many of the pharmaceutical compounds studied are continually introduced to surface waters, at low parts-per-trillion/parts-per-billion concentrations and possibly greater. Determination of degradation half-lives for such compounds in natural waters may help in the development of models for expressing the theoretical persistence of these pharmaceuticals. The long-term goal of research of this nature is to provide the data necessary to develop kinetic models that describe the underlying chemistry for insight into natural aquatic processes and for process applications, such as wastewater and desalination concentrate treatment. Transient spectra peaks ranged from 310 to 480 nm, with hydroxyl radical rate constants ranging from 3.38×10^{8} to 1.63×10^{10} $M^{-1}s^{-1}$ for compounds, such as ibuprofen, ketoprofen, tetracycline, diclofenac, and chloramphenicol.

INTRODUCTION

Pharmaceuticals/EPOCs and their bioactive metabolites can be continually introduced into the aquatic environment as complex mixtures via a number of routes but primarily by both untreated and treated sewage. Aquatic pollution is particularly troublesome because aquatic organisms are captive to continual life-cycle, multigenerational exposure. The possibility for continual but undetectable or unnoticed effects on aquatic organisms is particularly worrisome, because effects could accumulate so slowly that major change goes undetected until the cumulative level of these effects finally cascades to irreversible change, changes that would otherwise be attributed to natural adaptation or ecologic succession. As opposed to the conventional, persistent priority pollutants, EPOCs need not be persistent if they are continually introduced into surface waters, even at low parts-per-trillion/parts-per-billion concentrations (ng-mu g/L) [1]. The following table is measured concentrations of target EPOCs (ng/L) sorted by therapeutic class in influent and effluent grab samples collected from the Back River wastewater treatment plant (BRWWTP), Baltimore, MD [2].

Table 3.1. Concentrations of target EPOCs (ng/L) sorted by therapeutic class

Target EPOCs	Therapeutic class	Wastewater influent concentration (ng/L)	Wastewater effluent concentration (ng/L)	Removal efficiency (%)
Ibuprofen	NSAID	1900	250	87
Acetaminophen	NSAID	960	ND	>99
Naproxen	NSAID	3200	380	88
Ketoprofen	NSAID	1200	280	77
Diclofenac	NSAID	110	90	18

Relative standard deviations (R.S.D.) values were calculated using quadruplicate wastewater influent and effluent samples. Removal efficiency was calculated using the average influent and effluent EPOC concentrations [2].

Americans spend over $18 billion a year on over-the-counter products. Another example of a pharmaceutical chosen for study, and of a drug that is produced and consumed in mass is ibuprofen. Ibuprofen is a phenylpropionic acid, non-steroidal anti-inflammatory drug (NSAID) introduced into the United States in 1974 as a prescription product intended to treat arthritic conditions at daily doses of up to 2400 mg. It was subsequently approved for daily doses of up to 3200 mg/day, and then as a prescription drug to treat mild to moderate pain in 1978. Since it became available to consumers in 1984, over 100 billion 200 mg tablets of ibuprofen have been sold over-the-counter (OTC) in the United States alone. Today, consumption of OTC ibuprofen accounts for approximately one third of the market for OTC analgesics [3].

Environmental regulation of such chemicals is based on reports from pharmaceutical companies to the FDA [4]. Data to support environmental risk assessments are generated to support registration of products in the United States. In the

US, formal assessments are supplied to the FDA for any new drug with projected use that could result in a surface water concentration above one part-per-billion. The FDA uses two factors to determine the "no effect" concentrations for humans. First, safe exposure levels for the pharmaceuticals are normally directly related to therapeutic dose. Second, because many pharmaceuticals or their metabolites are ionic compounds, bioconcentration in fish tissue is not generally an important exposure pathway for human consumption [5]. The pharmaceutical industry in the US continues to investigate potential effects on the environment of trace levels of EPOCs in surface waters. Through the Pharmaceutical Research and Manufacturers of America (PhRMA), the industry has developed an environmental fate and effects model (PhATE) to predict concentrations of EPOCs in surface and drinking water to support risk assessment activities [6].

Another concentration model is reported by Huber. His study is investigating the oxidation of pharmaceuticals during conventional ozonation and advanced oxidation processes (AOPs) applied in drinking water treatment, and reported hydroxyl radical rate constants for two of the pharmaceutical in this study [7]. Ibuprofen's second order rate constant with $^{\cdot}OH$ was determined by UV/H_2O_2 method as $7.4\pm1.2 \times 10^9\ M^{-1}s^{-1}$, and diclofenac was determined by γ radiolysis as $7.5\pm1.5 \times 10^9\ M^{-1}s^{-1}$. Huber's study and a subsequent pilot study, model reactions of selected pharmaceuticals with ozone (k_{O3}) and OH radicals (k_{OH}) to show that the second order rate constants determined in pure aqueous solution could be applied to predict the behavior of pharmaceuticals dissolved in natural waters. Overall the studies concluded that ozonation and AOPs are efficient

removal processes of pharmaceuticals in drinking waters. Other various studies have also reported hydroxyl radical rate constants of pharmaceuticals examined in this study. Pulse radiolysis is the method used in this study and described in detail later, and it is an **absolute value measured directly**. Pharmaceuticals of various actions with representative structures and complexities were chosen for this study as shown in Table 3.2.

Table 3.2. EPOCs analyzed and their pharmacological effect

Compounds of Interest EPOC	**Pharmacological Effect**
ibuprofen	NSAID (non-steroid anti-inflammatory drug)
naproxen	NSAID
ketoprofen	NSAID
diclofenac	NSAID
tylosin	anti-bacterial agent
tetracycline	anti-bacterial agent
trimethoprim	anti-bacterial agent
fusidic acid	anti-bacterial agent
chloramphenicol	anti-bacterial agent
indole	anticancer
vanillin	anticancer, anticonvulsant
nadolol	antihypertensive, anti-arrhythmia

EXPERIMENTAL SECTION

All chemicals in this study were used as received. All solutions were made using deionized, Millipore-quality water (18 MΩ resistance, 120 μg L-1 TOC), and were prepared immediately before irradiation. The following chemicals were used as

received: chloramphenicol, diclofenac, fusidic acid, ibuprofen, indole, ketoprofen, nadolol, naproxen, trimethoprim, tylosin and vanillin. All chemicals were obtained at the highest purity available, and dissolved directly in water to make the standard solutions. All solutions were completely sparged with high-purity N_2O (for hydroxyl radical experiments) or N_2 (hydrated electron experiments) to remove dissolved oxygen.

Kinetic measurements on these solutions were performed using the linear accelerator/absorption spectroscopy system at the Department of Energy Radiation Laboratory, University of Notre Dame [8]. The model TB-8/16-1S linear electron accelerator, providing 5-50 ns pulses of 8 MeV electrons and generating radical concentrations of 1-3 μM per pulse in all investigated systems, was used for the pulse radiolysis experiments. The basic details of the equipment and data analysis have been given elsewhere [8, 9]. The dosimetry [10] was based on the oxidation of 0.01M thiocyanate anions (SCN^-) to $(SCN)_2^{\cdot -}$ in aqueous, N_2O-saturated solutions. During the irradiation process, the solution vessels were bubbled with only the minimum amount of gas necessary to prevent air ingress in order to prevent loss of chemical. The solution flow rates in these experiments were adjusted so that each irradiation was performed on a fresh sample.

Direct measurements of the growth kinetics were measured where possible. Most compounds gave a significant intermediate absorption in the UV-visible range of 260-800 nm. Where two peaks were absorbed, measurements were taken at each significant absorbance wavelength. Two compounds evaluated for their transient absorption, fusidic acid and tylosin, exhibited very weak transient intensity, which was

too small to allow accurate direct measurements of the growth kinetics of their intermediates. Therefore, the hydroxyl radical rate constants for those compounds were determined using SCN- competition kinetics, monitoring the change of absorption intensity of the produced $(SCN)_2^{\bullet-}$ transient at 475 nm. The experimental data were obtained by either direct transient or competition kinetics, and the confidence limit for each rate constant was calculated. The data for the ratio of [EPOC]/[SCN^-] and ratio of intensity was input into a linear curve fitting program (ORIGIN 7.5^{TM}) for plotting with the confidence limits identified as one standard deviation (S_X). The hydroxyl radical decay data are presented with the linear plotting data derived from the curve fitting program.

The rate constants for hydrated electron reactions with the pharmaceuticals examined were determined by fitting exponential decays to the pseudo-first-order kinetics of this species, monitored by its absorption at 700 nm, in pulse-electron irradiated, nitrogen-saturated, solutions at natural pH. These solutions also contained 0.50 M tert-butyl alcohol to scavenge the hydroxyl radicals and hydrogen atoms, converting them into relatively inert 2-methyl-2-propanol radicals. Each kinetic trace was obtained by averaging the data of 10-20 individual pulses.

RESULTS AND DISCUSSION

Kinetic Measurements. The radiolysis of water gives a distribution of transient and stable products according to the equation [11, 12]:

$$H_2O \text{ -}\wwwvv\rightarrow [0.28]\ {}^{\bullet}OH + [0.06]\ H^{\bullet} + [0.27]e_{aq}^{-} + [0.05]H_2 + [0.07]H_2O_2 + [0.27]H_3O^{+} \quad [1]$$

where the numbers in brackets are the G-values (yields) in μmol J^{-1}. Absolute dosimetry for kinetics measurements was based on the transient absorbance produced in N_2O-saturated 1.0 x 10^{-2} M KSCN solution at λ = 475 nm (Gε = 5.2 x 10^{-4} m^2 J^{-1}) with doses of 3-5 Gy per 2-3 ns pulse [13].

Hydroxyl radical reaction rates: Most of the pharmaceuticals analyzed had their hydroxyl radical rate constants determined by direct transient pulse radiolysis. Reactive radicals were observed at the wavelengths listed in Table 3.3, as a result of a series of different doses and solute concentrations. Figure 3.1 represents the transient absorption spectrum for ibuprofen with kinetics measured at 310 nm and a max concentration of 5.07 x 10^{-4} M. The products exhibited a sufficiently high extinction coefficient, ensuring that pseudo-first order kinetics are applicable. Figure 3.2 represents the transient spectra kinetics plot for ·OH reaction with ibuprofen at the wavelength of 310 nm, where the solid line is a weighted linear fit, corresponding to a slope of (6.08 ± 0.10) x 10^9. A pseudo first-order rate constant for ibuprofen reaction was derived where, k_1 = (6.08±0.11) x 10^9 $M^{-1}s^{-1}$. An example where two transient peaks are significant would be vanillin in Figure 3.3. The transient absorption spectrum for vanillin, with kinetics measured at 350 nm and 480 nm, had a max concentration of 2.50 x 10^{-4} M. As an additional example (Figure 3.4) of transient spectra kinetics plot for ·OH reaction, vanillin is presented at one of the wavelengths measured, 480 nm, where the solid line is a weighted linear fit, corresponding to a slope of (1.19 ± 0.03) x 10^{10}. A pseudo first-order rate constant for vanillin reaction was derived where, k_1 =

(2.46±0.03) x 10^9 $M^{-1}s^{-1}$. The hydroxyl radical rate constants for the pharmaceuticals measured by direct transient pulse radiolysis are listed in Table 3.2.

Two compounds of interest, fusidic acid and tylosin, had their oxidation by reaction with the hydroxyl radical give no significant transient absorbance over the range 260-800 nm. The radical rate constant determination was therefore performed using SCN^- competition kinetics, by monitoring the changes in absorption of the $(SCN)_2^{\bullet -}$ transient at 475 nm in the competition [11]:

$$^{\bullet}OH + (EPOC) \rightarrow \text{ products} \qquad [2]$$

$$^{\bullet}OH + SCN^- (+ SCN^-) \rightarrow OH^- + (SCN)_2^{\bullet -} \qquad [3]$$

This competition can be analyzed to give the expression:

$$\frac{[(SCN)_2^{\bullet -}]_o}{[(SCN)_2^{\bullet -}]} = 1 + \frac{k_2[EPOC]}{k_3[SCN^-]} \qquad [4]$$

where a plot of $[(SCN)_2^{\bullet -}]_o/[(SCN)_2^{\bullet -}]$ against the concentration ratio $[EPOC]/[SCN^-]$ gives a straight line of slope k_2/k_3. Based on the rate constant for hydroxyl radical reaction with SCN^-, $k_3 = 1.1 \times 10^{10}\ M^{-1}\ s^{-1}$ [11], the k_2 rate constant is readily determined [9]. To isolate the reaction of $^{\bullet}OH$ with these two pharmaceuticals, solutions were pre-saturated with N_2O, which quantitatively converts hydrated electrons, e_{aq}^-, and hydrogen atom, $^{\bullet}H$, to $^{\bullet}OH$ [11]:

$$e_{aq}^- + N_2O + H_2O \rightarrow N_2 + OH^- + {}^{\bullet}OH \qquad k_5 = 9.1 \times 10^9\ M^{-1}\ s^{-1} \qquad [5]$$

$$^{\bullet}H + N_2O \rightarrow {}^{\bullet}OH + N_2 \qquad k_6 = 2.1 \times 10^6\ M^{-1}\ s^{-1} \qquad [6]$$

The hydroxyl radical kinetic data were obtained using absorption spectroscopy at 475 nm. A typical kinetic plot of $(SCN)_2^{\bullet -}$ formation at 475 nm for the fusidic acid reaction

with ·OH is graphically presented in Figure 3.5. The transformed kinetic data for the hydroxyl radical of fusidic acid is graphically presented in Figure 3.6, representing hydroxyl radical rate constants of $(1.63\pm0.18) \times 10^{10}$ $M^{-1}s^{-1}$. Table 3.3 presents all of the calculated hydroxyl radical rate constants for the pharmaceutical compounds.

Table 3.3. Hydroxyl radical rate constants ($M^{-1}s^{-1}$) of environmental pollutants of concern (EPOCs), and the analytical method by which they were obtained

Compounds of Interest EPOC	**Peak λ of Transient and ·OH Rate Constant ($M^{-1}s^{-1}$)**	**·OH Analysis**
chloramphenicol	370 nm = $(2.71\pm0.07) \times 10^{9}$	Transient
diclofenac	380 nm = $(9.59\pm.11) \times 10^{9}$ 400 nm = $(8.12\pm0.23) \times 10^{9}$	Transient
ibuprofen	310 nm = $(6.08\pm0.11) \times 10^{9}$	Transient
indole	320 nm = $(9.29\pm0.32) \times 10^{9}$	Transient
ketoprofen	390 nm = $(4.63\pm0.23) \times 10^{9}$	Transient
nadolol	340 nm = $(3.38\pm0.46) \times 10^{8}$	Transient
naproxen	340 nm = $(3.49\pm0.18) \times 10^{9}$	Transient
tetracycline	400 nm = $(4.91\pm0.95) \times 10^{8}$	Transient
trimethoprim	320 nm = $(1.13\pm0.02) \times 10^{10}$ 340 nm = $(8.13\pm0.12) \times 10^{9}$	Transient
vanillin	350 nm = $(1.02\pm0.02) \times 10^{10}$ 480 nm = $(1.19\pm0.03) \times 10^{10}$	Transient
fusidic acid	$(1.63\pm0.18) \times 10^{10}$	Competition
tylosin	$(8.64\pm0.78) \times 10^{9}$	Competition

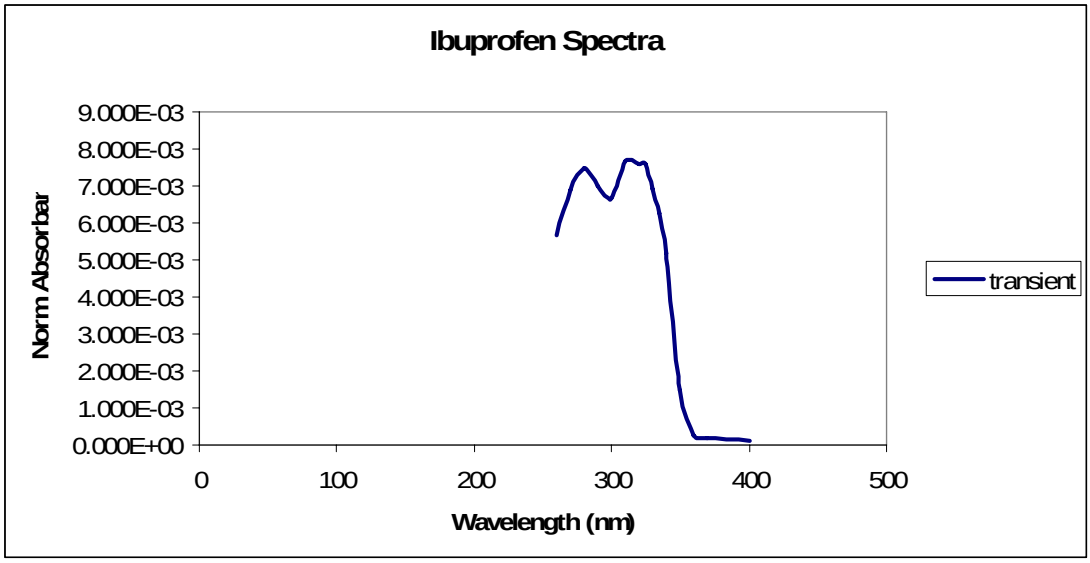

Figure 3.1. Transient absorption spectrum for ibuprofen (kinetics measured at 310 nm, a max concentration of 5.07 x 10^{-4} M)

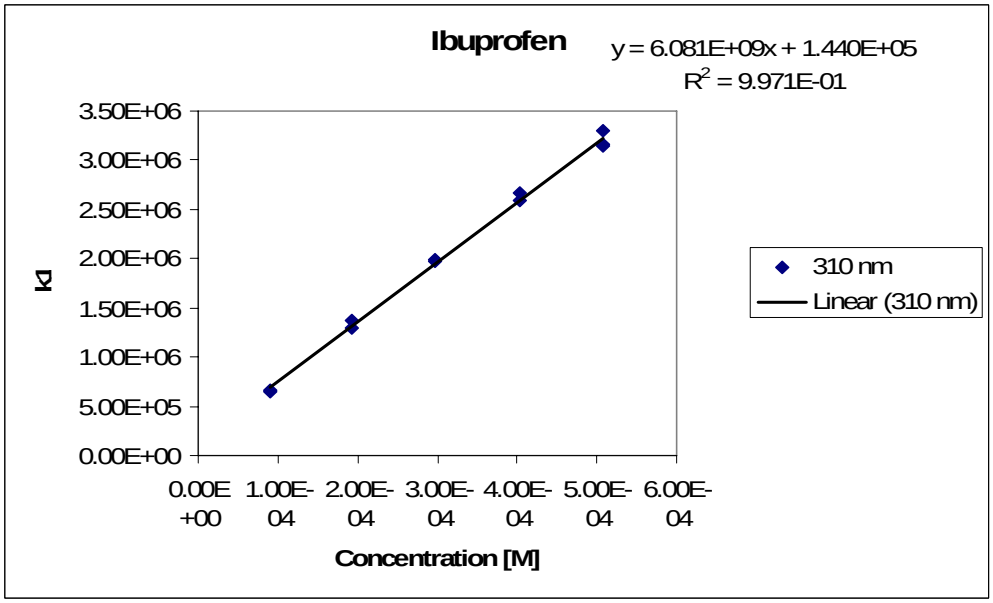

Figure 3.2. Transient spectra kinetics plot for ·OH reaction with ibuprofen at the wavelength of 310 nm, The solid line is a weighted linear fit, corresponding to a slope of (6.08 ± 0.10) x 10^9. A pseudo first-order rate constant for ibuprofen reaction was derived where, k_1 = (6.08±0.11) x 10^9 $M^{-1}s^{-1}$.

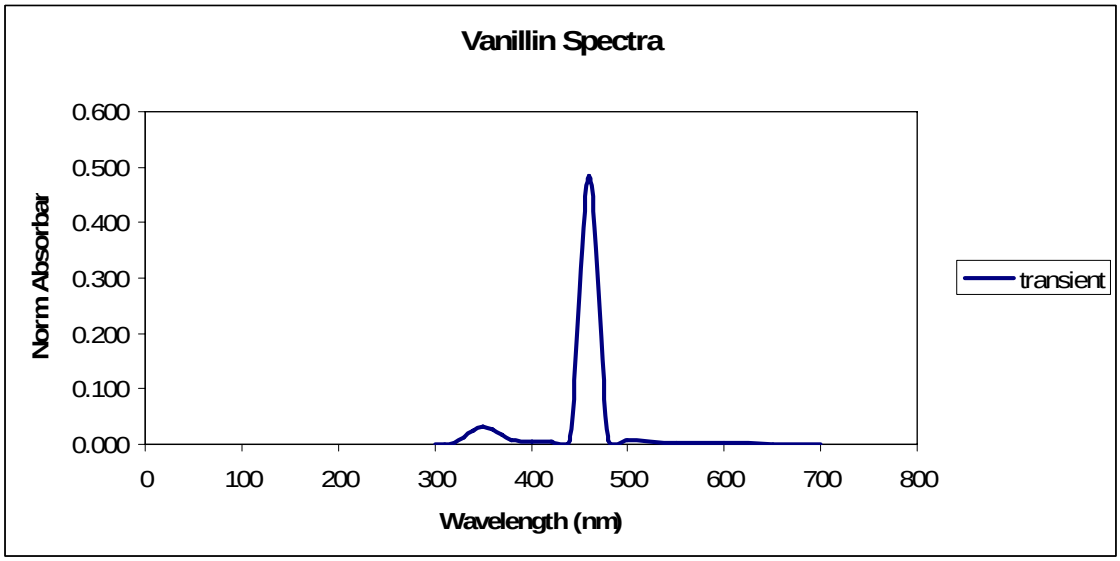

Figure 3.3. Transient absorption spectrum for vanillin (kinetics measured at 350 nm and 480 nm, a max concentration of 2.50 x 10^{-4} M)

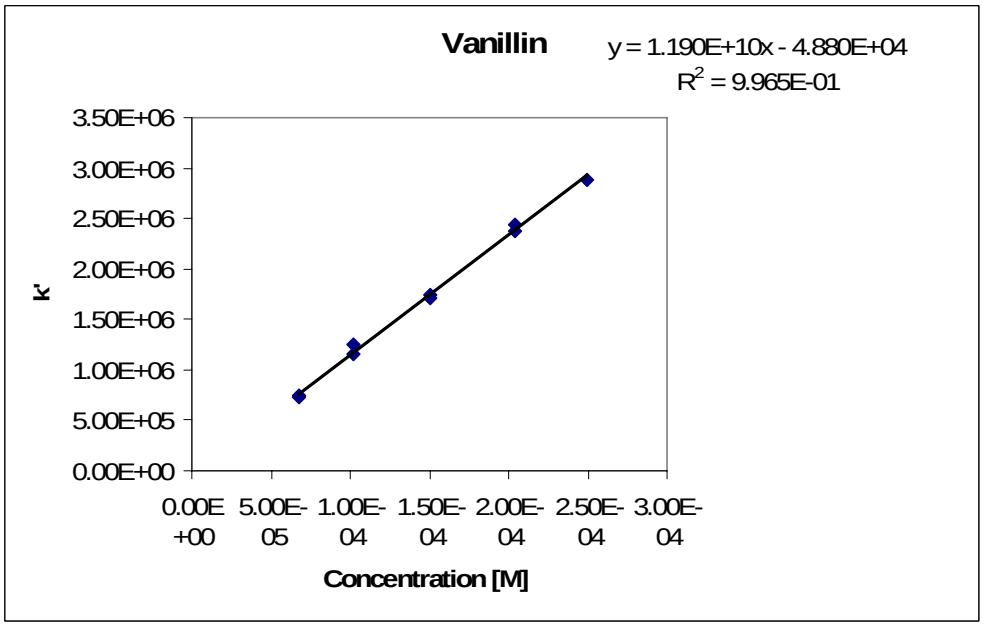

Figure 3.4. Transient spectra kinetics plot for $^{\cdot}OH$ reaction with vanillin at the wavelength of 480 nm, The solid line is a weighted linear fit, corresponding to a slope of $(1.19 \pm 0.03) \times 10^{10}$. A pseudo first-order rate constant for vanillin reaction was derived where, $k_1 = (2.46 \pm 0.03) \times 10^9\ M^{-1}s^{-1}$.

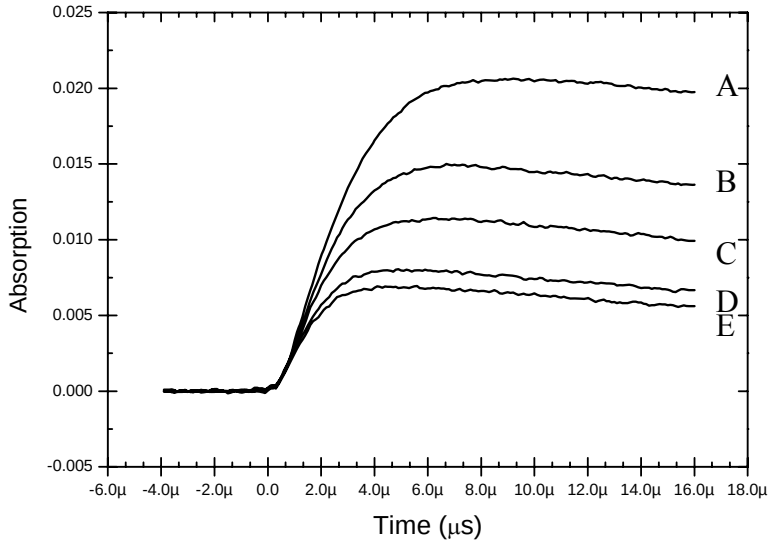

Figure 3.5. Typical kinetic plot of $(SCN)_2^{\cdot -}$ formation for fusidic acid reaction with $^{\cdot}OH$. Plot for 475 nm and N_2O^- saturated 6.15×10^{-5} M KSCN solution containing zero (A), 5.54×10^{-5} M (B), 1.15×10^{-4} M (C), 2.29×10^{-4} M (D), and 1.71×10^{-4} M fusidic acid at standard solution pH and 21°C. Kinetic traces shown were obtained from an average of 20 pulses.

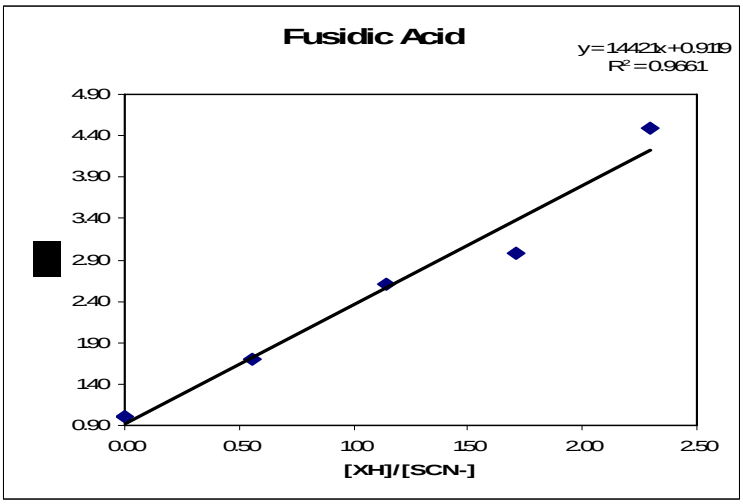

Figure 3.6. Competition kinetics plot for $^{\cdot}OH$ reaction with fusidic acid using SCN^- as a standard. The solid line is a weighted linear fit, corresponding to a slope of (1.44 $\pm$ 0.16). A pseudo first-order rate constant for domoic acid reaction was derived where, k_1 = (1.63$\pm$0.18) x 10^{10} $M^{-1}s^{-1}$.

Hydrated electron reaction rates: Seven EPOCs were analyzed for their hydrated electron reaction rates, and ketoprofen is shown as a representative of this group. Table 3.4 is the experimental data for the hydrated electron radical with ketoprofen. The reaction rate of e^-_{aq} with ketoprofen was determined using increasing concentrations of ketoprofen as graphically represented in Figure 3.7. The bimolecular rate constant for the reaction of e^-_{aq} with ketoprofen was determined from a plot of five kinetic traces. The solid line in Figure 3.8 corresponds to a weighted linear fit with a rate constant of (2.61$\pm$.05) x 10^{10} s^{-1}. The weighting corresponds to the S_X as applied in the ORIGIN^{TM} graphing program. Table 3.5 tabulates all of the hydrated electron reaction rates of the pharmaceuticals analyzed.

Table 3.4. Ketoprofen hydrated electron radical experimental data

[Keto] Added ($x10^{-4}$)	Nrml. Dose, Volts ($x10^{-1}$)	Absorb. Data	Absorb. ($x10^{-3}$)	k' ($x10^{-6}$)	Confid. Limit, S_X	Linear Plot k' ($x\ 10^{-4}$)	Linear Plot [Keto] (mM)
5.00	1.771	0.00251	2.51	14.7	18400	3.263	7.126
	1.793	0.00237	2.37	14.9		2.973	6.509
4.02	1.776	0.00259	2.59	12.6	142000	2.684	5.892
	1.784	0.00255	2.55	12.8		2.394	5.275
3.03	1.757	0.00302	3.02	10.2	58000	2.105	4.657
	1.771	0.00302	3.02	9.69		1.815	4.040
2.06	1.728	0.00406	4.06	7.21	138000	1.526	3.423
	1.750	0.00406	4.06	7.38		1.236	2.806
1.01	1.748	0.00757	7.57	4.64	146000	0.9473	2.189
	1.756	0.00801	8.01	4.41		0.6578	1.572

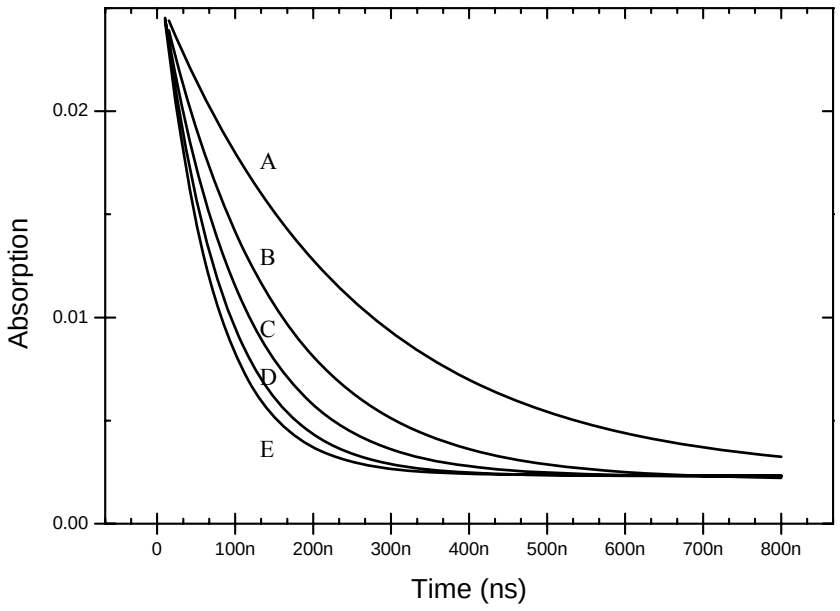

Figure 3.7. Typical kinetic decay profiles obtained for the hydrated electron absorbance at 700 nm for the electron pulse irradiated aqueous solution at natural pH and 21°C containing 1.01 x 10^{-4} (A), 2.06 x 10^{-4} (B), 3.03 x 10^{-4} (C), 4.02 x 10^{-4} (D), and 5.00 x 10^{-4} (E) M ketoprofen, respectively. Curves shown are the average of 15 individual

pulses. Solid lines correspond to a rate constant fitting with the pseudo-first order value of (2.61±.05) x 10^{10} s^{-1}.

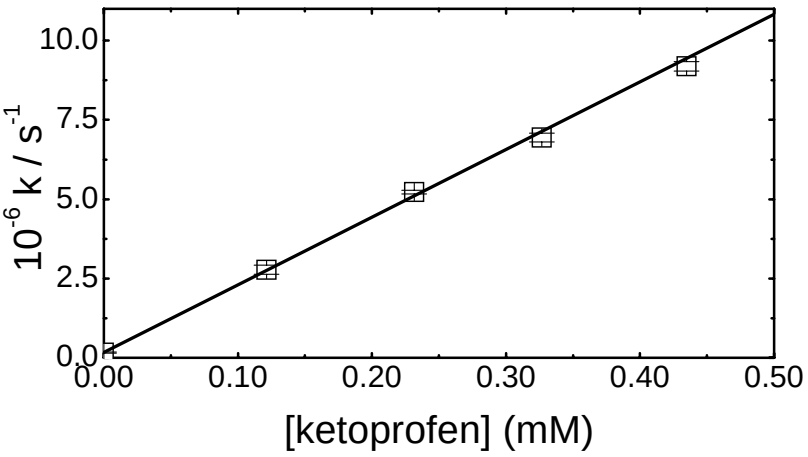

Figure 3.8. Second-order rate constant determination for the reaction of the hydrated electron with ketoprofen, Single point error bars are one standard deviation, as determined from the average of at least three kinetic traces. Solid line corresponds to weighted linear fit, giving k = (2.61 ± 0.05) x 10^{10} $M^{-1}s^{-1}$.

Table 3.5. Hydrated electron (e^-_{aq}) reaction rate constants for EPOCs

Compounds of Interest EPOC	**Hydrated electron Reaction rates ($M^{-1}s^{-1}$)**
chloramphenicol	(3.71±0.06) x 10^{10}
diclofenac	(1.684±0.05) x 10^9
ibuprofen	(8.86±0.08) x 10^9

ketoprofen	$(2.61 \pm 0.05) \times 10^{10}$
naproxen	$(4.86 \pm 0.20) \times 10^{9}$
trimethoprim	$(8.60 \pm 0.07) \times 10^{9}$
vanillin	$(1.81 \pm 0.06) \times 10^{10}$

Pulse radiolysis is the method used in this study, and it is an **absolute value measured directly**. Other methods represented in Table 3.6 are relative values measured by steady state. The following table is a compilation from both a literature search and the Notre Dame Radiation Lab's Data Center (refer to references listed with the Center, www.rcdc.nd.edu, accessed March 2007):

Table 3.6. Hydroxy radical rate constants for pharmaceuticals of interest (from literature)

Pharmaceutical	**second order hydroxyl radical rate constant**	**Experimental Method**
chloramphenicol	5.8×10^{9} $M^{-1}s^{-1}$	Pulse radiolysis
diclofenac	$7.5 \pm 1.5 \times 10^{9}$ $M^{-1}s^{-1}$	γ radiolysis
ibuprofen	$7.4 \pm 1.2 \times 10^{9}$ $M^{-1}s^{-1}$	UV/H_2O_2
indole	3.2×10^{10} $M^{-1}s^{-1}$	Pulse radiolysis
ketoprofen	1.6×10^{10} $M^{-1}s^{-1}$	Fenton's reaction
naproxen	$9.6 \pm 0.05 \times 10^{9}$ $M^{-1}s^{-1}$ 2.4×10^{10} $M^{-1}s^{-1}$	Fenton's reaction[14] Fenton's reaction
Tetracycline, conj. acid	4.3×10^{8} $M^{-1}s^{-1}$	γ radiolysis

Photodegradation Estimation for Pharmaceuticals in Natural Waters. Foundational to all of the reactions studied in this project, is that in the course of the chemical reaction, concentrations will change with time as reactants become products. Experimental chemical kinetics include the development of techniques that allow for the study of chemical reactions including the measurement and analysis of chemical reaction dynamics. Sunlight-induced photochemical processes, as previously mentioned, have been determined to be a primary degradation mechanism for the in situ, biologically produced amnesic shellfish poison (ASP), domoic acid [15-17]. The redox chemistry in surface waters has been linked to humic substances as initiators of photoreactions, and some of those reactions are considered secondary products. Photochemically mediated processes, both primary and secondary, have important ramifications with respect to modifications of pollutants, regulation of the redox properties of natural waters, and the decomposition of humic substances [18-20].

Direct sunlight photolysis of hydrogen peroxide is one possible mechanism for the formation of ·OH in surface waters, but it is not considered as a primary mechanism [21-23]. Significant sources of ·OH may come from secondary (indirect or sensitized) Photo-Fenton reactions, the oxidation of Cu(I) and Fe(II) by H_2O_2 and/or by nitrate ion photolysis [24-27]. Taking the photochemical reaction of the pharmaceuticals or EPOCs with ·OH to produce a product, a second order rate law would apply. However, if the initial concentration of the reactant ·OH is much larger than the concentration of the EPOC, the concentration of ·OH will not change appreciably during the course of the reaction. The concentration of the reactant in excess, [·OH], will remain almost constant. This may be a large assumption given the low steady-state concentrations of ·OH in

surface, but it is useful in modeling to determine relative half-lives of environmental pollutants of concern.

The steady-state concentration of the relatively short-lived photoreactant [·OH] was experimentally determined in a way that produced a simple second-order rate law. The rate of transformation of each pharmaceutical was first order in concentration of both the EPOC and ·OH, giving a second order overall.

$$\frac{d[EPOC]}{dt} = k_{EPOC,OH}[\cdot OH]_{SS}[EPOC] \quad [7]$$

$\cdot OH_{SS} = 2.5 \times 10^{-17}$ M (Midday, June, sunlight 1 kW/m^2 with DOM [27])

$$\frac{d[EPOC]}{dt} = (k_{EPOC,OH})(2.5 \times 10^{-17}\ M)[EPOC] \quad [8]$$

$$\frac{d[EPOC]}{dt} = k'[EPOC] \quad [9]$$

First order half life of EPOCs/Pharmaceuticals

$$t_{1/2}\ DA = \frac{-\ln 1/2}{k'} = \frac{0.693}{k'} = \frac{(1\ min)(1\ hr)(1\ day)}{(60\ s)(60\ min)(24\ hrs)} = \_\_\_\_\_\ \textbf{days} \quad [10]$$

Given the real life time in days of continual, maximum sunlight that most of these pharmaceutical half-lives might represent, significant photodegradation via ·OH mechanisms is unlikely. Reaction rates are rapid, but also, probably negligible in surface waters because of the low steady-state concentrations of ·OH.

Table 3.7. Hydroxyl radical rate constants ($M^{-1}s^{-1}$) of environmental pollutants of concern (EPOCs), and an approximated photolytic half life in natural waters (June, midday sunlight)

Compounds of Interest EPOC	**Peak λ of Transient and ·OH Rate Constant ($M^{-1}s^{-1}$)**	**$t_{1/2}$ (days)**
chloramphenicol	370 nm = (2.71±0.07) x 10^9	118
diclofenac	380 nm = (9.59±.11) x 10^9 400 nm = (8.12±0.23) x 10^9	33 39
fusidic acid	(1.63±0.18) x 10^{10}	20
ibuprofen	310 nm = (6.08±0.11) x 10^9	53
indole	320 nm = (9.29±0.32) x 10^9	35
ketoprofen	390 nm = (4.63±0.23) x 10^9	69
nadolol	340 nm = (3.38±0.46) x 10^8	949
naproxen	340 nm = (3.49±0.18) x 10^9	92
tetracycline	400 nm = (4.91±0.95) x 10^8	630
trimethoprim	320 nm = (1.13±0.02) x 10^{10} 340 nm = (8.13±0.12) x 10^9	29 39
tylosin	(8.64±0.78) x 10^9	36
vanillin	350 nm = (1.02±0.02) x 10^{10} 480 nm = (1.19±0.03) x 10^{10}	32 27

Hydroxyl radicals are considered to be one of the main oxidizing species in the advanced oxidation processes. Free radical AOPs have been well studied for degradation of many environmental pollutants [28-31]. Models of the fate of the EPOCs

in natural waters are complicated by the extremely variable composition, and in most cases relatively complex systems [32]. The chemical species that are most common are dissolved organic matter and a number of ions, such as chloride, nitrate, sulfate, carbonates and sodium. In attempting to model natural waters using the $^{\cdot}OH$ rate constants within a system, the consideration of initial solute concentrations and of $^{\cdot}OH$ scavenging in relation to pH becomes very important. Table 3.8 presents bimolecular rate constants ($M^{-1}s^{-1}$) of chemicals commonly found in natural waters [11]. Models have been considered with single solute systems [33-36], with natural chemical species [16, 37, 38], with the photochemical degradation [15, 39], with the microbial degradation [40], and even with mixtures of the microconstituents [37], and each meets with a level of success. However, they are each interdependent, and only pieces of a natural system that is extremely dynamic. Every rate constant, concentration value, absorption, degradation mechanism, relationship, etc. brings conceptual models one step closer to agreement between empirical and modeled results.

The reaction of a solute with $^{\cdot}OH$ or e^{-}_{aq} is a bimolecular process, as shown in Equations [2] and would be similar for e^{-}_{aq}. The overall rate depends on the solute and radical concentrations. Second-order rate constants can be measured using several methods, with pulse radiolysis being the most versatile. Using the bimolecular rate constants, it is possible to calculate the relative importance of the three primary products of water radiolysis on the removal of some EPOCs [41]. These calculations are important to consider when predicting the overall efficacy of the process for a particular problem. The extension of these calculations to natural water must also consider scavengers, such as those listed in Table 3.8. For example, carbonate ion and dissolved

organic matter react with all three reactive species.

Table 3.8. Bimolecular rate constants ($M^{-1}s^{-1}$) of chemicals commonly found in natural waters (Buxton et al., 1988)[11]

Compound	$OH^{\cdot}$	e^{-}_{aq}	$H^{\cdot}$
O_2	NR	1.9×10^{10}	1.2×10^{10}
HCO_3^-	8.5×10^6	$<1.0 \times 10^6$	4.4×10^4
CO_3^{2-}	3.9×10^8	3.9×10^5	NR
Cl^-	3.0×10^9	$<1.0 \times 10^6$	$<1.0 \times 10^5$
NO_2^-	1.1×10^{10}	3.5×10^9	7.1×10^8
NO_3^-	NR	9.7×10^9	1.4×10^6
DOC	2.0×10^8	NR	NR

For pure water case, the overall removal of solute can be described by the following kinetic expression [41]:

$$\frac{d[R]_t}{dt} = k_1[R][{}^{\cdot}OH] + k_2[R][e^-_{aq}] + k_3[R][{}^{\cdot}H] \quad [11]$$

Where k_1, k_2, and k_3 are the respective second-order constants. Given radiation chemical yields expressed as G values, it is possible to calculate the concentrations of oxidative and reductive species in pure water at a known absorbed dose. The SI unit of dose is the gray (Gy), which equals an energy deposition of 1 (Joule/kilogram) J kg^{-1}. For example, the concentration of $^{\cdot}OH$ produced in pure, neutral water by absorbing 1 kGy is:

$$[{}^{\cdot}OH] = 1000 \text{ J kg}^{-1} \times 0.28 \text{ μmol J}^{-1} = 280 \text{ μmol kg}^{-1} \quad [12]$$

This calculated value is a maximum concentration. Reactions with solutes and other radiolytically produced species will decrease this concentration via scavenging reactions. The relative contributions to solute removal by the three species may now be compared, using an absorbed dose of 1 J. The product of the radical concentration and the bimolecular rate constant (with appropriate unit conversions) is a pseudo-first-order rate constant (k') for reaction with solute R, with units of reciprocal time:

$$G(\mu molJ^{-1}) \times 1\ JL^{-1} \times k(Lmol^{-1}s^{-1}) = k'(s^{-1}) \quad [13]$$

(For aqueous solutions, 1 kg = 1 L and the appropriate value is included to account for 106 μmol/mol.) A high first-order rate constant indicates high removal efficiency, such as the solvated electron radical rate constant found for tetracycline. The total removal rate is given by:

$$\text{Removal rate}[R] = (k'_1 + k'_2 + k'_3)[R] \quad [14]$$

The rate of removal due to an individual reactive species may be found by dividing the individual pseudo-first-order rate constant by the sum of the three:

$$\%\ \text{Removal}[R] = 100 \times (k'_1/k'_1 + k'_2 + k'_3)[R] \quad [15]$$

An example of the relative importance of the hydroxyl radicals measured for tetracycline removal in pure water, at an absorbed dose of 1 kGy, is shown in Table 3.9. Tetracycline was the only pharmaceutical where all three radical reaction rates could be found. The use of pseudo-first-order dose constant assumes that the removal of solutes is exponential, which is common in waste-treatment applications or AOP [42]. Tetracycline shows a high percent removal via solvated electron (66%), and to a lesser extent (34%) via ·OH, also indicating that ·H should play a very minute role in the degradation process.

Table 3.9. Removal rate (%) efficiency of tetracycline (A comparison of reaction of e^-_{aq}, $^{\cdot}H$, and $^{\cdot}OH$ with tetracycline in pure water at an absorbed dose of 1 kGy)

Species	Concentration (M)	$k(M^{-1}s^{-1})$	$k'(s^{-1})$	%
$^{\cdot}OH$	2.8×10^{-4}	4.91×10^{8}	2.65×10^{6}	33.8
e^-_{aq}	2.7×10^{-4}	1.9×10^{10}	5.13×10^{6}	65.5
$^{\cdot}H$	6.0×10^{-5}	8.9×10^{8}	5.34×10^{4}	0.7

In conclusion, the use of kinetic data in modeling is foundational to understanding complex aquatic systems, as well as developing a quantitative understanding of pollutant degradation processes. Important considerations for extending laboratory data to natural waters would be such things as pH, carbonate/bicarbonate alkalinity, and dissolved oxygen.

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Chapter 4 Environmental Relevance

A. Chemical – Direct and Indirect Photolysis

The chemical composition of natural waters is attained through a variety of chemical reactions and physiochemical processes, such as acid-base reactions, gas-solution processes, precipitation and dissolution of solid phases, complexation reaction of metals and ligands, oxidation-reduction reactions, adsorption processes at interfaces, and distribution of solutes between aqueous and non aqueous phases [1]. Two types of models are typical for idealized (either considered open or closed systems) natural water systems; thermodynamic or equilibrium models and kinetic models. Thermodynamic models have been more extensively developed, however, when the assumptions of equilibrium models no longer apply, kinetic information needs to be brought to bear in the analysis of natural water systems. Since rates of different chemical reactions in water can greatly differ, kinetic and equilibrium descriptions will often be needed for the same system. Thermodynamic information enables us to identify reactions that are possible, to calculate the equilibrium composition of a solution, and to find the maximum useful work done or minimum energy needed for a process, but definite conclusions concerning the time required to reach equilibrium require kinetic information. Kinetic information must be used to describe the rate of approach to the appropriate stationary state for closed and open systems. Chemical kinetics are concerned with the rate at which chemical change takes place. In order to better assess the environmental relevance of the compounds analyzed as potential environmental

pollutants of concern, the hydroxyl radical rate constants will be applied in two different models.

The first will use an estimate of the hydroxyl radical concentration found in natural waters to estimate half lives for the EPOCs analyzed. Sunlight-induced photochemical processes, as previously mentioned, have been determined to be a primary degradation mechanism for domoic acid and pharmaceuticals [2-4]. The redox chemistry in surface waters has been linked to humic substances as initiators of photoreactions, and some of those reactions are considered secondary products. Photochemically mediated processes, both primary and secondary, have important ramifications with respect to modifications of pollutants, regulation of the redox properties of natural waters, and the decomposition of humic substances [5-7].

Ultraviolet radiation, primarily between 200-400 nm, has been shown to degrade organic compounds by direct photolysis of photolabile compounds as a consequence of light of absorption [1]. For a compound to be photolabile, it needs to have the capacity to absorb photons of the incident light. Degradation predictions have been studied by measuring the decadic molar absorption coefficient, which indicates the probability that a compound will absorb light at a certain wavelength [8]. It was shown that for two compounds that are included in this study, naproxen and ketoprofen, absorbance was present only at the minima of approximately 250 nm. Degradation of naproxen and ketoprofen by LP/UV (low pressure/ultraviolet light) photolysis was not expected to be high as a result of the model presented. However, another report by Packer et al showed rapid direct photolysis under sunlight of naproxen and diclofenac, with ibuprofen showing photostability due to little absorbance in the solar spectrum region [9].

Diclofenac reacted rapidly via direct irradiation with a half-life of 39 minutes in both natural and Milli-Q water. Naproxen was also rapidly transformed with a half-life of 42 minutes reported for the approximation of summer sunlight at 45^{o} latitude. This same report added the ·OH radical quencher isopropyl alcohol to both the Milli-Q water and natural water experiments. The quencher was added in order to assess the radical mediated indirect processes that may also be important in the removal mechanisms of EPOCs. Naproxen experienced a decrease in reaction rate and diclofenac an increase, upon the addition of isopropyl alcohol. It was suggested that a radical of naproxen itself may have been the cause of the decrease in the reaction rate. The acceleration in reaction rate for diclofenac was suggested to have been due to the formation of a carbon centered radical from the isopropyl alcohol which could react with molecular oxygen resulting in superoxide and hydroperoxyl radicals. Previous studies suggest that direct photolysis is still the dominant degradation mechanism for diclofenac.

Direct sunlight photolysis of hydrogen peroxide is one possible mechanism for the formation of ·OH in surface waters, but it is not considered as a primary mechanism [10-12]. Significant sources of ·OH may come from secondary (indirect or sensitized) Photo-Fenton reactions, the oxidation of Cu(I) and Fe(II) by H_2O_2 and/or by nitrate ion photolysis [13-16]. Taking the photochemical reaction of DA with ·OH to produce a product, a second order rate law would apply. However, if the initial concentration of the reactant ·OH is much larger than the concentration of DA, the concentration of ·OH will not change appreciably during the course of the reaction. The concentration of the reactant in excess, [·OH], will remain almost constant. This may be a large assumption given the low steady-state concentrations of ·OH in surface, but it is useful in modeling

to determine relative half-lives of environmental pollutants of concern, as shown in the previous chapter.

The photodegradation of domoic acid has recently been presented for natural water matrices in two studies. The first by Bouillon et al analyzed the importance of the photodegradation rate for extracellular domoic acid in the removal process in coastal seawater [2]. Kinetic data were presented regarding the molar absorption coefficient and quantum yield, then potential in situ loss rates and turnover rate constants for domoic acid photodegradation were modeled. Direct photochemical pathways were reported to be a major sink degradation reported on a time scale of days.

The second study by Fisher et al used a multivariate model approach assessing the roles of Fe(III), phosphate, dissolved organic matter (DOM), and nitrate during photodegradation [3]. It was found that Fe(III) and DOM were significant promoters of domoic acid photooxidation. Domoic acid half lives were reported between 12-36 hours with half-life a function of Fe(III) and phosphate, and DOM loadings. The multifactor approach to this study provided valuable insight into how the different variables that affect bloom growth may act alone or in concert to moderate the environmental impact of the biotoxin, domoic acid.

B. Biological – Focus on Microbial Impact

The enormous turnover of carbon in nature depends partly upon catabolic reactions catalyzed by microorganisms [17]. Biodegradability is another important factor that determines the residence time of organic pollutants in the receiving waters. Synthetic compounds may persist in the environment if their chemical structures

preclude attack by these microbial enzymes [1]. Understanding of the microbial processes can assist with both prevention and remediation of EPOCs. Sometimes degradability of a molecule may be improved by modifying its structure. Biodegradability may be enhanced by replacing a sulfonate group by a carboxylic group or more generally by incorporating degradophores, that is, molecular groupings that are substrates for attack by microbial oxidases [18]. These enzymes affect hydroxylation and convert persistent molecules into more water-partitioning derivatives which are excreted rather than bioconcentrated. In regards to remediation, the microbial impact on the degradation of EPOCs has primarily been studied in terms of wastewater treatment removal. Many toxic organic compounds have been shown to undergo rapid, extracellular microbial degradation in wastewater and natural systems [17, 19, 20]. Table 1 from the Introduction on pharmaceuticals presents a study on the percent removal of several of the compounds in this study. One report found no ibuprofen in effluent, and presented > 99% biological removal of trimethoprim and > 90% removal of indole [19]. An additional study presented a removal rate from a wastewater treatment plant for ibuprofen of 93% [21]. Although removal rates are high, the continuous input into natural waters of these highly bioactive compounds may be significant. With such low concentrations and long-term exposure, determining ecological impact may prove extremely difficult.

Studies of the biodegradation of domoic acid by a variety of bacteria isolated from the marine environment indicate that the ability to grow on or degrade domoic acid is rare. In fact, domoic acid was inhibitory to resting cells or growing cultures of most of these bacteria [22, 23]. Hagstrom et al, recently reported the dissolved toxin to be

stable in the presence of the bacteria studied for at least 20 days [23]. Another study suggested that photodegradation seemed to be the pathway to degradation, rather than bacterial degradation [4].

C. Physical – Focus on Particle Adsorption

The significance of the solid-solution interface in natural waters becomes apparent when one considers the state of solids typically present in natural waters. The dispersed phase in a natural body of water consists predominantly of inorganic colloids, such as clays, metal oxides, metal hydroxides, and metal carbonates, and of organic colloidal matter of detrital origin, as well as living microorganisms, such as algae and bacteria [1]. Adsorption of a solute molecule on the surface of a solid can involve removing the solute molecule from the solution, removing solvent from the solid surface, and attaching the solute to the surface of the solid. The net energy of interaction of the surface with the adsorbate, in this case an EPOC, may result from short-range chemical forces (covalent bonding, hydrophobic bonding, hydrogen bridges, steric or orientation effects) and long-range forces (electrostatic and van der Waals attraction forces). Whether a particle with the adsorbed pollutant will settle depends on its density, its size, and the water movement.

Natural organic substances, such as dissolved organic matter (DOM), are found in most natural waters. These humic substances not only play a role in adsorption and flocculation, but they play a major role in the photoprocesses of surface waters [5]. DOM tends to be ubiquitous and among the most highly absorbing compounds found in

natural waters. A recent study of aquatic colloids and endocrine disrupting chemicals found that between 10 and 29% of the dissolved concentrations were associated with aquatic colloids [24]. As 10-40% of marine total organic carbon is colloidal in nature [25], the speciation, bioavailability, transport, and ultimate fate of trace pollutants are controlled by their sorption onto colloids because of their large surface area and a great number of sorption sites. To understand the role of colloids in the fate and behavior of EPOCs in the aquatic environment, it is essential to obtain and characterize colloids of different origins for determining their key physicochemical properties [24].

A recent study on the role of various particles on the adsorption of dissolved domoic acid suggested that major ions in seawater neutralize electrostatic attractions to particles, and domoic acid and its isomers are not very particle reactive [26]. Transport of domoic acid to bottom sediments may be mainly biologically driven.

D. Future Research

Improving our ability to predict removal efficiency of EPOCs from water sources for use in kinetic modeling, should be a high priority of future research [27]. Additional kinetic data with regards to the hydrogen atom reaction rate constants, and the hydrated electron reaction rate constants, for those that were not determined for all of the pharmaceuticals examined, should be analyzed.

Advanced oxidative technologies (AOT) are more recently incorporating the use of ionizing radiation to selectively decompose target pollutants in solution [28-30]. Radioisotope sources, especially ^{60}Co, are inexpensive and already used in other process applications. Most radiolysis research has been performed with steady state Co γ-rays,

often in anticipation that the results will be used for scale-up to process applications with electron beams (e-beams). The reactions resulting from γ-irradiation are the same as those of e-beam irradiation. The advantage of photons is that they carry no charge, allowing deep penetration into the irradiated medium prior to energy deposition. The use of photon sources fills a niche that complements the use of e-beams for waste treatment. Three of the pharmaceuticals (ibuprofen, naproxen, diclofenac) analyzed for radical reaction rates in this study were also ^{60}Co irradiated for degradation product analysis. Total organic carbon, total organic nitrogen, and LC-Mass Spec analysis will assist in future mechanistic studies of the degradation process.

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Appendix

Appendix A
Materials

	Name (Amount) Pharmacological Effect	CAS	Company Lot #	MW	Formula	% pure +
1	Pyrrolidine (100mL)	[123-75-1]	Sigma Aldrich 02840EB	71.12	C_4H_9N	99.5
2	L-proline (100g)	[147-85-3]	Sigma P0380 045K0102	115.13	$C_5H_9NO_2$	99
3	L-pyroglutamic acid (25g)	[98-79-3]	Fluka 83160 1174032 54305064	129.12	$C_5H_7NO_3$	99
4	(R)-(-)-5-(Hydroxymethyl) -2-pyrrolidinone (1g)	[66673-40-3]	Aldrich 366358 05415TD	115.13	$C_5H_9NO_2$	99
5	trans-4-Hydroxy-L-proline (10g)	[51-35-4]	Aldrich H54409 14328DD	131.13	$C_5H_9NO_3$	99
6	(-)-(a)-Kainic Acid (hydrate) (50mg) Antinematodal Agents Excitatory Amino Acid Agonist	[487-79-6]	Cayman Chem Cat 78050	231.20	$C_{10}H_{15}NO_4$ 4.H_2O	98
7	Domoic acid (1mg x 2) Neuromuscular Depolarizing Agents	[14277-97-5]	Fluka 44246	311.30	$C_{15}H_{21}NO_6$	97
8	Trimethoprim Anti-Infective Agents, Urinary Antimalarials Folic Acid Antagonists	[738-70-5]	016K1157	290.3	$C_{14}H_{18}N_4O_3$	99
9	(-)-Naproxen sodium salt 5g Anti-Inflammatory Agents, Non-Steroidal Gout Suppressants Cyclooygenase Inhibitors	[26159-34-2]	084K1666	252.2	$C_{14}H_{14}O_3$	

Appendix A
Materials Continued

	Name (Amount) Pharmacological Effect	CAS	Company Lot #	MW	Formula	% pure +
10	(S)-(+)-Ketoprofen Anti-Inflammatory Agents Non-Steroidal Cyclooxygenase Inhibitors	[22161-81-5]	03908KO	254.3	$C_{16}H_{14}O_3$	99
11	Ibuprofen sodium salt Anti-Inflammatory Agents Non-Steroidal Cyclooxygenase Inhibitors Analgesics, Non-Narcotic	[31121-93-4]	085KO716	228.3	$C_{13}H_{18}O_2Na$	99
12	Fusidic acid sodium salt Anti-Bacterial Agents Protein Synthesis Inhibitors	[751-94-0]	09TK9047	538.7	$C_{31}H_{48}O_6$ Na	99.5
13	Diclofenac sodium salt Anti-Inflammatory Agents Non-Steroidal Cyclooxygenase Inhibitors	[15307-79-6]	075K1896	318.1	$C_{14}H_{11}Cl_2NO_2$ Na	98
14	Vanillin Anticonvulsants Antioxidants Antimutagenic Agents	[121-33-5]	V110-4 00922TT	152.15	$C_8H_8O_3$	99
15	Tetracycline Anti-Bacterial Agents Protein Synthesis Inhibitors	[64-75-5]	095K1318	480.91	$C_{22}H_{24}N_2O_8$ HCl	95

Appendix A
Materials Continued

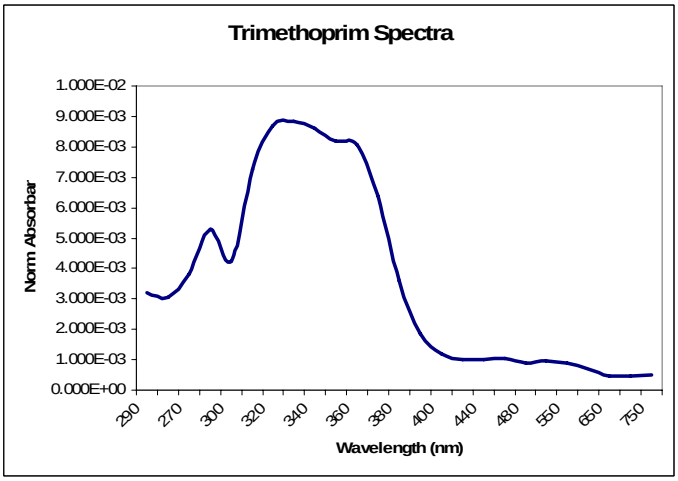
	Name (Amount) Pharmacological Effect	CAS	Company Lot #	MW	Formula	% pure +
16	Indole Anticancer	[120-72-9]	L23N49	117.15	C_8H_7N	99
17	Indole-3-acetic acid Plant Growth Regulators	[87-51-4]	10105606	175.18	$C_{10}H_9NO_2$	98
18	Chloramphenicol Anti-Bacterial Agents Protein Synthesis Inhibitors	[56-75-7]	10107516	323.13	$C_{11}H_{12}Cl_2N_2O_5$	99
19	Tylosin Anti-Bacterial Agents	[1401-69-0]	487H8918	916.1	$C_{46}H_{77}NO_{17}$	99
20	Nadolol Adrenergic beta-Antagonists Anti-Arrhythmia Agents Antihypertensive Agents Sympatholytics	[42200-33-9]	035K1196	309.4	$C_{17}H_{27}NO_4$	98

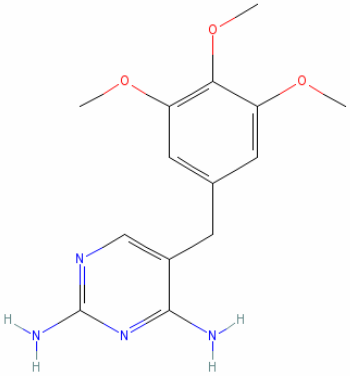
Appendix B
·OH Experimental Data

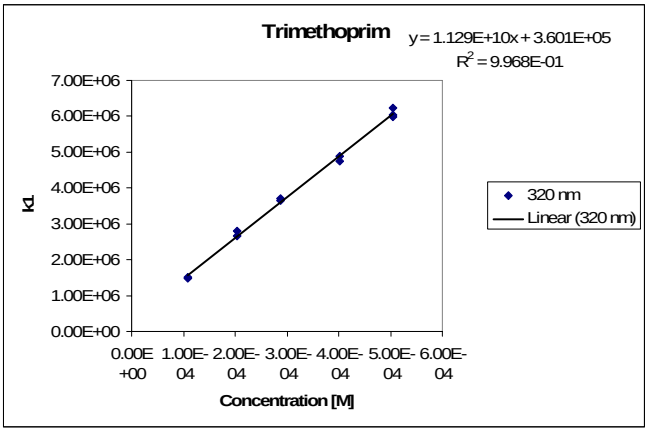
·OH Trimethoprim Experimental Data

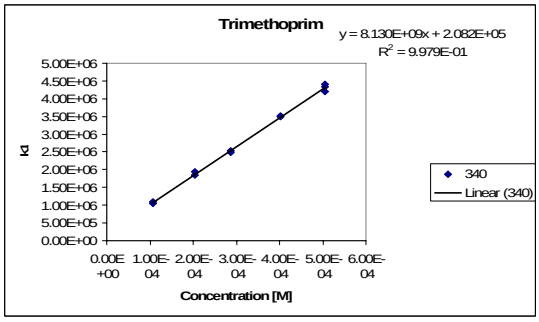
Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = tem60606.kin FW = 290.3
Two spectal analysis (320 nm and 340 nm)

Second-order rate constants for 320 nm = **(1.13±0.02) x 10^{10} $M^{-1}s^{-1}$**
Second-order rate constants for 320 nm = **(8.13±0.12) x 10^{9} $M^{-1}s^{-1}$**







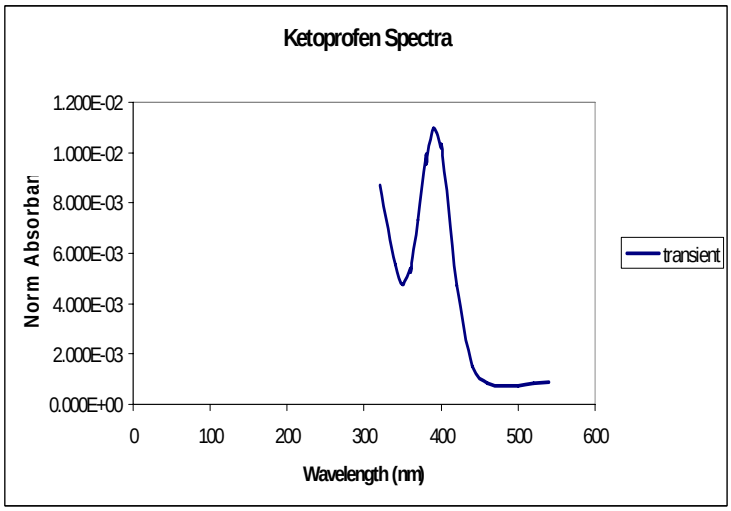


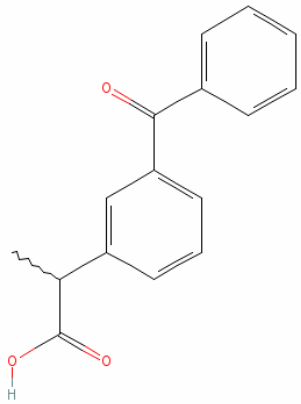
Appendix B
·OH Experimental Data

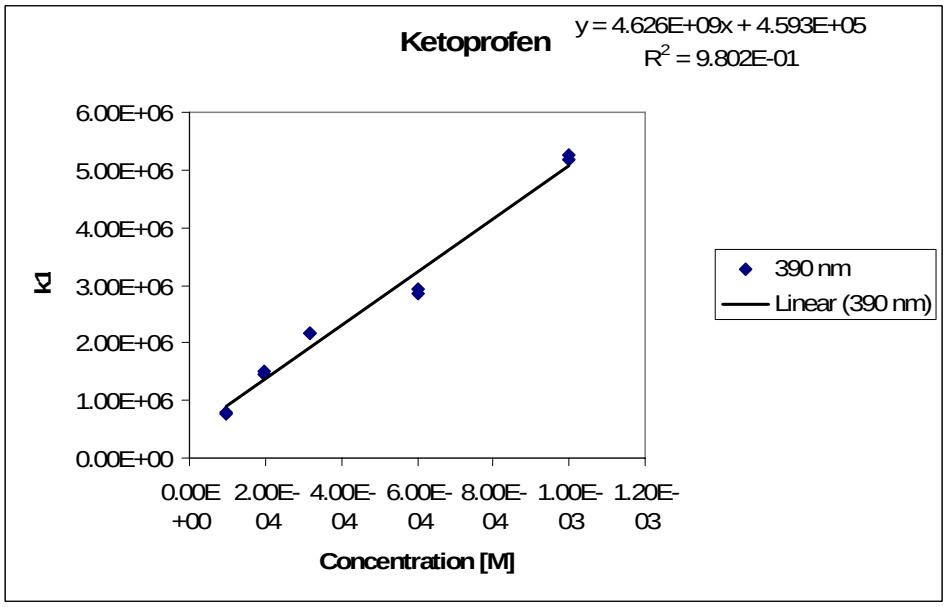
·OH Ketoprofen Experimental Data

Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = kimspectra.kin FW = 254.26
Spectal analysis (390 nm)

Second-order rate constants for 390 nm = **(4.63±0.23) x 10^9 $M^{-1}s^{-1}$**







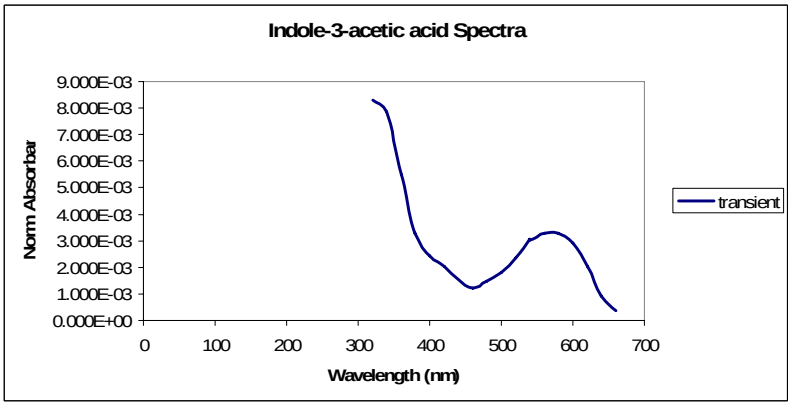
Appendix B
·OH Experimental Data

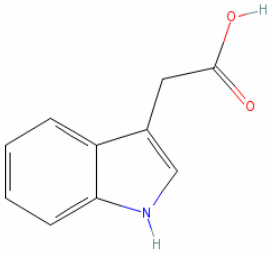
·OH Indole-3-acetic acid Experimental Data

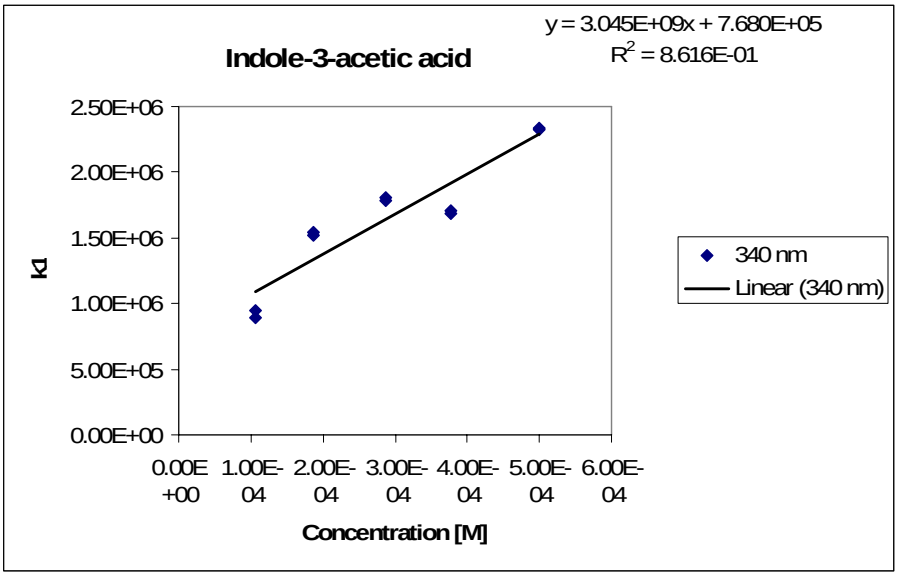
Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = kimspectra.kin FW = 175.18
Spectal analysis (340 nm)

Second-order rate constants for 340 nm = **(3.05±0.43) x 10^9 $M^{-1}s^{-1}$**

Ran data many times.





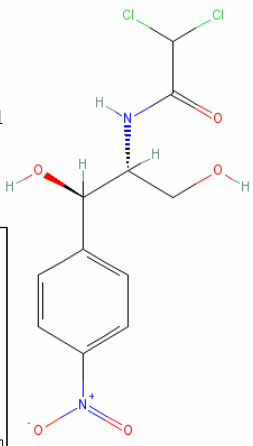


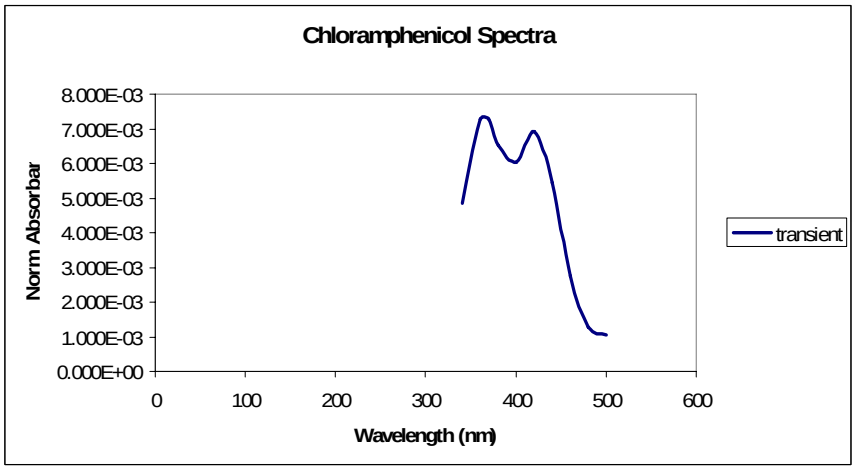
Appendix B
·OH Experimental Data

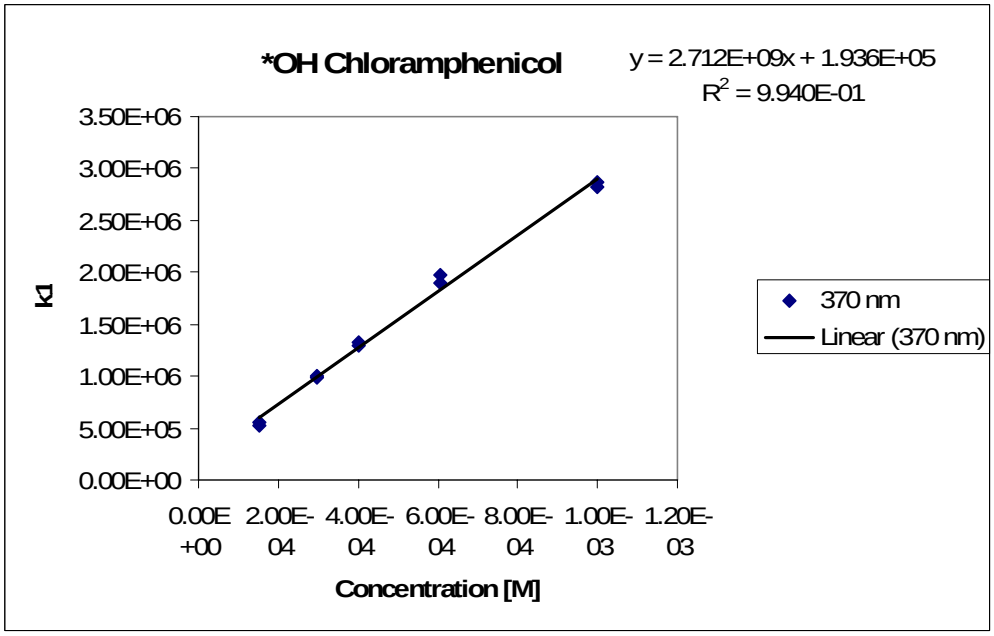
·OH Chloramphenicol Experimental Data

Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = kimspectra.kin FW = 323.1
Spectal analysis (370 nm)

Second-order rate constants for 340 nm = **(2.71±0.07) x 10^9 $M^{-1}s^{-1}$**





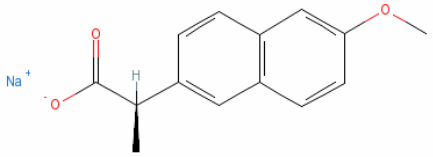


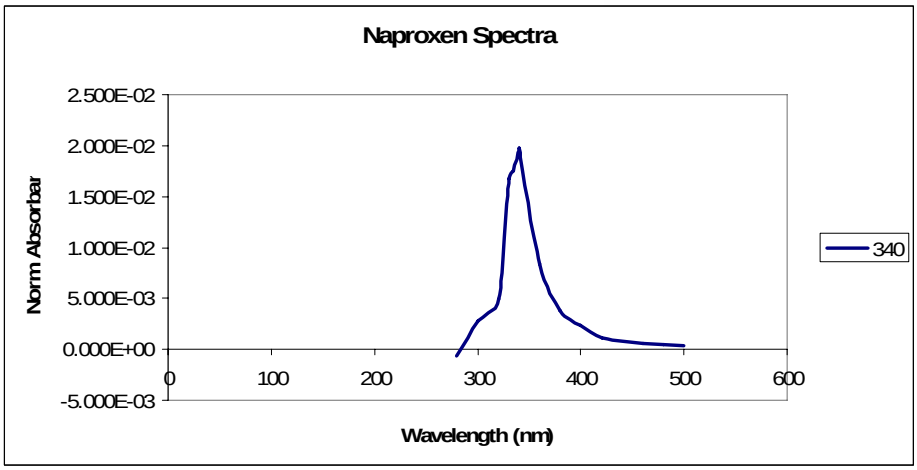
Appendix B
·OH Experimental Data

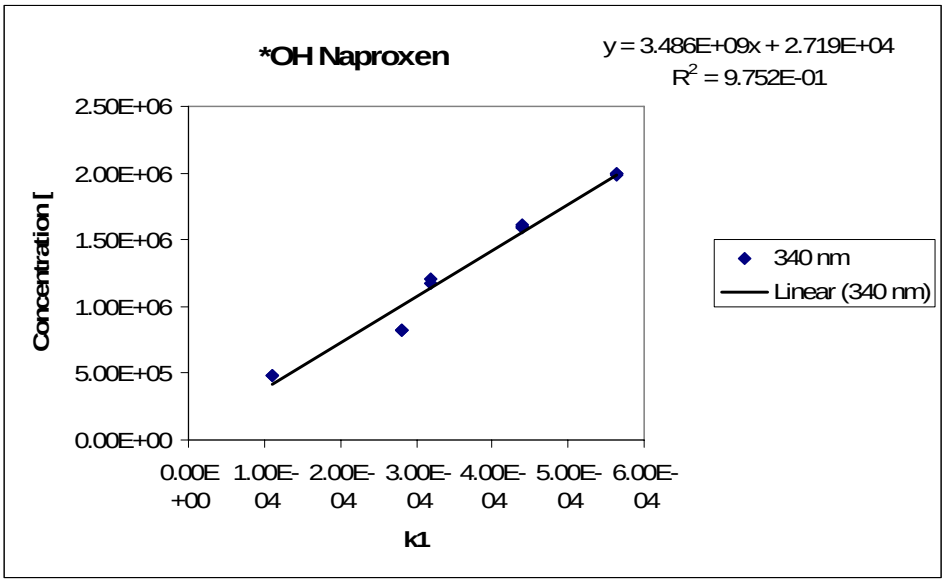
·OH Naproxen Experimental Data

Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = naproxen.kin FW = 252.2
Spectal analysis (340 nm)

Second-order rate constants for 340 nm = **(3.49±0.18) x 10^9 $M^{-1}s^{-1}$**





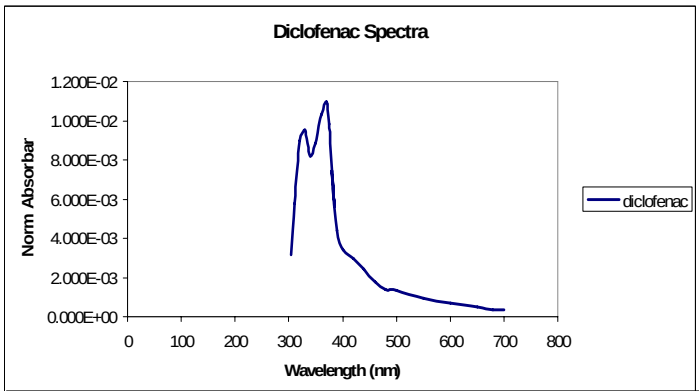


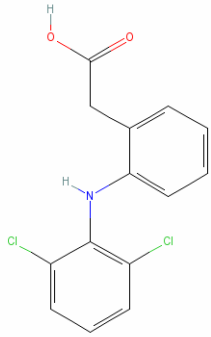
Appendix B
·OH Experimental Data

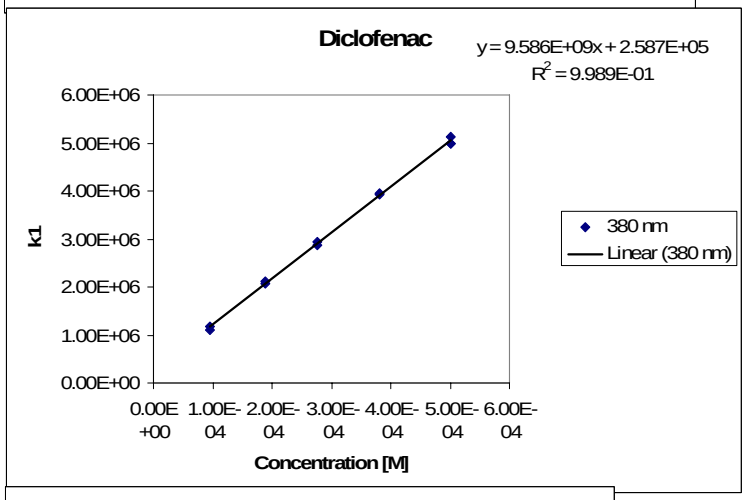
·**OH Diclofenac** Experimental Data

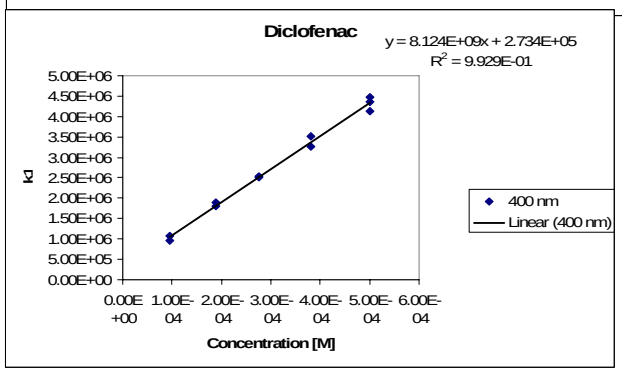
Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = tem60606A.kin FW = 318.1
Two spectal analysis (380 nm and 400)

Second-order rate constants for 380 nm = **(9.59±0.11) x 10^9 $M^{-1}s^{-1}$**
Second-order rate constants for 400 nm = **(8.12±0.23) x 10^9 $M^{-1}s^{-1}$**







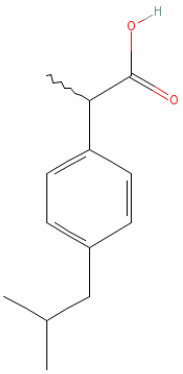


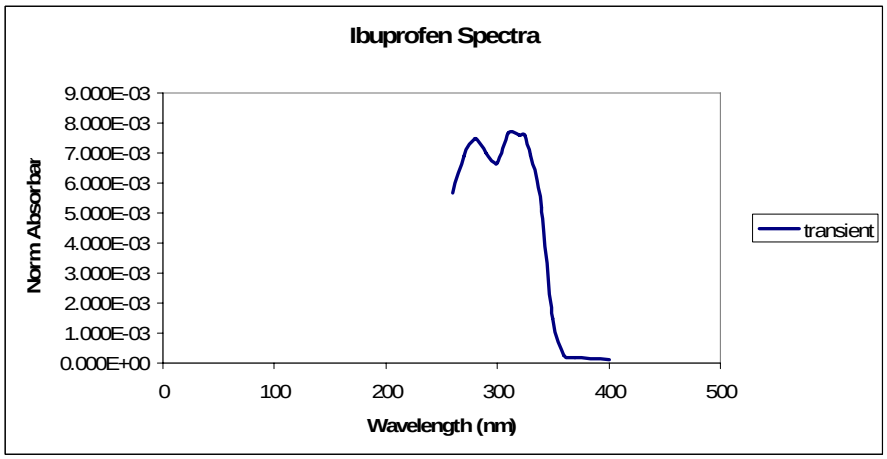
Appendix B
·OH Experimental Data

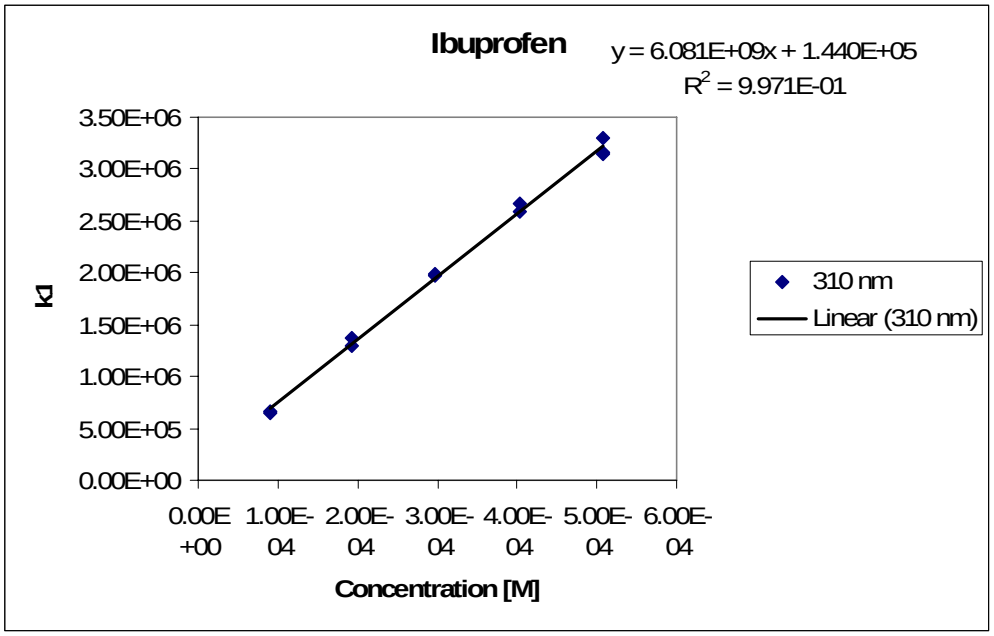
·OH Ibuprofen Experimental Data

Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = tem60606.kin FW = 228.29
Spectal analysis (310 nm)

Second-order rate constants for 310 nm = **(6.08±0.11) x 10^9 $M^{-1}s^{-1}$**





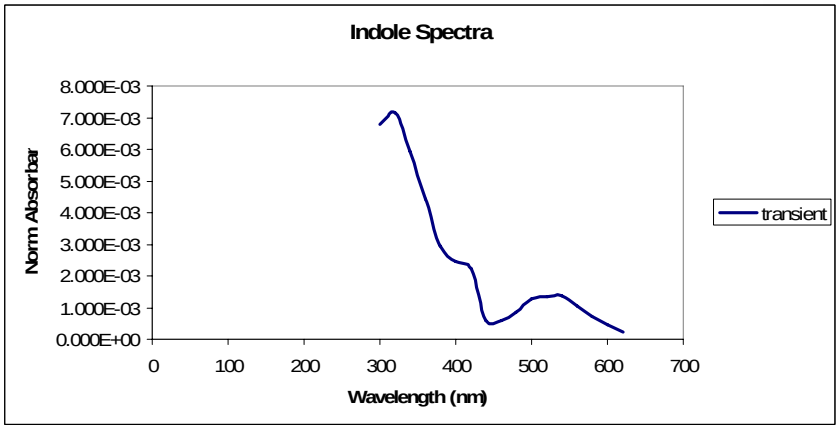


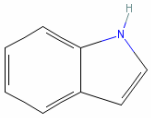
Appendix B
·OH Experimental Data

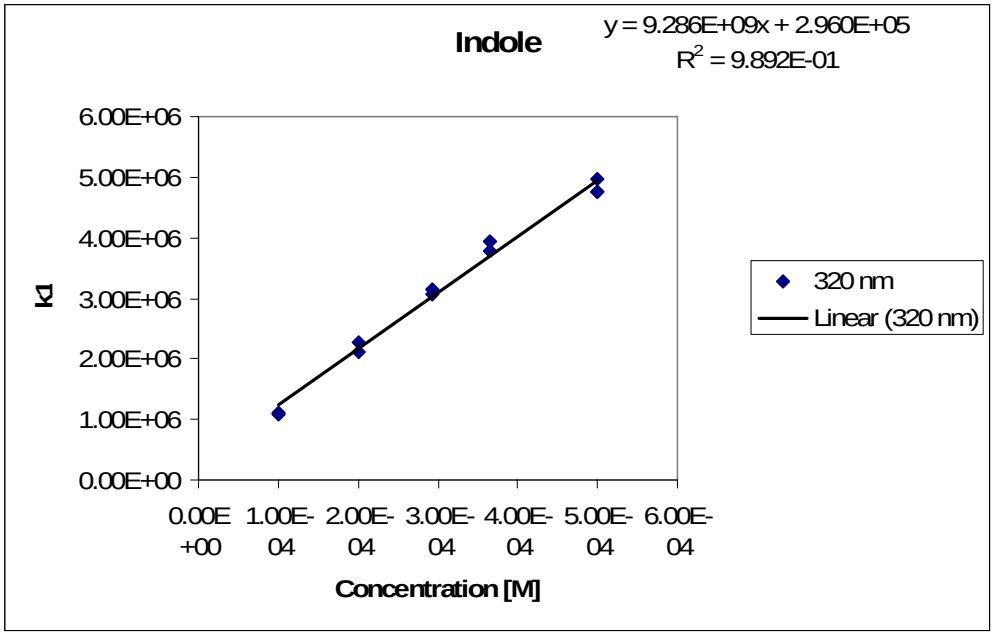
·OH Indole Experimental Data

Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = 4hydroxyacet06620.kin FW = 117.15
Spectal analysis (320 nm)

Second-order rate constants for 380 nm = **(9.29±0.32) x 10^9 $M^{-1}s^{-1}$**



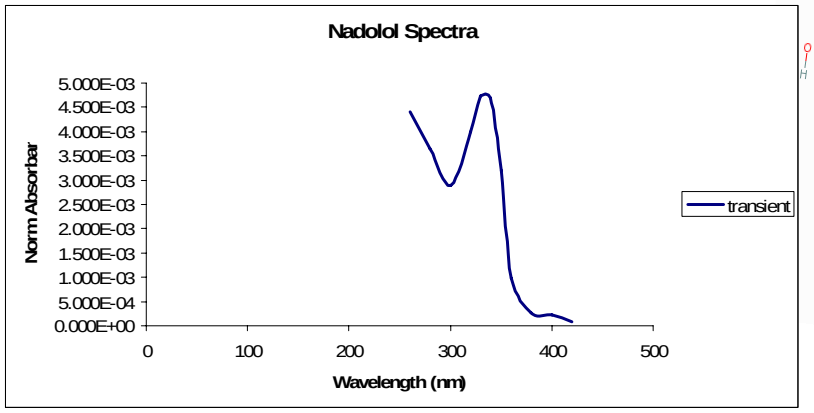


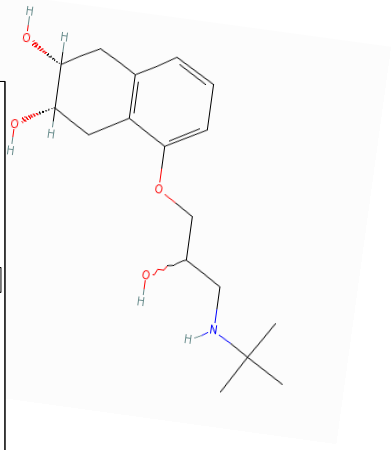


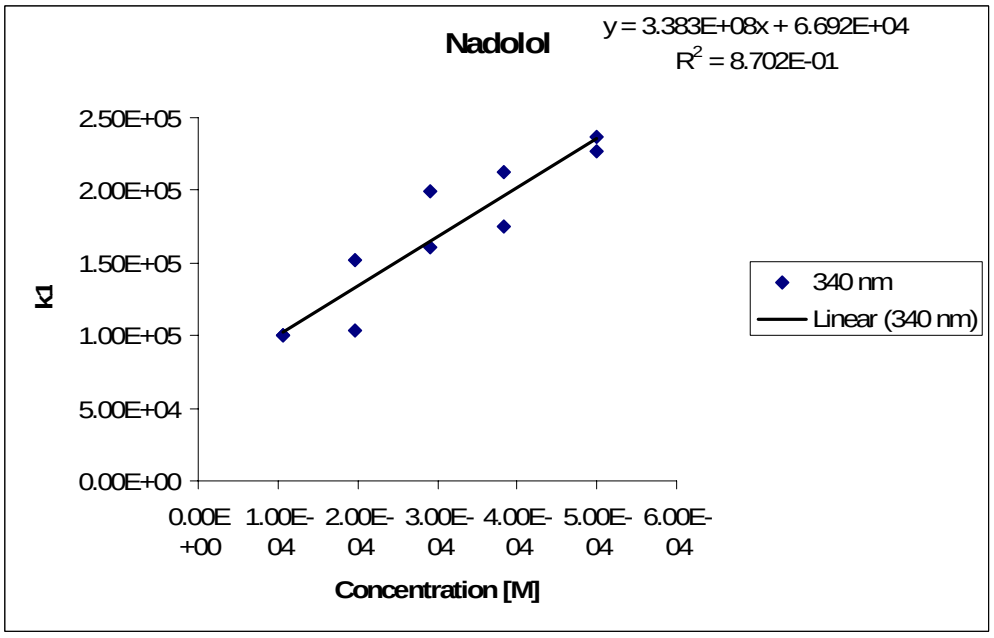
Appendix B
·OH Experimental Data

·**OH Nadolol** Experimental Data

Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = nadolol_OH.kin FW = 309.40
Spectal analysis (340 nm)
Ran this data 3 times to confirm.
Second-order rate constants for 380 nm = **(3.38±0.46) x 10^8 $M^{-1}s^{-1}$**



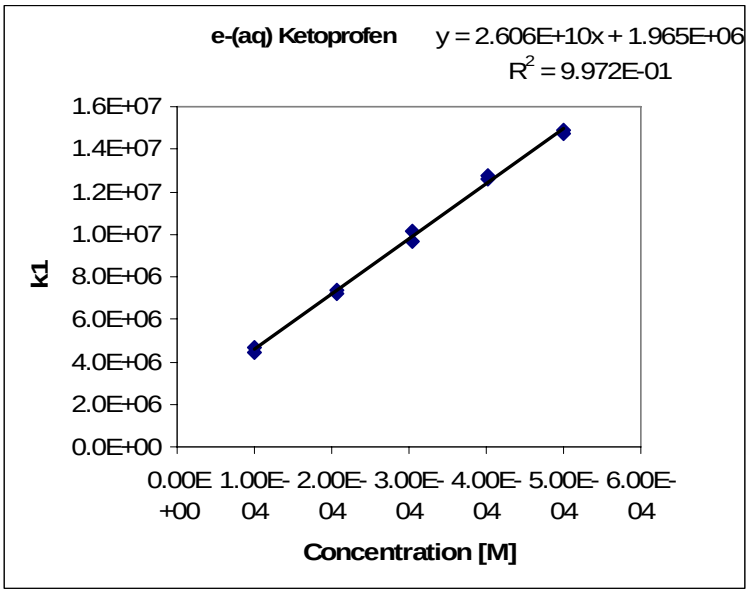


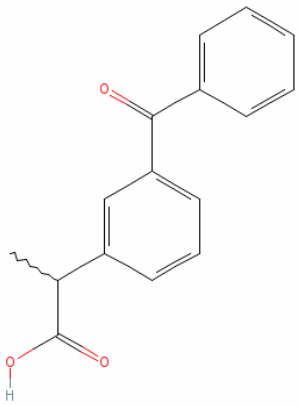


Appendix C
Hydrated Electron Reaction Rate Experimental Data

e^-_{aq} Ketoprofen Experimental Data
Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = kimspectra.kin FW = 254.26
Analysis (500ns) 700 nm

Second-order e^-_{aq} rate constants = **$(2.61 \pm 0.05) \times 10^{10}$ $M^{-1}s^{-1}$**



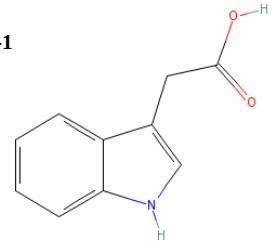


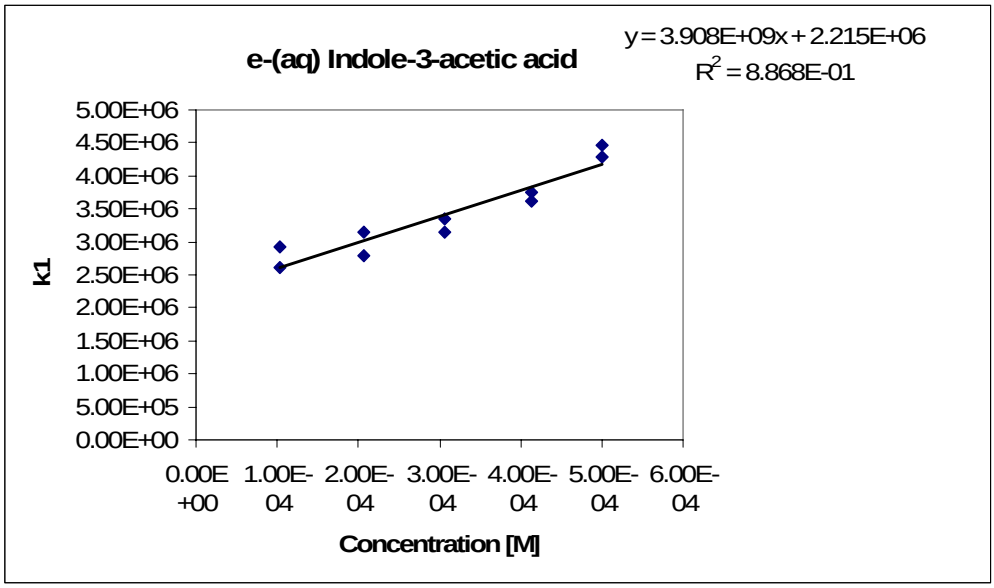
Appendix C
Hydrated Electron Reaction Rate Experimental Data

e^-_{aq} Indole-3-acetic acid Experimental Data
Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = kimspectra.kin FW = 175.18
Analysis (500ns) 700 nm

Second-order e^-_{aq} rate constants = **$(3.91 \pm 0.49) \times 10^9$ $M^{-1}s^{-1}$**

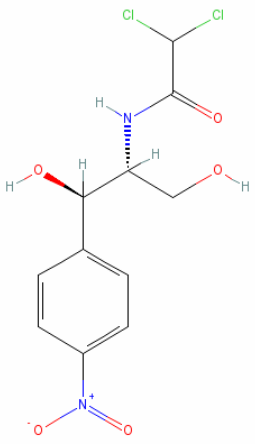
Not great numbers, calculated 3 times



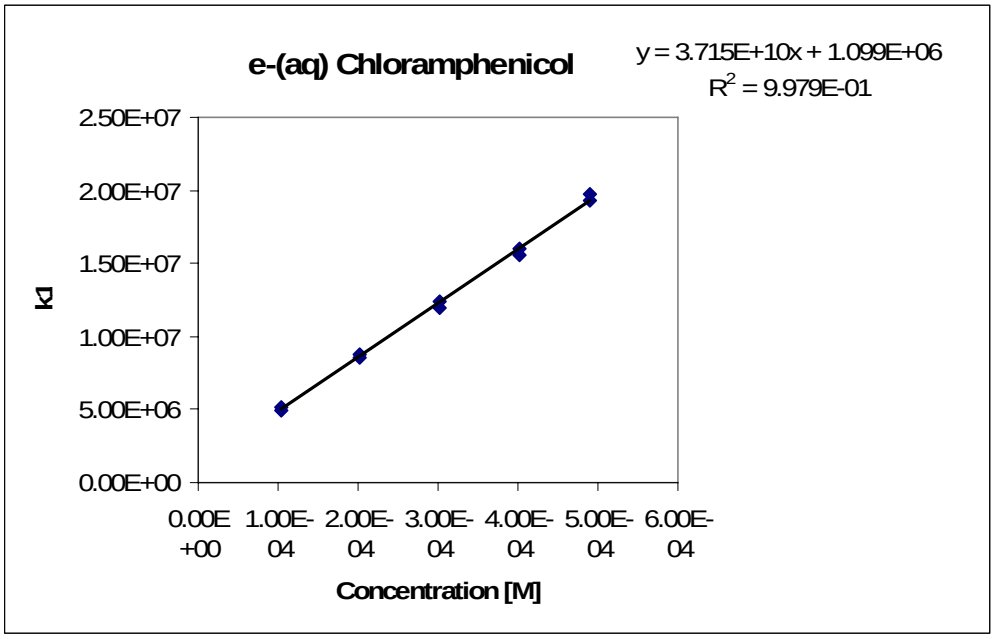


Appendix C
Hydrated Electron Reaction Rate Experimental Data

e^-_{aq} Chloramphenicol Experimental Data
Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = chloramphenicol-e.kin FW = 323.1
Analysis (500ns) 700 nm



Second-order e^-_{aq} rate constants = **(3.71±0.06) x 10^{10} $M^{-1}s^{-1}$**



Appendix C
Hydrated Electron Reaction Rate Experimental Data

e^-_{aq} Naproxen Experimental Data
Pulse Radiolysis, Direct Transient Absorption Spectra – LINAC
File = naproxen_e.kin FW = 252.2
Analysis (2us) 700 nm

Second-order e^-_{aq} rate constants = **(4.86±0..20) x 10^9 $M^{-1}s^{-1}$**