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臭氧去除 Diclofenac 及其中間產物、副產物生成之研究

Formation of the intermediates and by-products during the degradation of diclofenac by ozonation

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本論文係胡乃心君(學號 r98541107)在國立臺灣大學環境工程學研究所完成之碩（博）士學位論文，於民國一百七月二十二日承下列考試委員審查通過及口試及格，特此證明

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Abstract

Diclofenac (DFC) is a widely used anti-inflammatory drug and thus enters the aquatic environment. The realistic environmental concentration levels at harmful effects to different organisms have been demonstrated by many previous studies. Many investigations have revealed that diclofenac can not be completely removed by conventional sewage treatment plants (STP) and was detected in STP effluents at trace levels. Therefore, the presence of diclofenac in the aquatic environment should be assessed critically.

The objective of this study was to evaluate the removal of diclofenac using ozonation process. The effect of various operating parameters including ozone dose, pH, and the presence of phosphate buffer on the removal of diclofenac and TOC in ozonation process was investigated. In addition, the formation of ozonation by-products, including chloride, ammonia ions, intermediates and aldehyde, was also studied. Meanwhile, a simplified mass balance based on intermediates containing carbon, chlorine, and nitrogen was developed to determine the formation rate constants of CO_2, chloride, and ammonia. Furthermore, kinetic studies based on the degradation of diclofenac and formation of chloride and ammonia were also developed to determine the selectivity of reaction pathway and rate constants of diclofenac. Finally, the constants obtained in this study were used to propose the possible pathway and evaluate the optimum operational parameters.

The results show that ozonation was efficient in degrading diclofenac. In absence of phosphate buffer, the removal of diclofenac and TOC, and formation rate of chloride basically increased as the ozone doses increased. In presence of phosphate buffer, the maximal diclofenac removal and CO_2 formation rate constant is at pH 7.4 at two levels

of ozone dose. The reaction rate constants of DFC can be determined in a second order reaction. The diclofenac degradation models can predict the selectivity of pathway. In addition, the aldehyde concentration increased with increasing pH in the ozonation process, which indicated the involvement of hydroxyl radical in aldehyde formation.

Key words: Diclofenac , Ozonation, Ozonation by-product,

Kinetic constants, Intermediates, Pathway, Optimum operational condition

摘要

雙氯芬酸 (Diclofenac)為一種非常廣泛使用的非類固醇抗發炎藥物，目前已有許多文獻證明在不同的生物體以及環境中，雙氯芬酸可能造成的危害影響以及濃度。許多研究調查指出，雙氯芬酸不能完全藉由傳統的汙水處理廠去除，並可被許多污水處理廠檢測出微量濃度，且進而進入自然水體之中。因此，評估雙氯芬酸存在環境水體之問題應被重視。

本研究目的在於評估臭氧處理程序對雙氯芬酸去除的影響。評估不同的操作條件，例如：臭氧劑量、pH、及磷酸緩衝溶液的添加對雙氯芬酸以及總有機碳去除影響之調查。更進一步利用測量氯離子、銨根離子、中間產物與臭氧副產物的生成潛勢，加上對元素碳、氯、以及氮的植量平衡，發展雙氯芬酸降解預測模式，可決定反應動力常數與解釋雙氯芬酸降解機制，以及決定實驗對去除水中的雙氯芬酸的最佳化操作條件與參數。

研究結果顯示出，利用臭氧處理程序可有效的去除雙氯芬酸。在不添加磷酸緩衝液，使溶液的 pH 值呈現變動的狀態下，雙氯芬酸和總有機碳的去除效率大致會因臭氧劑量增加而增加，而臭氧無機副產物形成率，如氯離子以及銨根離子，會與臭氧劑量無顯著的關係。另外，在添加磷酸鹽緩衝液，固定溶液的 pH 值於 5.5、7.4、和 8.9 下，最大雙氯芬酸的消耗反應速率常數，和二氧化碳形成反應速率長數，在兩個不同臭氧劑量下，均在 pH 7.4 時得到最大值。雙氯芬酸的反應速率常數可藉由假一階以及推測的二階反應求得，而預測模型可以計算出

反應途徑的選擇性。此外，研究指出，在紫外光處理程序中，臭氧副產物醛類生成濃度隨操作條件 pH 增加而增加生成量，主要原因為較有多氫氧自由基，容易將有機物質氧化成小分子醛類物質。最後利用考慮副產物生成速率、雙氯芬酸降解速率，以及健康風險的數值可評估雙氯芬酸降解的最佳操作條件與參數。

關鍵字：雙氯芬酸、臭氧、臭氧副產物、反應速率常數、動力模式

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Chapter 1 Introduction

Many resent studies have focused on the presence of pharmaceutical and personal care products (PPCPs) at large quantities in the aquatic environment. These compounds have been studied extensively due to their potential impacts on human health and environment. The group of PPCPs is classified as antibiotics, estrogens, beta-blockers, lipid regulators, and non-steroidal anti-inflammatory drugs (NSAIDs). These drugs have been widely used and sometimes remain and excrete through human body after oral administration. Among the PPCPs, NSAIDs are the most frequently detected as both unmetabolized and active metabolites except for the parent compounds and enter the ecosystem, including the surface water, groundwater, and the effluent of wastewater treatment plants.

Diclofenac is one of the NSAIDs, and commonly prescribed as pain-killers. In Taiwan, the amount of diclofenac used has been reported as thousands tons annually. The removal efficiency of diclofenac by conventional wastewater treatment plants is low. Therefore, diclofenac can enter the ecosystem and source water. Although diclofenac is highly photodegradable in surface water, many studies still reported trace concentration of the chemical in water. Diclofenac causes renal lessions in kidney. It has been reported that diclofenac has adverse effects on rainbow trouts with a no observed effect concentration (NOEC) of 1 $\mu g\ L^{-1}$, EC_{50} in the range from 11.5 to 22.7 $mg\ L^{-1}$ and predicted no effect concentration (PNEC) of 116 $\mu g\ L^{-1}$.

Diclofenac can be readily removed from water by activated carbon, membrane, and advanced oxidation processes or ozonation. Because of its low degree of minerization during ozonation, it is necessary to investigate the intermediates and the kinetics. Although there are some investigations on the kinetics and degradation pathway, detailed and systematic information on the ozonation of diclofenac is not

available. Furthermore, operational conditions that affect the treatment efficiencies have not been studied.

This study was to achieve the following objectives:

1. To investigate the effect of various operation conditions on the formation of by-products and the degradation of diclofenac and TOC by O_3.
2. To develop kinetic models for the ozonation of diclofenac in various operation conditions
3. To establish reaction pathway for the degradation of diclofenac and identify intermediates during ozonation process.

Chapter 2 Literature Review

2-1 The Characteristics of Pharmaceuticals and Personal Care Products (PPCPs)

In the last decade, there has been a dramatic increase in the number of pharmaceuticals and personal care products (PPCPs) circulating in the drug market. PPCPs are d emerging containments having harmful l effects on the ecosystem and human. PPCPs found in the environment may include– analgesics/non-steroidal anti-inflammatories (NSAIDs), antibiotics, antiepileptics, antihypertensives, antineoplastics, antiseptics, contraceptives, sympathomimetics, lipid regulators, musks fragrances, anti-anxiety/hypnotic agents, sun screen agents, and X-ray contrast agents (Esplugas et al., 2007). PPCPs have been detected in the aquatic environment including surface water, ground water and wastewater (Klavarioti et al., 2009). Most PPCPs are non bio-degradable, therefore, conventional wastewater treatment processes are not effective in removing them (Ternes, 1998; Daughton and Ternes, 1999). Previous investigations also demonstrated that residuals of certain pharmaceutical compounds found in the environment were harmful to organisms in the ecological system. (Beno et al., 2004; Kim et al., 2009).

2-2 The Characteristics of Diclofenac

Diclofenac (2-[(2,6-dichlorophenyl)amino] bezeneacetic acid) is one of the NSAIDs, and mostly used as sodium salt. It belongs to a group known as analgesic, antiarthritic, and antirheumatic NSAID. Diclofenac is normally known to reduce inflammation, relieve pain, and used during acute injury. It can also be used to reduce menstrual pain and dysmenorrhea. After oral administration, diclofenac is eliminated in a short period, e.g.,elimination half life about 2 h (Wishart et al., 2006). Approximately 65% of the dosage is excreted through urine in which six metabolites have been identified as shown in Figure 2-1. Besides, diclofeanc is also available in

other forms for dermal applications, eye drop and injection. It is used in the form of tablets, capsules, suppositories, intravenous solutions, and in ointments and gels for dermal application. Diclofenac is used worldwide and estimated to be in the amount of hundreds of tons production per year. In Taiwan, the amount of diclofenac used has been reported as thousands tons annually (A. Y-C Lin et al, 2009).

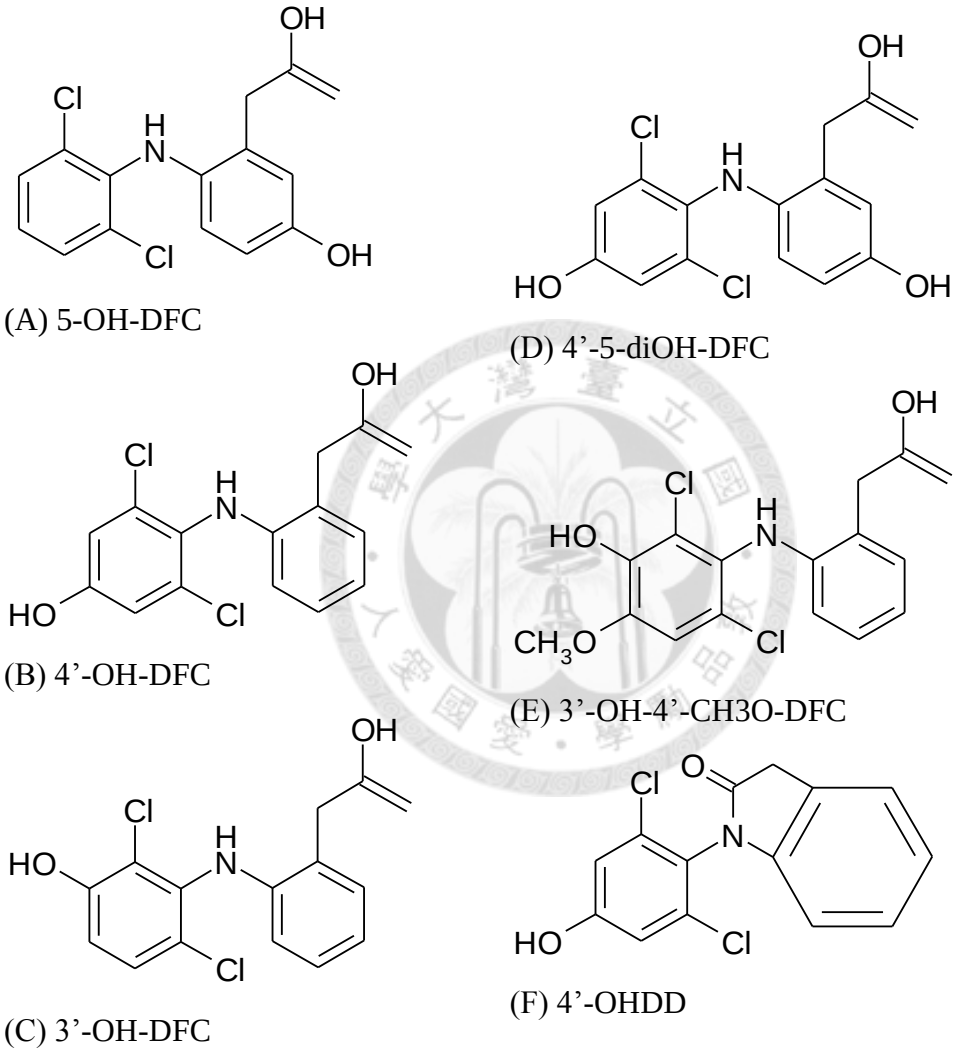


Figure 2-1 The chemical structures of metabolites of diclofenac in urine (Zhang et al, 2008)

Diclofenac is widely detected in many surface water bodies worldwide. Although diclofenac is highly photodegradable in surface water, its occurrence in the aquatic environment was at concentration up to 1.2 μg/L (Buser et al, 1998).

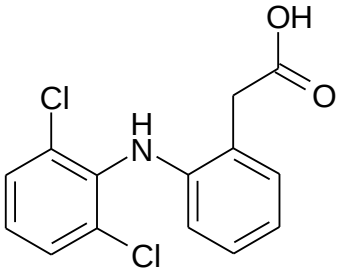
Diclofenac has been found in estuaries as well. Thomas and Hilton (2004) investigated five UK estuaries and detected diclofenac at a maximum concentration of 195 ng/L (e.g., the Mersey estuary) and a median concentration of less than 8 ng/L. In the estuary of the river Elbe at the North Sea, it was detected at a concentration of 6.2 ng/L (Weigel et al., 2002). No data have been reported on its presence in the marine environment. The maximum concentration of diclofenac in surface water reported was 1030 ng/L, detected in Berlin by Heberer et al. (2002). In Taipei, Taiwan, the concentration of diclofenac varies from 124 to 417500 ng/L (Lin, et al, 2009).

The contributors of diclofenac to the aquatic environment are primarily the effluents of wastewater treatment plants and secondarily the hospitals (Esplugas et al, 2007), and pharmaceutical production industries effluents. After oral intake, diclofenac can be partly digested to simple carbohydrates of low molecular weight and are biodegradability with the remaining diclofenac and other metabolites being of high molecular weight, complex structures and low biodegradability which can be excreted through urine or feces into wastewater treatment plans. In the effluent of conventional wastewater treatment plants, the removal efficiency of diclofenac is insignificant (Joss et al, 2006). The removal efficiency of diclofenac by WWTPs varies, ranging from 0 up to 80%, but mainly in the range of 21 to 40% (Zhang et al, 2008). Therefore, diclofenac and its parent compounds can still enter the ecosystem and source waters (Stulten et al, 2008). In Europe, the detected residue of diclofenac is about 10 to 30 ng/L in surface water. Moreover, improper household discharge of drugs is another way to increase the amount of diclofenac in wastewater. On the other hand, diclofenac is widely detected in the effluents of hospitals and pharmaceutical production facilities worldwide at concentration up to hundreds ng/L.

Although the ecotoxicity of diclofenac is relatively low and acute effects rather

improbable at the concentration levels pCresent in the environment, it has been demonstrated that in combination with other pharmaceuticals present in water samples, the toxic effect can be considerably increased, even the combined substances alone showed either no effect at all or very insignificant (Cleuvers et al, 2004). On the other hand, there is evidence that prolonged exposure to environmentally relevant concentrations of diclofenac leads to impairment of the general health of fish, inducing renal lesions and alteration of the gills, at the lowest observed effect concentration (LOEC) of 5 μg/L (Schwaiger et al, 2004). Diclofenac is also associated with a low, but significant, incidence of hepatotoxicity and bone marrow toxicity (Uetrencht et al, 1997). Moreover, the no observed effect concentration (NOEC) was 1 μg/L, (Schwaiger et al, 2004) , the EC50 was in the range from 11.5 to 22.7 mg/L and the predicted no effect concentration (PNEC) was 116 μg/L. (Ferrari et al, 2003) The physical, chemical, and pharmacological toxic properties of diclofenac (DFC) are listed in Table 2-1.

Table 2-1 Physical, chemical and pharmacological toxic properties of diclofenac

Diclofenac	
Molecular structure	
CAS number	15307-86-5
Formula	$C_{14}H_{11}Cl_2NO_2$
M.W (g/mol)	296
Water solubility (mg/L)[a]	0.003-21.3 (@25 ℃)
pKa[b]	4.15
$logk_{ow}$ [b]	0.7-4.5
Elimination half-life (h)	0.2-1.7
Excretion (%)	65 (in urine)
Volume of distribution (L/kg)	1.06
Dosage (mg)	75-150
Acute toxicity effects of diclofenac acid to aquatic organism[c]	EC_{50}: 11.5-22.7 mg/L (Ferrari et al, 2003)
	EC_{50}: 3.3-142.2 mg/L (Laville et al, 2004)
Predicted environmental concentrations[c] (PECs) (μg L^{-1})	0.8
Predicted no-effect concentration[c] (PNEC)	138.74

[a]Iwasaki et al. (2007)
[b]SRC physProp Database
[c]Jones et al. (2002)

2-3 NSAID Analytical Method

Recently, many methods have been developed for detecting drugs in the aquatic environment at low concentrations ranging from the ng L^{-1} to μg L^{-1} level. The analytical procedures include solid-phase extraction (SPE), solid-phase microextraction (SPME), derivatization and gas chromatography mass spectrometry

(GC-MS), gas chromatography tandem mass spectrometry (GC-MS/MS) and liquid chromatography electrospray tandem mass spectrometry (LC-ES/MS/MS) (Farré et al., 2007).

A quantitative method for detecting NSAID at low concentrations in the environment has been developed. Kostopoulou et al. (2008) indicated that using advanced analytical techniques such as GC-MS, GC-MS/MS, LC-MS and LC-MS/MS, it is possible to achieve a low limit of detection (LODs) of complicated matrices in the aquatic environment. Common features of analytical methods for the determination of pharmaceuticals are illustrated in Figure 2-2.

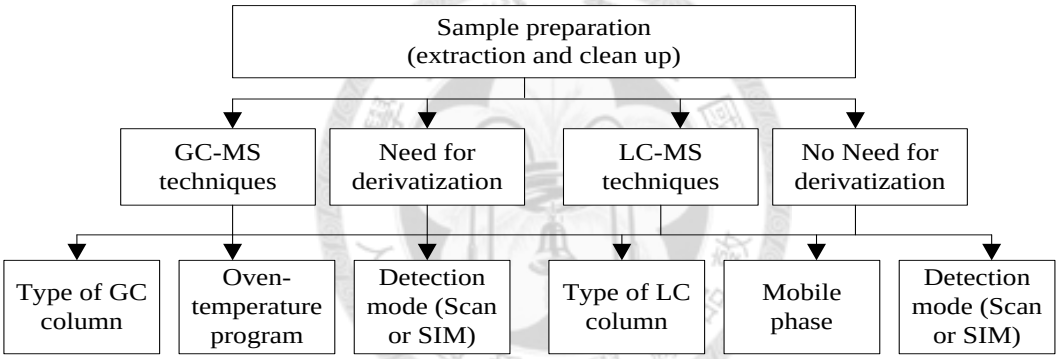


Figure 2-2 Common features of analytic methods for the determination of pharmaceuticals in water. (Kostopoulou et al., 2008)

Kostopoulou et al. (2008) pointed out that SPE and SPME were the most commonly used extraction techniques for analyzing pharmaceuticals. In order to solve analytical problems, such as trace concentration level and complex matrices in aquatic environment, two extraction techniques were often combined as to enhance precision and sensitivity.

SPME is an alternate sample preparation method for the extraction of pharmaceutical compounds from water samples. The technique has advantages over others in pharmaceutical analysis. For instance, it can reduce the sample intake, utilize

re-usable fibers, avoid the use of organic solvents and minimize the time of extraction steps involved in sample preparation. In addition, SPME, particularly suitable for combination, is gas chromatography based technique, since the SPME fiber is directly desorbed in the hot injector of the GC instrument (Kostopoulou et al. 2008). Information regarding the GC–MS method in combination with in situ derivatization headspace SPME for the determination of the NSAID in water samples is shown in Tables 2-2., 2-3, and 2-4. These methods were used by Moeder et al., (2000), Carpinteiro et al., (2004), Rodr´ıguez et al., (2004), Canosa et al., (2005), and Araujo et al., (2008). The application of novel analytical method was effective to quantify NSAID in the aquatic environment.

Table 2-2 Selected GC-MS methods for determination of pharmaceuticals in aqueous samples.

Compounds	Sample preparation	Column and temperature program used	Regents	LOD (ng/L)	LOQ (ng/L)	Reference
Ibuprofen, Paracetamol, Phenazone, Carbamazepine, and Nonylphen	1. Solid phase microextration (SPME) and Solid phase microextration (SPE) 2. Fiber coating polyacrylate, (Carbowax-DVB,65μm;PA 85μm;PDMS–DVB65μm)	HP5-MS (70℃ for 2 min,10℃/min to 250℃,5 ℃ /min, increased to280℃ and held for 10 min)	1. Derivatization reagent: bis(trimethylsilyl)trifluoracetamide (BSTFA) 2. Internal standard: 2-bromo-2,3-dihydro-1 H-indene-1-ol (2.5μg/ml)	200-50,000	—	Moeder. M., et al. 2000
Ibuprofen, naproxen, ketoprofen, tolfenamic acid, and diclofenac	1. SPME and SPE 2. Fiber coating: (1) Dimethylsiloxane, (PDMS, 100μm); (2) Dimethylsiloxane-divinilbenzene, (PDMS-DVB,65μm); (3) Polyacrylate, (PA, 85μm); (4) Poly carboxen-PDMS, (CAR-PDMS, 75μm) (5) Carbowax-DVB, (CW-DVB, 65μm)	BP5-MS (50℃ for 3 min, The GC–MS interface and the ion-trap temperature were set at 250 and 200℃)	1. Ethyl acetate 2. Derivatization reagent: N-methyl-N-(tert-butyldimethylsilyl)trifluoroacetamide (MTBSTFA) 3. Internal standard: meclofenamic acid	—	12-40	Rodr´ıguez, I., 2004

Table 2-2 Selected GC-MS methods for determination of pharmaceuticals in aqueous samples. (Continues)

Compounds	Sample preparation	Column and temperature program used	Regents	LOD (ng/L)	LOQ (ng/L)	Reference
Ibuprofen, naproxen, tolfenamic acid and diclofenac	1. SPME 2. Fiber coating polyacrylate, (PA, 85μm)	BP5-MS (50℃ for 3 min, The GC–MS interface and the ion-trap temperature were set at 250 and 200℃)	1. Derivatization reagent: N-methyl-N-(tert-butyl dimethylsilyl)trifluoroacetamide (MTBSTFA) 2. Internal standard: meclofenamic acid (80 ng/ml : 50 μl)	—	50-5000	Carpinteiro et al., 2004
Ibuprofen, naproxen, ketoprofen, mefenamic acid, and diclofenac	1. Solid phase microextration (SPE) : The cartridge 10mM pH phosphate buffer (5mL) dried under vacuum for 30 min. 2. The analytes were eluted with 2×1.5mL of ethyl acetate into 2mL microcentrifuge tubes.	HLB (2 min at 60℃, ramp5 ℃/min to 290℃and held for 6 min. The GC–MS injector and transfer line temperatures were set at 250 and 290℃	1. Derivatization reagent: N,O-bis [Trimethylsilyl] trifluoroacetamide (BSTFA) 2. Internal standard: PCB-30 and PCB-204	6-45	18-72	Thomas et al., 2004

Table 2-2 Selected GC-MS methods for determination of pharmaceuticals in aqueous samples. (Continues)

Compounds	Sample preparation	Column and temperature program used	Regents	LOD (ng/L)	LOQ (ng/L)	Reference
Triclosan, methyl Triclosan, 2,4-dichlorophenol , 2,3,4-trichlorophenol	1. SPME and SPE 2. Fiber coating: (1) PDMS, (100μm), (2) PA, (85 μm), (3) PDMS-DVB, (65μm) (4) CAR-PDMS, (75μm), (5) CW-DVB, (65μm)	CPSIL8 (50 for 3 min, 10 ℃/min to 260℃ held for 10 min). The GC–MS interface and the ion trap temperature were set at 260 and 220 ◦C.	1. Derivatization reagent: N-methyl-N-(tert-butyldimethylsilyl)trifluoroacetamide (MTBSTFA)	10	120-14,000	Rodr´ıguez, et al., 2004
Ibuprofen Flufenamic acid Naproxen Mefenamic acid Tolfenamic acid Meclofenamic acid	1. SPME 2. Fiber coating: (1) PDMS, (100μm), (2) PA, (85 μm), (3) PDMS-DVB, (65μm) (4) CAR-PDMS, (75μm), (5) CW-DVB, (65μm)	HP-5MS (50℃ for 3 min, 30℃/min to 250℃)	1. Derivatization reagent : dimethyl sulfate (DMS) 2. Ion-pairing reagent: Tetrabutylammonium hydrogen sulfate (TBA-HSO4)	0.3-2.9	100-10,000	Araujo et al., 2008.

Table 2-3 Selected Solid phase microextration (SPME) methods for determination of pharmaceuticals in aqueous sample.

Compounds	SPME operation factors						Reference
	Fiber selection	Sample Volume (ml)	Striring velocity	NaCl	pH	Extraction			
						Type	T (min)	T (℃)	
Ibuprofen, Paracetamol, Phenazone, Carbamazepine, and Nonylphen	1. PA(85μm);PDMS –DVB(65μm); CW–DVB(65μm) 2. Optimum fiber : CW–DVB	4	1000 rpm	1 g	2	Direct immersion	1. 20-60 2. optimum:30	25	Moeder. M., et al. 2000
Ibuprofen, naproxen, ketoprofen, tolfenamic acid, and diclofenac (30 g/ml)	1. PA (85μm);PDMS (100μm);PDMS–DVB(65μm);CW–DVB : (65μm) 2. Optimum fiber : CW–DVB	1. 10, 22, 115 2. Optimum: 22	With	0-0.32 (g/ml)	1. 2-6 2. Optimum:3	Direct immersion	1. 10-180 min 2. Optimum:40	25	Rodr´ıguez, I., 2004
Ibuprofen, naproxen, tolfenamic acid, and diclofenac	1. PA (65 μm)	22	With	—	2.5	Direct immersion	40 min	25	Carpinteiro et al, 2004

Table 2-3 Selected Solid phase microextration (SPME) analytical methods applied to the determination of pharmaceuticals in aqueous samples. (Continues)

Compounds	SPME operation factors							Reference
	Fiber selection	Sample Volume (ml)	Striring velocity	NaCl	pH	Extraction Type	Extraction T (min)	Extraction T (℃)	
Triclosan, methyl triclosan, 2,4-dichlorophenol, and 2,3,4-trichlorophenol	1. PA (85μm);PDMS (100μm);PDMS–DVB(65μm);CW–DVB : (65μm) 2. Optimum fiber :PA and PDMS-DVB	1. 10, 22, 110 2. Optimum: 22	With (500 rpm) (positive)	0.025–0.050 (g/ml)	1. 3-6 2. Fixed pH: 4.5	Direct immersion	1. 10-120 min 2. Fixed : 30 min	25, 40	Canosa et al., 2005
Ibuprofen, flufenamic, acid, naproxen, mefenamic acid, tolfenamic acid, and meclofenamic acid	1. PA (85 μm ; 100 μm)	6	500 rpm	1. 0-2.88 g, or Na2SO4 2.TBA-HSO_4 (0.1M added 60 μl)	6	Headspace	45 min	70±2	Araujo et al., 2008.

Table 2-4 Selected Derivatization-GC-MS methods for determination of pharmaceuticals in aqueous samples. (Continues)

Compounds	Derivatization				Reference
	Reagent	Volume	Temperature	Time	
Ibuprofen, naproxen, ketoprofen, tolfenamic acid, and diclofenac (30 ng/ml)	N-methyl-N-(tert-butyldimethylsilyl)trifluoroacetamide (MTBSTFA)	1. 20-150 µl 2. Optimum:50 µl	1. 25, 40, 60, 100 ℃ 2. Optimum:40 ℃	1. 5, 20, 30, 60, 120 min 2. Optimum:20 min	Rodr´ıguez, I., 2004
Ibuprofen, naproxen, tolfenamic acid and diclofenac	N-methyl-N-(tert-butyldimethylsilyl)trifluoroacetamide (MTBSTFA)	50 µl	40 ℃	20 min	Carpinteiro et al, 2004
Ibuprofen, naproxen, ketoprofen, mefenamic acid, and diclofenac	N,O-bis [Trimethylsilyl] trifluoroacetamide (BSTFA)	1. 20-100 µl 2. Optimum:20 µl	1. 40-70 ℃ 2. Optimum:40 ℃	1. 10-40 min 2. Optimum:10 min	Thomas et al., 2004
Triclosan, methyl triclosan, 2,4-dichlorophenol , and 2,3,4-trichlorophenol	N-methyl-N-(tert-butyldimethylsilyl)trifluoroacetamide (MTBSTFA)	20 µl	25 ℃	10 min	Canosa et al., 2005
Ibuprofen, flufenamic acid, Naproxen, mefenamic acid, tolfenamic acid, and meclofenamic acid	Dimethyl sulfate (DMS)	1. 5-100 µl 2. Optimum:15 µl	1. 40-80 ℃ 2. Optimum:70 ℃	1. 10-90 min 2. Optimum:45 min	Prieto, A., et al. 2008

2-4 Analytical Methods for Diclofenac and Intermediates

As a frequently studied compound, the analytical methods for diclofenac have been developed extensively. Due to its salt form commonly used in the society, the water solubility is so high that most of the methods have taken LC or LC-MS as the main equipment to analyze diclofenac. On the other hand, to analyze the small amount of diclofenac in natural water bodies, such as rivers or lakes, LC-MS or GC-MS can be applied. Sometimes the pre-treatments before analysis, namely, liquid-liquid extraction or solid-phase extraction, is necessary. Some quantitative methods for detecting intermediates at low concentrations during the reaction have been developed. To investigate the presence of intermediates of diclofenac during oxidation, GC-MS, LC-MS, LC-MS/MS, or LC/TOF-MS in combination with specific extraction can be used. Information regarding the analytical methods for diclofenac is shown in Tables 2-5., and 2-6.

T able 2-5 Analytical methods of diclofenac

Matrix	Sample preparation	Instrument	olumn and erational condition	Regents	Reference
Effluent of WWTP Rivers and lakes	SPE	GC-MS	DB5-MS (60℃ for 2 min,20℃/min to 140℃,8℃/min, to 280℃)	Methanol	Buser, et al. 1998
Synthetic water	-	HPLC (UV diode array detector)	RP-max column Flow rate: 1.0 ml/min Wavelength: 274 nm	CH_3CN: 0.07M (60%) Phosphate buffer pH 2 with 5% CH_3CN (40%)	Vogna et al, 2004
Effluent of WWTP	SPE 1. Cartidges: C18, 6 ml, Baker, Germany 2. Preconditioned:2 × 5 ml methanol and 2 × 5 ml Millipore water (pH 6.3 with citric acid/NaOH) 3. Washed: 2 × 5 ml Millipore water (pH ~ 6.3) and dried under vacuum for 15 min 4. Eluted: 3 × 2 ml methanol.	LC-MS	Nucleodur Sphinx RP column Flow rate: 0.2 ml/min Gradient program: linear gradient from 20% to 45% for 5 min; isocratic at 45% for 25 min, linear gradient 45% to 55% within 2 min, linear gradient 55% to 65% within 14 min, 65% to 100% within 1 min maintained 20% for 10 min.	Double distilled water containing 0.1% formic acid Acetonitrile containing 0.1% formic acid	Spiteller et al, 2008
Synthetic water	-	HPLC (diode array detection)	Nucleodur 100-5 C18 Flow rate: 0.3 ml/min Wavelength: 204 nm Gradient program: 5-43 %	Acetonitrile Water pH 4.6, adjusted with dilute formic acid	Sein, et al, 2008

T able 2-5 Analytical methods of diclofenac (Continues)

Matrix	Sample preparation	Instrument	Column and operational condition	Regents	Reference
Synthetic water	-	HPLC-UV	RP-Tracer Extrasil ODS2 Micromet Flow rate: 1.25 ml/min Wavelength: 280 nm	Acetonitrile (50%) Ammonium formate 10mM (50%)	Coelho et al, 2009
Effluent of waste streams from hospitals and pharmaceutical production facilities	SPE 1. Cartidges: Oasis HLB preconditioned: 5 ml methanol, 5 ml DI water 2. Washed: 3-6 ml/min, 6 ml DI water and dried by nitrogen for 15 min. 3. Eluted: 8 ml methanol, dried by nitrogen, heated at 37 ℃, 0.5 ml with 50% methanol, and filtered through 0.45 μm filter	LC-MS/MS	ZORBAX Eclipse XD8-C18 Column Flow rate: 1 ml/min Binary gradient systems	0.1% formic acid in DI water 0.1% formic acid in 100% methanol	A.Y-C Lin et al, 2009
Synthetic water	-	LC-UV-DAD	Agilent Zorbax SB-C_{18} column Flow rate: 1.0 ml/min Wavelength: 275 nm linear gradient: 12 min from 40 to 100%	Isocratic with 30% of DI water 0.1% formic acid and 70% acetonitrile	Verstraete et al, 2010

T able 2-6 Analytical methods of intermediates of diclofenac via oxidation

Matrix	Sample preparation	Instrument	Column and temperature program used	Regents	Reference
Synthetic water	1. Water was removed by freeze-drying 2. dissolved in methanol (10 mL), and NaBH4 or NaBD4 (30 mg) was added at 0 ℃. 3. warm to room temperature and stirred for 3 hours 4. acidified with a mixture of 2% hydrochloric acid in methanol and evaporated to dryness in vacuo\ 5. treated with reagent 6. shaken vigorously for about 60 s and was then allowed to stand for 5 min at room temperature	GC-MS	Zorbax MS: 80℃ for 1 min, 7℃ /min up to 150℃, hold time 5 min, 7℃/min up to 200℃, hold time 5 min.	0.2 mL of anhydrous pyridine, 0.1 mL of hexamethyldisilazane, and 0.05 mL of chlorotrimethylsilane.	Vogna et al. 2004
Synthetic water	SPE 1. Oasis HLB conditioned with 2 mL of methanol, 2 mL of deionized water, 2 mL of 0.1 N chlorhydric acid, and 2 mL of water 2. 50 ml aliquots of the water samples were loaded at a flow rate of approximately 10 mL/min 3. Elution was performed with 2 × 4 mL of methanol at 1 mL/min and dried by nitrogen	GC-MS	HP-5 MS: initial pulse pressure 30 psi (1.5 min), split flow 50.0 mL/min, and split time 1.5 min. The helium carrier gas flow was 1 mL/min. The oven temperature program was 1.0 min at 105 ℃, 25 ℃/min to 180 ℃, 5 ℃/min to 230 ℃ (1 min).	Methanol	Aguera et al, 2005

T able 2-6 Analytical methods of intermediates of diclofenac via oxidation (Continues)

Matrix	Sample preparation	Instrument	Column and temperature program used	Regents	Reference
Synthetic water	-	LC/TOF-MS	Reverse-phase 150 mm × 4.6 mm C_8 analytical column and 5-μm particle size (Zorbax Eclipse XDB-C8) Flow rate: 0.6 ml/min A linear gradient progressed from 15% A to 100% A in 30 min, and it was maintained at 100% A for 5 min Mass spectra: from 50 to 1000 m/z	Acetonitrile Water with 0.1% formic acid	Pérez et al, 2005
Synthetic water	SPE 1. AccuBond SPE ODS-C18 conditioned with 5 mL methanol followed by 5 mL of pH 2 water 2. sample (250 mL) was introduced onto the SPE cartridge at a flow rate of 10 ml/min 3. extracted with methanol (2 × 3 mL). The eluent was brought to dryness by nitrogen	HPLC-MS	Nucleodur 100-5 C18 Flow rate: 0.3 ml/min Wavelength: 204 nm Gradient program: 5-43 % The ion source temperature was 550 ℃ and ion spray voltage -4500 V	Acetonitrile Water pH 4.6, adjusted with dilute formic acid	Sein, et al, 2008

T able 2-6 Analytical methods of intermediates of diclofenac via oxidation (Continues)

Matrix	Sample preparation	Instrument	Column and temperature program used	Regents	Reference
Synthetic water	SPE 1. Oasis™ HLB onditioned with 3 mL of methanol and 3 mL of deionised HPLC-grade water (pH adjusted to 2 with HCl 2N) 2. 10 mL aliquots of the water samples (pH adjusted to 2) were loaded at a flow rate of 10 ml/min 3. Elution was performed with 2 × 2 mL of methanol at a flow rate of 1 mL/min	LC-MS LC/TOF-MS	ZORBAX, SB-C18, Flow rate: 0.4 ml/min Linear gradient progressed from 20% A to 100% A in 35 min and was maintained at 100% A for 1 min	Acetonitrile Water with 0.1% formic acid	Coelho et al, 2009
Synthetic water	-	HPLC-tandem MS	Agilent Zorbax Eclipse XDB-C8 column Flow rate: 0.3 ml/min Gradient progress 0-1 min: 0% acetonitrile; 1-25 min: linear gradient to 100% acetonitrile; 25-34 min: 100% acetonitrile; 34-34.1 min: back to 0% acetonitrile; 34.1-40 min: 0% acetonitrile.	Acetonitrile Water with 10mM formic acid	Verstraete et al, 2010

2-5 Ozonation and Ozonation By-Products Formation

Recently, many studies have indicated that the ozonation or advanced oxidation processes (AOP) can improved the removal of pharmaceutical drugs (Zwiener and Frimmel, 2000, Esplugas et al., 2007; and Klavarioti et al., 2008). In addition, some investigations on the removal of MEF from wastewaters by means of advanced oxidation processes (O_3, UV/H_2O_2, and O_3/H_2O_2) (Kim et al., 2009; Rosal et al., 2008) have been conducted. In general, ozonation may be widely applied to the degradation of organic pollutants. Above all, it is necessary to understand the effectiveness of different processes for the removal of micro-polutants and their biological activities (Esplugas, et al., 2007). Table 2-7 summarizes treatment of pharmaceuticals in waters by ozonation and AOP.

Table 2-7 Treatment of pharmaceuticals in waters by AOP

Target drug	Matrix	Reactor	Process	AOP features	Measure of degradability	Summary of results	Reference
Clofibric acid, diclofenac, ibuprofen	Distilled water Natural river water	Batch	O_3 O_3/H_2O_2	1. C_0:2 μg L^{-1} 2. O_3:1–5mg L^{-1} 3. O_3/H_2O_2 (2:1)at pH=7	Specific drug	1. Reactivity order: diclofenac＞ ibuprofen＞clofibric acid. 2. Rates decrease in river water compared to distilled water. 3. H_2O_2 enhances performance.	Zwiener and Frimmel , 2000
Human and veterinary antibiotics	Synthetic wastewaters	Semi-bch	O_3 O_3/H_2O_2	1. COD:450 mg L^{-1} 2. pH 3; 7 and 11 3. O_3:2.96 g h^{-1}	Specific drug TOC, COD, BOD, UV_{254}	1. O_3 g/TOC g of 1.4 g/g is needed to obtain anaromaticity removal of 44%. 2. Human antibiotic I wastewater 50% TOC and 74% COD removal.	Akmehmet BalcIoglu et al., 2003

Table 2-7 Treatment of pharmaceuticals in waters by AOP (continues)

Target drug	Matrix	Reactor	Process	AOP features	Measure of degradability	Summary of results	Reference
Bezafibrate, carbamazepine, diazepan, diclofenac, 17β-ethinylestradiol, ibuprofen, iopromide, sulfametoxazol and roxithromycin	Milli Q River and lake water	Batch	O_3 O_3/H_2O_2	1. C_0:0.5μmol L^{-1} 2. O_3:0.1-2mg L^{-1} 3. O_3/H_2O_2 at pH=8 4. Natural water properties: pH 7.2–7.9; COD= 0.8–3.7 mg L^{-1}; alkalinity = 0.7–5.8 mol L^{-1} HCO_3	Specific drug	1. Ozone doses ranging from 0.2 up 0.5 mg L^{-1} were observed with 97% removal of all compounds. 2. Removal of bezafibrate was lower.	Gunten et al. (2003)
Diclofenac	Distilled water	Semi-batch Batch	O_3 O_3/H_2O UV/ H_2O_2	1. C_0:0.1 mmol L^{-1} 2. pH:5.0; 5.5 and 6.0; 3. Radical scavengers (*tert*-butyl alcohol) 4. O_3:0.1 mmol L^{-1}	Specific drug TOC, COD	1. 100% of chlorine release and 32% mineralization. 2. 52% of chlorine release and 39% mineralization with H_2O_2/UV system.	Vogna et al., 2004

Table 2-7 Treatment of pharmaceuticals in waters by AOP (continues)

Target drug	Matrix	Reactor	Process	AOP features	Measure of degradability	Summary of results	Reference
Amoxicillin	Synthetic water	Semi-batch Batch	O_3 O_3/H_2O_2	1. C_0:0.5 mmol L^{-1} 2. pH:2.5-5.0 3. Radical scavengers (2-methyl-2-propanol) 4. O_3:0.16mmol L^{-1}	Specific drug TOC	1. The low degree of mineralization. 2. Some indications recorded on the structures of intermediates and products.	Andreozzi et al., 2005.
Macrolide, sulfonamide antibiotics, estrogens, diclofenac, naproxen, indomethacin	Effluents from activated sludge and membrane bioreactor spiked with pharmaceuticals/ estro gens		O_3	1. C_0:0.5–5 μg 2. O_3:0.5–5 mg L^{-1} at pH=7	Specific substrate	1. 90–99% Degradation for $O_3 > 2$ mg/L. 2. Water matrix in terms of suspended solids has minor effect on efficiency. 3. More important is the effect of dissolved organic matter.	Huber et al. (2005)

Table 2-7 Treatment of pharmaceuticals in waters by AOPs (continues)

Target drug	Matrix	Reactor	Process	AOP features	Measure of degradability	Summary of results	Reference
Sulfamethoxazole	Synthetic water	Semi-batch	O_3 O_3/UV O_3/TiO_2 O_2/TiO_2/ UVA O_3/UVA/ TiO_2	1. C_0: 10^{-4} M 2. O_3:0.025-0.1mg L^{-1}	Specific drug,, TOC,	1. Ozonation allows for fast removal of SMT in water. 2. The O_3/UVA/TiO_2 oxidation is especially recommended for total SMT disappearance.	Beltra´n et al. (2008)
Analgesic,anti-inflammatory agents, anti-arrhythmia agents and antibiotics (30 kinds)	Synthetic water	Semi-batch Batch	O_3 UV UV/ H_2O_2, O_3/UV O_3/H_2O_2.	1. C_0: 8.2-122.6 μg L^{-1} 2. O_3:0.15;0.30; 0.60 mg L^{-1} 3. O_3:2;4;6 (mg L^{-1}) 4. H_2O_2:1.2;3.1;6.2 mg L^{-1}	Specific drug,	O_3 and AOP (O_3/UV) could effectively remove PPCPs except for 2-QCA, DEET and cyclophosphamide.	Kim et al. (2008)

2-5-1 Ozonation

Ozone is a commonly used disinfectant in drinking water and wastewater treatments. Because ozone is a strong oxidant, it can eliminate odor, taste, color, and even micropollutants (Klavarioti et al., 2009). Ozone is unstable in water, however. There is the special feature of ozone, which is its decomposition into OH radical. The decomposition of ozone is due to a chain reaction involving OH radicals (Staehelin and Hoigné, 1985). The reaction mechanism of ozone is shown in Figure 2-3.

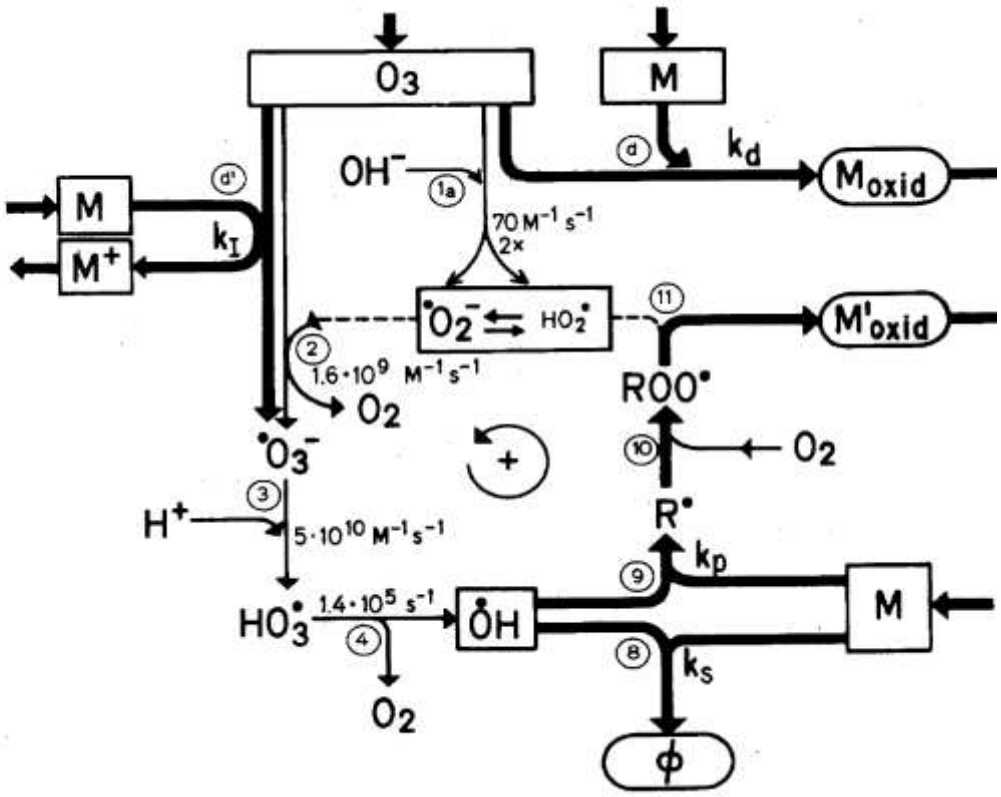


Figure 2-3 The reaction mechanism of aqueous ozone with organic matter (M) in the solutes. (Staehelin and Hoigné, 1985)

Ozone can attack the organic molecules through not only a direct mechanism but also an indirect mechanism which can be self-decomposed to generate hydroxyl radicals in water (Sotelo et al., 1987). Hoigné et al. (1998) proposed the reaction mechanism of ozone with organic or inorganic compounds, including direct and

indirect processes. Hence, ozone reactions can be classified as direct and indirect reactions.

(1) Direct ozone reaction

Direct reaction usually has selective ability for reaction with unsaturated compounds, for instance, aromatics and non-protonated animes, and so on. The details of direct reactions are described as follows:

In water, ozone has different reactions that may be due to its electronic configuration. In general, direct oxidation is more predominant under acidic conditions than radical oxidation under basic conditions (Chu et al., 2000). The reactions include oxidation-reduction, dipolar cycloaddition, and electrophilic substitution reactions. Cycloaddition reaction is developed between the base compound with π electrons and the acid compound with electrophilic compounds. As a general rule, cycloaddition reaction follows the mechanism of Criegge and is shown in Figure 2-4. Usually, the mechanism can lead to 1,3-dipolar cycloaddition aromatic structure. In this reaction, ozone molecule acts as an electrophilic agent, and easily attack the nucleoplilic unsaturated position of compounds such as aromatic compounds. The reaction mechanism of ozone and aromatic compounds is illustrated in Figure 2-5 (Langlais et al., 1991). Aromatic compound is prone to undergoing electrophilic substitution reactions rather than cycloaddition reaction. Due to the structure of aromatic compounds, the substitution reaction increases the stability of the aromatic ring (Fernando, 2004).

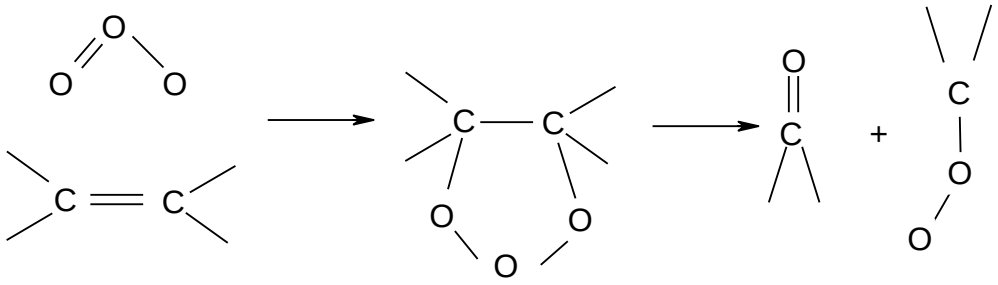


Figure 2-4 Scheme of Criegee mechanism

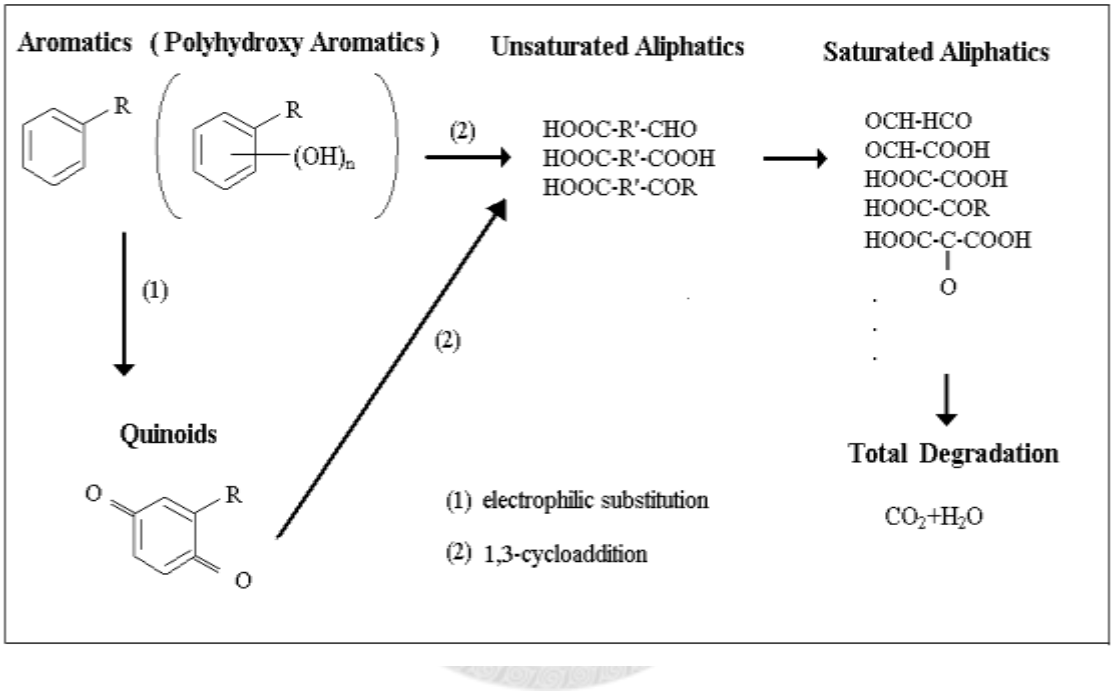


Figure 2-5 The reaction mechanism of ozone and aromatic compound (Langlais et al., 1991)

(2) Indirect ozone reaction

The indirect ozone reactions are due to the action of free radical species resulting from the decomposition of ozone. The reaction includes self-decomposition and a free radical chain reaction generation. The hydroxyl radical from the ozone decomposition is the main species responsible for the indirect reactions. Ozone usually reacts with hydroxyl ions (OH^-) as a catalyst. The reaction yields various free radicals such as $O_2^{-\cdot}$, $HO_2^{-\cdot}$, and $HO_3^{-\cdot}$ under basic conditions. The indirect reaction is different from

direct reaction in distinct characteristics which are described as follows: higher oxidative ability, and nonselective property in hydroxyl radical. In general, the reaction of aromatic compounds with hydroxyl can lead to ring cleavage and formation of oxidative products such as formic acid, C_2-C_6 dicarboxylic acids, and aldehydes under the attack of hydroxyl radical (Gilbert, 1978).

The reaction mechanism is divided into three steps between hydroxyl radical and organic compound. It involves hydroxyl addition, hydrogen abstraction and electron transfer (Huang et al., 1993). The reaction mechanism is shown in Figure 2-6

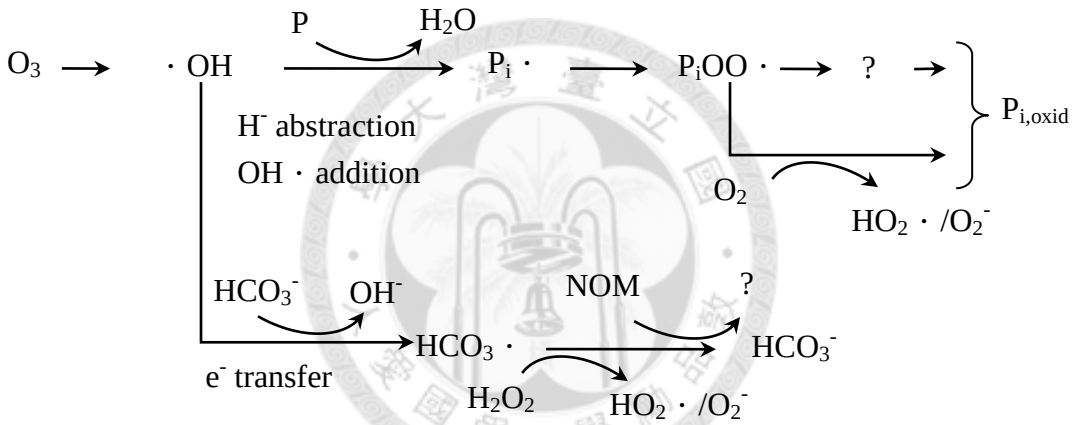


Figure 2-6 Reaction of hydroxyl radical with organic pollutant (P) leading to a great diversity of oxidized compounds. P: pollutant; Pi: i species of P; Pi,oxid: oxidized compounds; NOM: natural organic matter (Hoigné, 1998)

(3) Stability of ozone in water

The stability of ozone depends on the water matrix including pH, alkalinity, and the type of natural organic matter (NOM) (Hoigne, et al., 1998). The pH may be the crucially important factor of the water for ozone self-decomposition and hydroxyl radical generation. Because there are different reaction mechanisms (direct or indirect reaction) for ozonation by various (acid or base) pH values in the water (Paul et al.,

1998; Daniel et al., 1999), the pH value plays an important role in removing organic compounds. Likewise, alkalinity and NOM can affect the ozone stability in two i.e., direct or indirect reaction with ozone.

2-5-2 Ozonation by-products formation

In general, the formations of the typical ozonation by-products include aldehydes carboxylic acids, and ketones (Richardson et al., 1999; Huang et al., 2005). Because ozonation by-products, such as aldehyde and ketone, were harmful to human, these by-products are of more concern and are the subject of various studies, therefore, it is important to clarify by-products formation of organic compounds during ozonation.

Ozonation at different pH conditions will affect aldehyde formation. According to Chang et al. (2007), the formation of aldehydes was high at pH 9 and then decreased at pH 7 and then 5 by ozonation of low MW compounds such as resorcinol. The authors explained that hydroxyl radicals formed during ozonation at pH 9 could destroy the organic compounds and generate more short chain by-products such as formaldehyde than ozone molecules at pH 5. The phenol oxidation reaction mechanism is shown in Fig. 2-7 (Hammes et al., 2006). According to the reaction mechanism, the most important oxidation products are shown in Figure 2-7. The major oxidation products include muconic acid, glyoxalic acid, and oxalic acid.

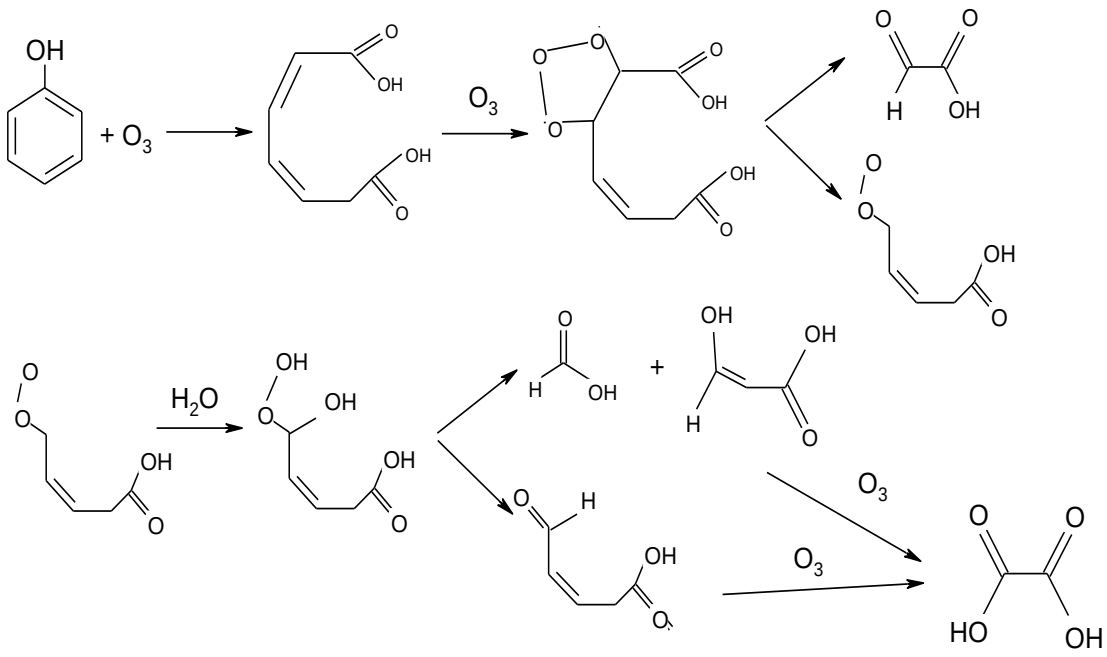


Figure 2-7.Schematic representation of the mechanism of phenol oxidation with ozone. For simplicity only a partial mechanism leading to the most important oxidation products are shown. (1) Muconic acid; (2) glyoxalic acid; (3) a hydroxy-hydroperoxide;(4) formic acid; (5) 3-hydroxy -2-propenoic acid; (6) 4-oxo-2-butenoic acid; (7) oxalic acid. (Hammes et al., 2006)

2-6 Possible pathway and mechanisms of diclofenac during ozonation

The degree of mineralization of diclofenac via ozonation is insignificant. Moreover, the high photodegradation of diclofenac in natural water bodies has made it important the investigation of intermediates, mechanisms and pathway of diclofenac degradation. Many studies have identified the possible intermediates, developed some pathway and mechanisms of diclofenac during oxidation. Table 2-8 summaries intermediates reported in previous studies.

Table 2-8 Chemical structure of intermediates of diclofenac during oxidation

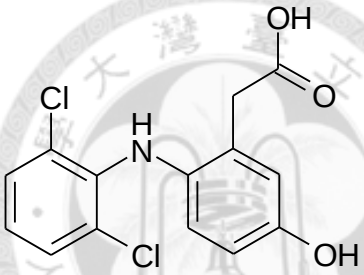
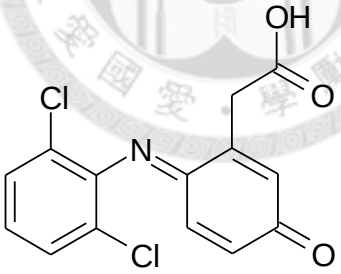
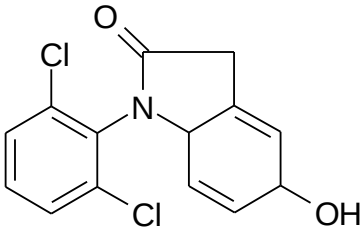
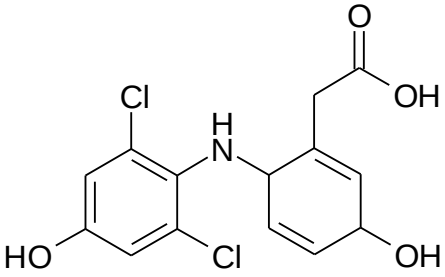
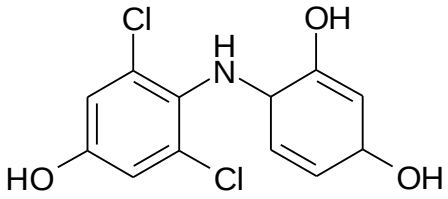
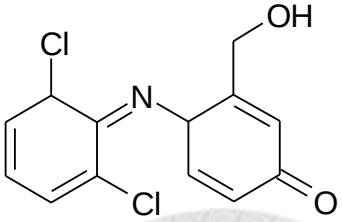
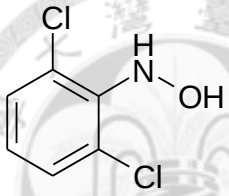
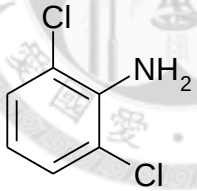
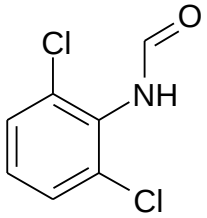
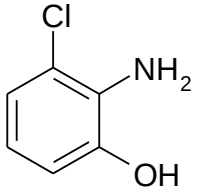
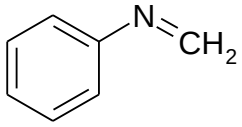
Number	Chemical structure	Previous identification
(A)		Vogna et al, 2004 Perez-Estrada et al, 2005b Calza et al, 2006
(B)		Calza et al, 2006
(C)		Perez-Estrada et al, 2005b Calza et al, 2006
(D)		Calza et al, 2006

Table 2-8 Chemical structure of intermediates of diclofenac during oxidation (Continues)

Number	Chemical structure	Previous identification
(E)		Vogna et al, 2004 Perez-Estrada et al, 2005b Calza et al, 2006 Hohmann et al, 2007
(F)		Perez-Estrada et al, 2005b
(G)		Perez-Estrada et al, 2005b
(H)		Vogna et al, 2004 Perez-Estrada et al, 2005b Bartels and Von Tumpling, 2007 Hohmann et al, 2007
(I)		Coelho et al, 2009
(J)		Coelho et al, 2009
(K)		Coelho et al, 2009

2-6-1 Mechanisms

Sein et al (2008) has proposed some possible mechanisms by adding other compounds into reaction. To investigate the mechanisms that OH radical or other radical formed in ozonation may undertake, the OH radical scanvenger *t*-BuOH,has been used to prove the hypothesis. After the calculation of Hammet free enerhy value, the major reaction is an ozone addition on the amine nitrogen of diclofenac. Along with the OH radical, the diclofenac aminyl radical is formed, as shown in Figure 2-8.

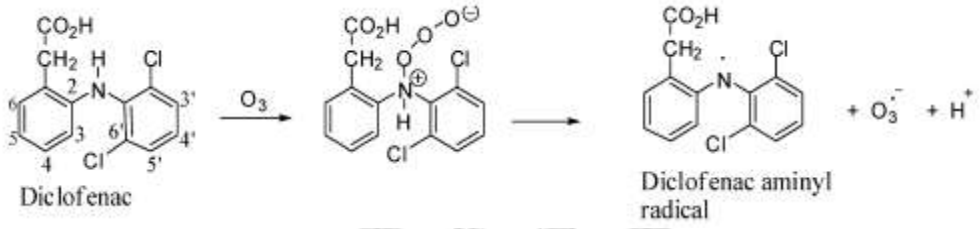


Figure 2-8 The mechanism of forming diclofenac aminyl radical. (Sein et al, 2008)

One of diclofenac decay routes is the addition of O_3-• to the para-position of the activated ring of the aminyl radical, which would form 5-hydroxydiclofenac. 5-hydroxydiclofenac is the minor product in the O_3-based reaction and the mechanism is shown in Figure 2-9. The major detected product is diclofenac-2,5-iminoquinone. The formation of diclofenac-2,5-iminoquinone may be conducted by a reaction of the aminyl radical with O_3. The reaction pathway is depicted in Figure 2-10. The aminy radical formed reacts with O_3 especially at the paraposition to nitrogen on the more electron-rich aromatic ring having the electron-donating group (CH_2COO-). A 1,2-H shift gives rise to a hydroxycyclohexadienyl radical, and subsequent oxidation by O_2 leads to the formation of diclofenac-2,5-iminoquinone.

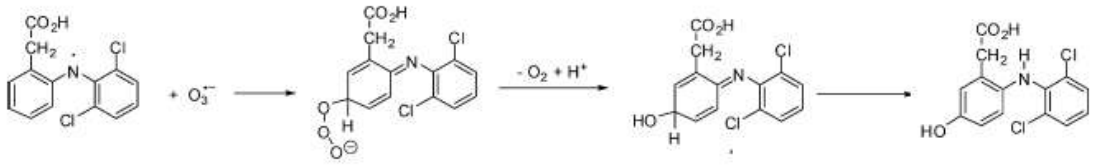


Figure 2-9 The formed mechanism of 5-hydroxydiclofenac (Sein et al, 2008)

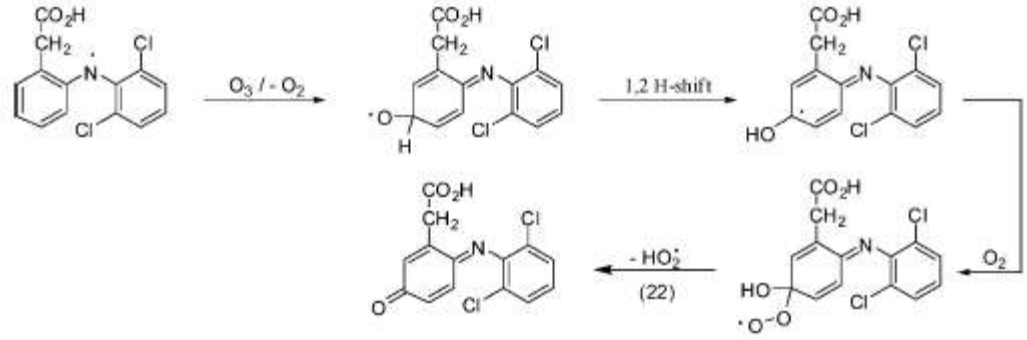


Figure 2-10 The formed mechanism of diclofenac-2,5-iminoquinone (Sein et al, 2008)

The OH radical, on account of its electrophilic nature, will preferentially attack the activated sites of aromatic rings often resulting in the formation of stable hydroxylated compounds via transition through an unstable carbon-centered radical. Figure 2-11 shows the formation of 5-hydroxydiclofenac as an expected major product in the OH radical-mediated reaction. Upon addition of OH radical, a cyclohexadienyl-type radical is formed. In competition with other reactions, HO_2 • is eliminated, while 5-hydroxydiclofenac is formed.

Diclofenac must also become hydroxylated at other positions. Another important OH radical-related product is 2,6-dichloroaniline. Figure 2-12 shows OH radical addition at the *ipso*-position of the amino group. Such adducts are known to release the substituent rapidly. The phenoxyl-type radical which is formed besides 2,6-dichloroaniline in this reaction does not react with O_2, but will add to other radicals present (Jin et al, 1993). In addition to the chlorine-containing positions of

diclofenac, 2,6-dichloroaniline, or other chlorinated target compounds will cause Cl^- release, Cl^- release may be taken as an approximate measure of mineralization of diclofenac. The chloride release can also determine the structure of quinines. This type of reaction, shown in Figure 2-13, may also take part as a cage reaction with aminyl and O_3- radicals as partners. Ortho-quinones are considerably less stable than para-quinones, and it is conceivable that the second chloride is hydrolytically cleaved in subsequent reactions.

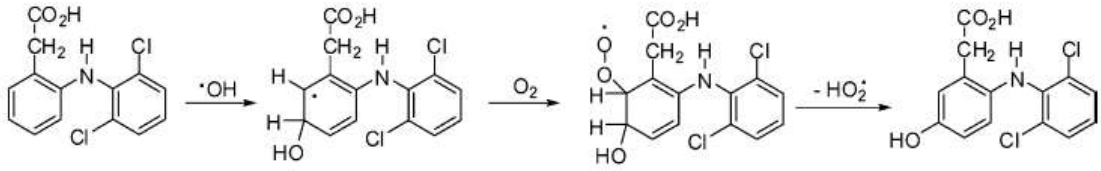


Figure 2-11 The mechanism of forming 5-hydroxydiclofenac with OH radical (Sein et al, 2008)

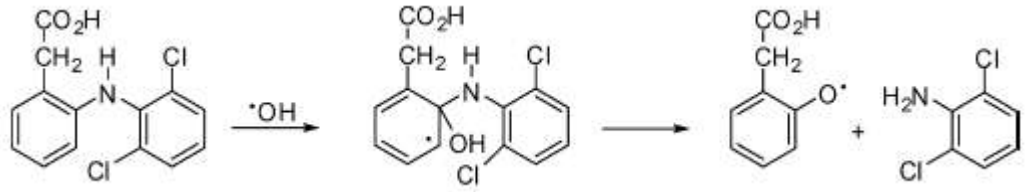


Figure 2-12 The formed mechanism of 2,6-dichloroaniline (Sein et al, 2008)

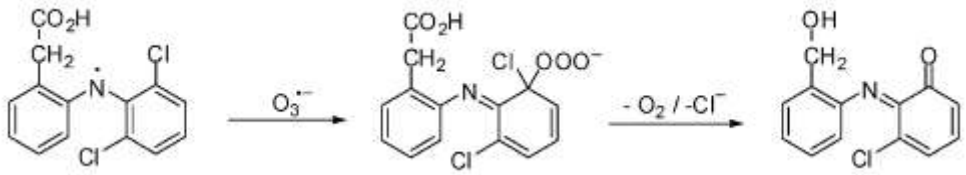


Figure 2-13 The formed mechanism of Ortho-quinones (Sein et al, 2008)

2-6-2 Degradation pathway

As discussed in previous publications (Pérez-Estrada et al., 2005b), diclofenac degradation follows different pathways, depending on the treatment applied. Although some similitude is observed in all the treatments and presence of common

intermediates is reported, substantial mechanistic differences are observed and the predominance of one or other route depends on the treatment applied. The pathway of diclofenac degradation is shown in Figure 2-13

The main intermediates formed during ozonation are 2-[2,6-dichlorophenyl)amino]-5-hydroxyphenylacetic acid (D1) and 2,6-dichloro-4-hydroxybenzenamine (D8). Hydroxylation reactions are common in most of the oxidative processes but, while by TiO_2 photocatalysis the non-selectivity of the OH radical attack lead to the formation of several hydroxylated species as the first step in the diclofenac degradation (Calza et al., 2006), the selectivity associated with ozonation conducts to the formation of the 5-hydroxil derivative (D1) as the main product, following a different mechanistic route as proposed by Vogna et al. (2004). The DFC degradation is preferentially initiated by the hydroxylation of the phenylacetic ring in C5 in the early stage of reaction. Important differences are also observed with respect to the photo-Fenton treatment (Pérez-Estrada et al., 2005b). By photo-Fenton reaction, further oxidation of D1 into the corresponding quinone-imine intermediate (D2), is favored because it provides an alternative of quicker pathway for ferrous iron regeneration as proposed by Chen and Pignatello (1997). Thus, in this case several intermediates conserving the quinone imine structure are identified.

The fast and abundant appearance of D8 also points to the cleavage of the C–N bond of diclofenac as a preferential route, which originates a series of C–N cleavage products (compounds D7 to D13). Coelho et al (2009) suggest that oxidation of diclofenac by ozone, under the experimental conditions used, mainly proceeds by hydroxylation reactions and cleavage of the C – N bond. Decarboxylation, cyclization and ring opening reactions in the phenylacetic acid moiety also occur in the further steps of the degradation process.

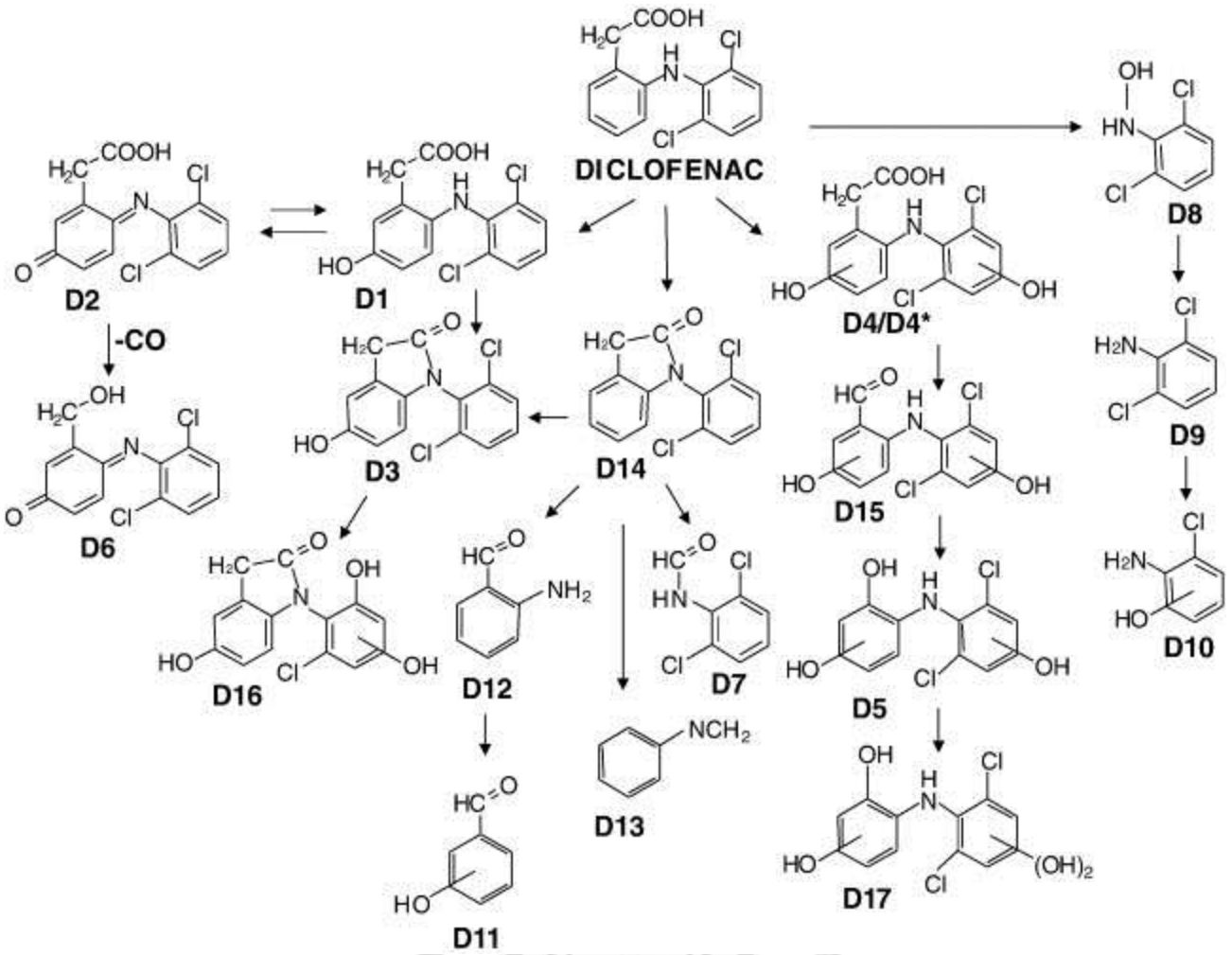


Figure 2-13 Diclofenac degradation pathway (Coelho et al, 2009)

2-7 Predictive Model of Diclofenac Decay

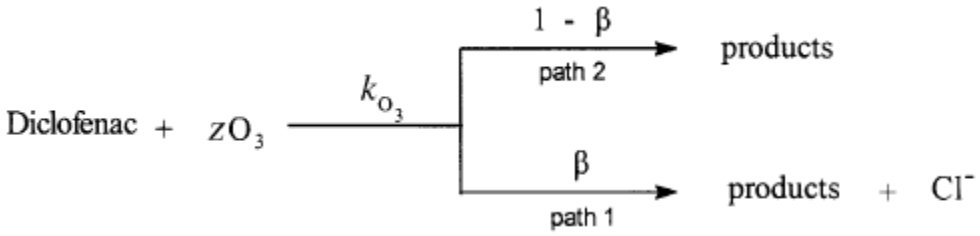
2-7-1 Ozonation Decay

In semi-batch reactor, the ozone concentration can be determined by several methods. Since the mass transfer of ozone from gaseous to the aqueous phase can be a limiting factor, causing ozone loss in the off-gas, the absorbed ozone dose can be represented as a function of time with accumulation of the varied value of ozone concentration between in-gas and off-gas (Coelho et al, 2009). It could be defined as:

$$ozone \quad dose = \frac{\int_t G(C_{O3(g)}^{in} - C_{O3(g)}^{out})dt}{V_L} \qquad \text{Eq. (2-7-1)}$$

where $C_{O3(g)}^{in}$ and $C_{O3(g)}^{out}$ (mg/L) are the values of the ozone concentrations in the gas stream in the inlet and outlet of the reactor, G (L/s) is the volumetric flow rate of the gas stream, V (L) the ozonation reactor volume and t (s) the time of ozonation.

Another method is based on the two-film theory, taking the mass transfer into consideration (Andreozzi et al, 1996; Vogna et al, 2004). It assumed that the process develops under a fast kinetic regime of absorption with reaction. The formula is defined as:



$$\frac{d[O_3]_B}{dt} = \frac{Q}{V_B}([O_3]_{in} - [O_3]_B) - \frac{k_L^0 aE([O_3]_B \alpha - [O_3]_L)}{V_B} V_L \quad \text{Eq. (2-7-2)}$$

$$\frac{d[O_3]_F}{dt} = \frac{Q}{V_B}([O_3]_B - [O_3]_F) \quad \text{Eq. (2-7-3)}$$

$$\frac{d[O_3]_L}{dt} = k_L^0 aE([O_3]_B \alpha - [O_3]_L) - z\gamma_{diclofenac} \quad \text{Eq. (2-7-4)}$$

$DFC + Ozone \rightarrow Ozonation\ \ by-products$ (1-β)

$$\frac{d[S]}{dt} = -\frac{1}{z} K_{O_3}[S][O_3]_L = \gamma_{diclofenac} \quad \text{Eq. (2-7-5)}$$

$DFC + Ozone \rightarrow Ozonation\ \ by-products + Cl^-$ (β)

$$\frac{d[Cl]}{dt} = -\beta K_{O_3}[S][O_3]_L \quad \text{Eq. (2-7-6)}$$

where β indicates the selectivity of the oxidation, ($[O_3]_B$), ($[O_3]_F$), ($[O_3]_L$) designates ozone in the bubble, freeboard and liquid phases, and $k_L{}^0$ a, $k_L{}^0$, a, D_{o3} ; V_B V_L and V_F are the constants.

Chapter 3 Materials and Methods

3-1 Research Flowchart

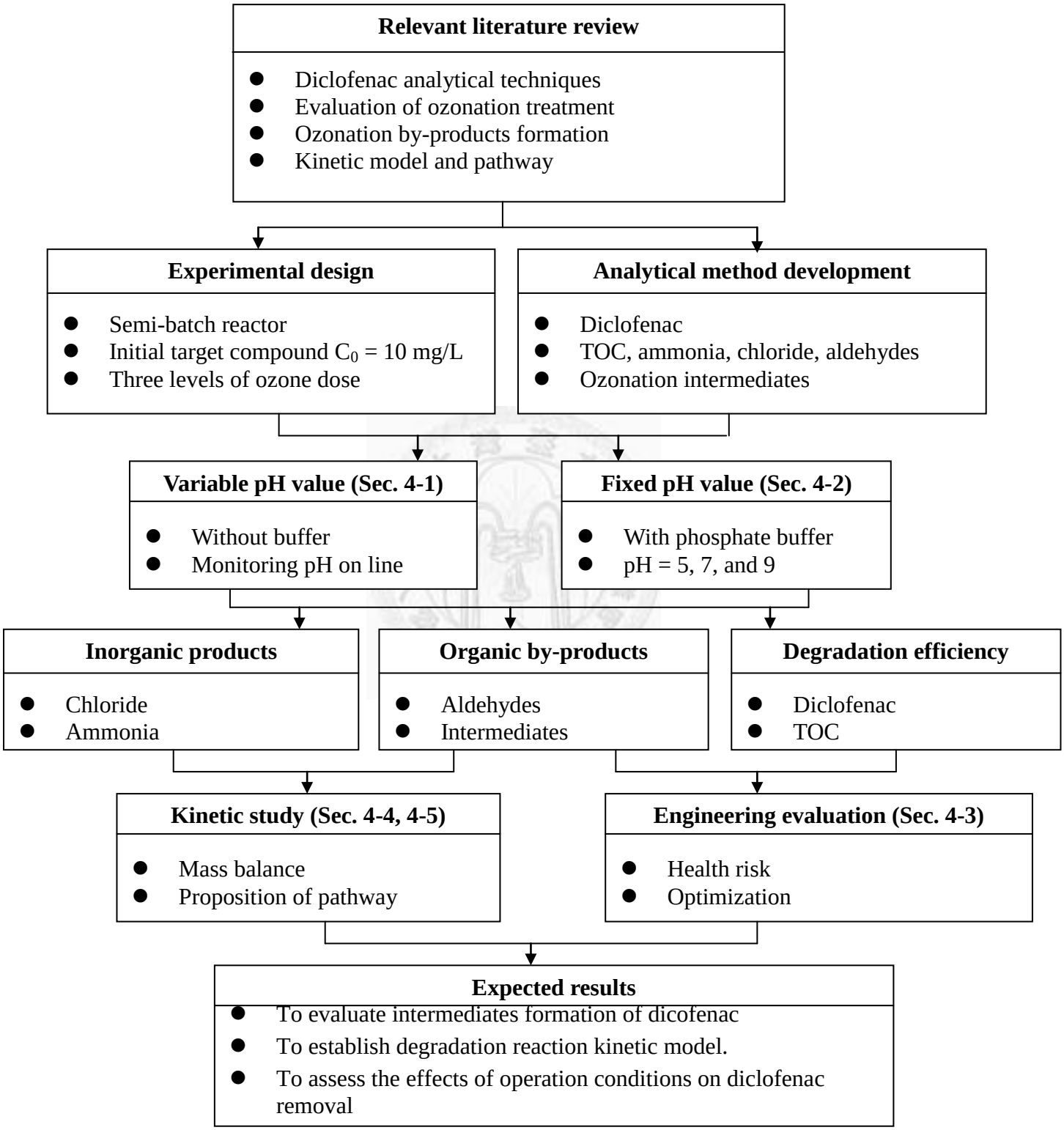


Figure 3-1 Research flowchart

3-2 Synthetic Water Preparation

The synthetic water of diclofenac salt was prepared in 10 mg/L, phosphate buffer, including monosodium and disodium phosphate, were added to adjust pH values ,to 5.1, 7.4, and 8.9, and ionic strength was controlled at 50 mM.

3-3 Methods

3-3-1 Experimental Design

The experiment could be divided into two stages. The detailed experiment design is shown in Figure 3-2. In stage 1, a quantitative method for the extraction and determination of diclofenac in synthetic water was developed and this method was applied to the analysis of diclofenac concentration in the ozonation.

The purpose of stage 2 was to evaluate the diclofenac decay and ozonation intermediates and by-products formation in ozonation and O_3/UV process. In stage 2, in order to predict diclofenac decay and by-products formation in the ozonation, experiments conducted a period of 60 min. Sampling time was 0, 1, 3, 5, 10, 20, 40, and 60 min or 0, 1, 2, 4, 6, 8, 10,15, 20,25, 30, 40, 50, and 60 min.

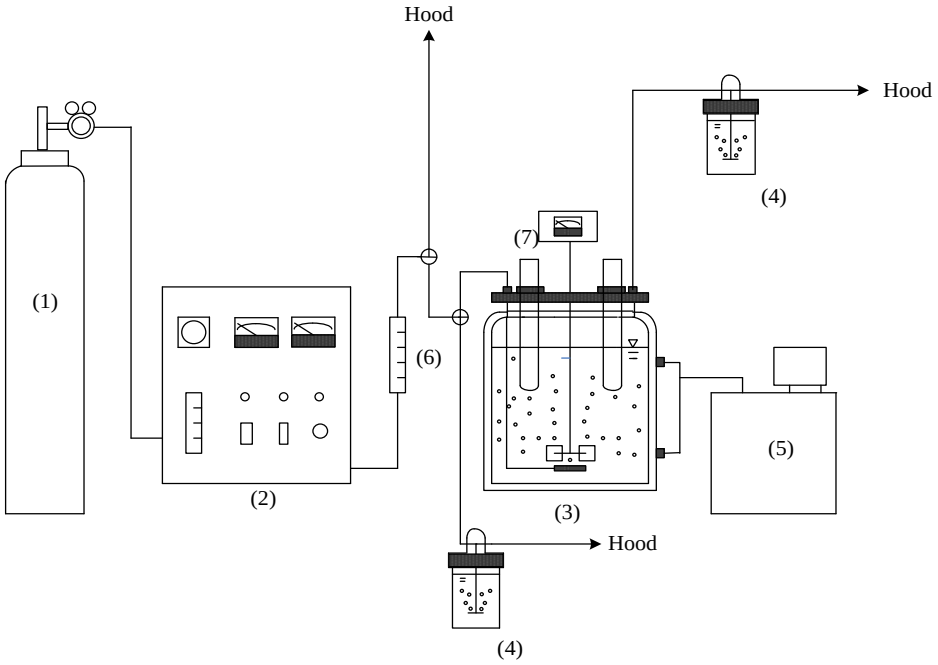


Figure 3-2 The experiment apparatus of ozone semi-batch reactor: (1) Oxygen cylinder, (2) ozone generator, (3) Ozone reactor, (4) KI traps, (5) thermostat, (6) flow meter

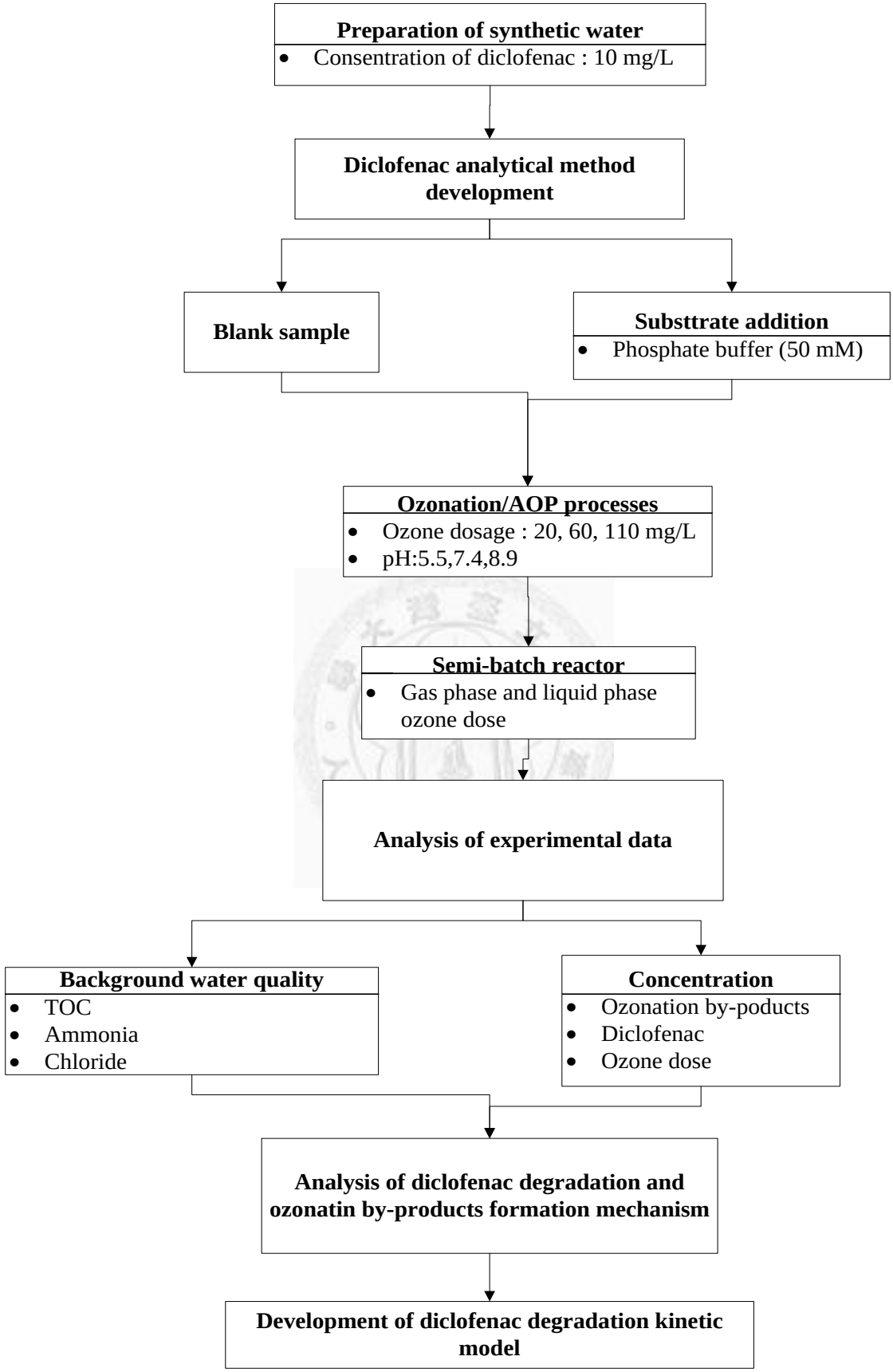


Figure 3-3 Flowchart of experiments

3-3-2 Establish Intermediates Analytical Method

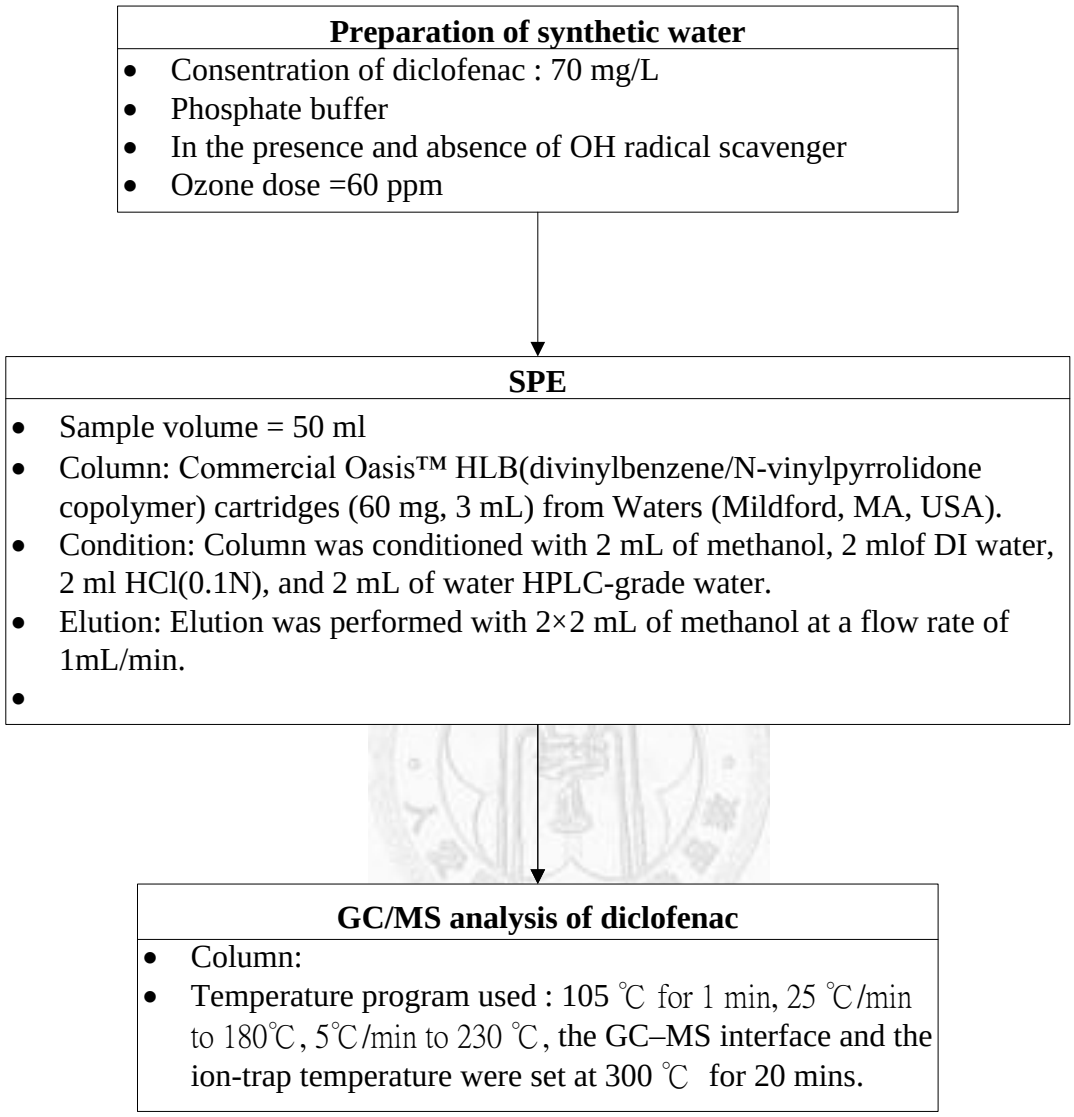


Figure 3-4 Flowchart of experiments to analyze intermediates of diclofenac.

1. Method

   According to Pérez-Estrada et al, 2005

2. Apparatus

   a. GC (HP 7890)

   b. EI-MASS (HP 5973)

3. Reagents

   a. Organic free water for rinse and sample dilution

   b. Methanol (LC/MS grade, purity 100%, made by J.T. Baker)

   c. Hydrochloric acid (made by Merck)

   d. Standards: 2,6-dicloroaniline (Sigma-Aldrich);

      5-hydroxyldiclofenac (Sigma-Aldrich)

4. Procedure of pretreatment

   a. The cartridges made by Oasis HLB were conditioned with 2 mL of methanol, deionized water, 0.1 N of HCl, and water.

   b. Loaded 50-mL water samples and eluted with 2 mL of methanol.

   c. The eluates were evaporated by nitrogen stream and recomposed to a final volume of 0.1mL.

   d. Analyze by GC-MS.

5. Condition of GC-MS: Separation in GC-MS was carried out after 10 μL of the samples were injected into the capillary column (30 m × 0.25 mm × 0.25 μm VF-5ms, Agilent, USA). The temperature program was: initial 105 ^{o}C for 1 min, then rising to 180 ^{o}C at 25 C^{o}/min, and finally rising to 250 ^{o}C at 5 C^{o}/min standing for 1 min. The spilt-splitless injector was operated at initial pressure of 30 psi standing for 1.5 min and the spilt flow was 50 mL/min.

3-3-3 Analytical Methods

3-3-3-1 General Analytical Methods

The detailed analytical methods for traditional methods are shown as the following; or in the Appendixes.

Chloride: The concentration of chloride was determined by ion chromatography (Metrohm 790 personal IC; Metrosep A Supp 4-250 column; 1.8 mM Na_2CO_3/1.7 mM $NaHCO_3$ eluent; 1 mL/min eluent flow rate).

Ammonia: The concentration of ammonia was determined by flow injection analysis (FIA), using Berthelot reaction to produce a high absorbable dark blue color. By measuring the absorbance at wavelength 630 nm, one can calculate then know the concentration of ammonia.

TOC : Total organic carbon (TOC) was determined by a total organic carbon analyzer (O.I. Corporation, Model 700).

Residual ozone: Orbisohere Model 3600

Ozone dose : Ozone in the in-gas and off-gas were monitored continuously by means of UV-mini 1240 UV-Vis spectrophotometer at 258 nm quipped with a quartz cell.

pH value: Metrohm 780 pH meter

3-3-3-2 Analytical Methods for diclofenac

The concentration of diclofenac was measured by HPLC with UV detector. For the analysis of diclofenac, a C-18 column (Varian, 250x4.6mm) was equipped and the detection wavelength was set at 280 nm. The flow rate was 1.25 mL/min, and the mobile phase was consisted of 50% of ammonium formate (10 mM) and 50% of acetonitrile. (Coelho et al., 2009)

3-3-3-3 Analytical Methods for Ozonation By-Products

1. Method

   According to Standard method 6252 (APHA, 2005)

2. Apparatus

   a. GC (HP 7890)

   b. EI-MASS (HP 5973)

3. Reagents

   a. Organic free water for rinse and sample dilution

   b. Methanol (LC/MS grade, purity 100%, made by J.T. Baker)

   c. Anhydrous potassium biphthalate, KHP (made by Merck)

   d. O-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine・HCl, PFBHA (made by Aldrich)

   e. Sulfuric acid (made by Merck)

   f. n-Hexane (ACS grade, purity > 99.0%, made by Merck)

   g. Standards:

Compound	Origin	Purity (%)	Density
Formaldehyde	Merck	37.0	1.083
Acetaldehyde	R.D.H.	99.5	0.78
Glyoxal	Sigma	40	1.265
Methyl glyoxal	Sigma	40	1.178
Acetone	J.T. Baker	98	
1,2-dibromopropane (internal standard)	Acros	97	1.937

4. Procedure of pretreatment

   a. Remove samples and standard solution from storage and equalize them at room temperature (about 10 min).

b. Take 20- mL samples from the original sample vials and place in another vial.

c. Add 200 mg of potassium hydrogen phthalate (KHP) to each sample.

d. Add 1 mL of 15 g L^{-1} of PFBHA solution to each sample vial, and swirl gently.

e. Place all samples in a constant-temperature water bath with temperature which was controlled at 35 ± 0.5 ℃ for 2 h.

f. Remove samples from water bath and cool to the room temperature.

g. Add 0.05 mL of concentrated H_2SO_4 to each sample as to quench the derivatization reaction.

h. Add 4 mL of Hexane working solvent containing the internal standard and then shake the mixture manually for about 3 min.

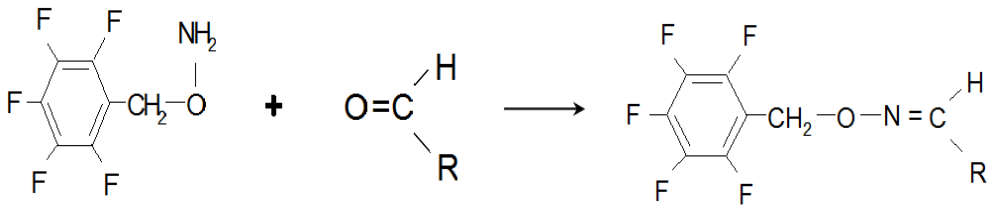
i. Stand by approximately for 5 min until the samples are delaminated.

j. Draw off top hexane layer into a 7- mL vial containing 3 mL of 0.2 N H_2SO_4.

k. Shake for 30 sec and let it stand for approximately 5 min until the samples are delaminated.

l. Draw off top hexane layer and place the sample into a 1.8- mL vial.

m. The proposed scheme of PFBHA derivatization is shown below:



n. GC/MS separation and quantification

3-3-4 Risk Assessment

Both the carcinogenic risk of aldehyde in the water distribution systems of the advanced and the conventional water treatment plants were assessed. Equations 3-3-1 and 3-3-2 show the human exposure concentration through ingestion and dermal pathway, respectively.

$$Ingestion\ \ dose\ (mg/kg/day) = \frac{CW \times IR \times EF \times ED}{BW \times AT} \qquad \text{Eq. (3-3-1)}$$

$$Dermal\ \ dose\ (mg/kg/day) = \frac{CW \times SA \times PC \times ET \times EF \times ED \times CF \times k}{BW \times AT} \qquad \text{Eq. (3-3-2)}$$

where CW is the concentration of the chemical in question in the water (mg/L), IR is the ingestion rate (L/d), EF is the exposure frequency (d/y), ED is the exposure duration (y), BW is the body weight (kg), AT is average time (d), SA is the surface area of skin (cm^2), PC is the permeability contact (cm/h), ET is the exposure time (h/d), CF is the conversion factor (L/cm^3), and k is the permeability coefficient. The following parameters were selected: IR = 2 L/d, EF = 365 d/y, ED = 70 years, BW = 70 kg, AT = 70 y × 365 d/y, SA = 18000 cm^2, PC = 1.9×10^{-3}, ET = 0.29 h/d, and CF = 10^{-3} L/cm^3 (Chinery et al., 1993, US EPA).

The carcinogenic risk (Equation 3-3-3) was calculated based on a carcinogenic risk of 10^{-6} as the maximum acceptable value.

$$Cancer\ \ risk = Exposure\ \ dose \times Slope\ \ factor \qquad \text{Eq. (3-3-3)}$$

Information on exposure dose (ED) and slope factor (SF) of chemicals through various exposure pathways were adapted from the Office of Environmental Health Hazard Assessment of US OEHHA. The SF of formaldehyde for ingestion exposure route is 2.1×10^{-2} $(mg/day/kg)^{-1}$. The exposure concentration needs to be modified to the risk level of 10^{-6}.

Chapter 4 Results and discussion

4-1 Ozonation at Variable pH Values

A series of experiments were conducted without phosphate buffer, and at three different ozone doses of 110, 60, and 20 mg/L as detected respectively in the inlet gas stream. The ozone dose was represented as $[O_3]$/[DCF], and the values were 68, 37, and 12. Briefly, the ratios were 3 to 1. Furthermore, the residual diclofenac, total organic carbon (TOC), chloride, ammonia, and aldehyde were evaluated and discussed in the following sections.

4-1-1 Degradation of diclofenac

The degradation of diclofenac with time at variable pH values was shown in Figure 4-1. The diclofenac was almost vanished by ozonation within one hour. For the highest ozone dose, the diclofenac was rapidly oxidized and eliminated to almost zero within the first 5 min. Regarding to the other ozone doses, the concentration of diclofenac decreased rapidly to almost zero within the first 10 and 25 min at the ratio 2 and 1 respectively. As the ozone dose increased about three times from 60 mg/L to 20 mg/L, the time of reaching the same removal rate would be approximately equal to three. It could be concluded that higher ozone dose the diclofenac was removed faster and the removal rate of diclofenac was linearly correlated to the ozone dose.

On the other hand, after the diclofenac was removed, the ozone was still introduced consistently into the reactor and it started to dissolve in the water. As a result, the ozone dose detected in the liquid phase increased. The pH values detected with time decreased from 5.13-5.2 initially to 3.38-3.5 in the end of reaction of 60 min. The change of pH values indicated the not only the increasing dissolved ozone in the solution but also the possible production of acidic compounds during ozonation. Moreover, the removal conditions were also inferred by the data of ozone doses in the liquid phase, which were

measured with time and presented in Figure 4-2. The concentration of ozone in the liquid phase remained zero when the diclofenac was still present in the solution, and then increased with time, as the concentration of diclofenac was no longer detectable by HPLC.

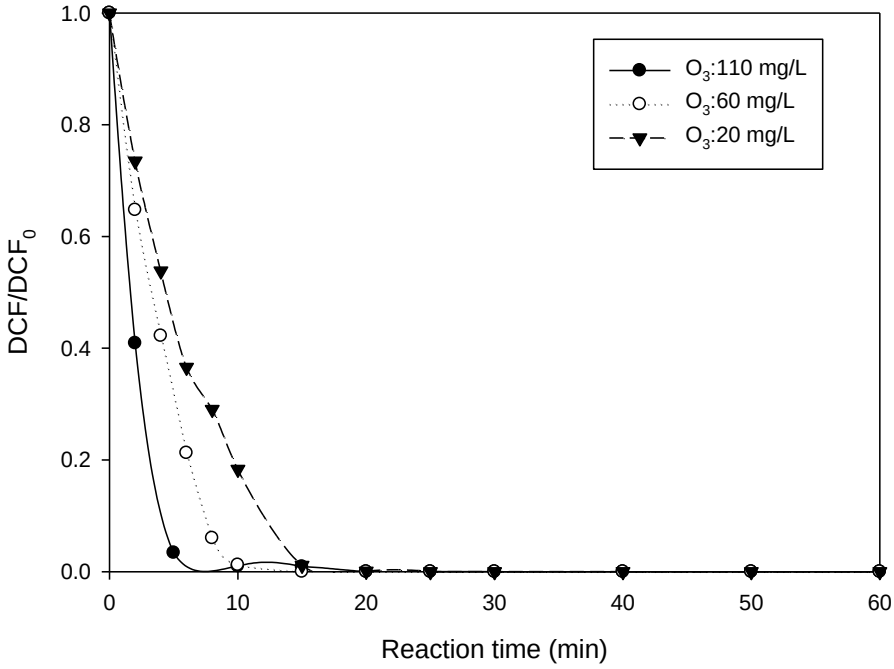


Fig. 4-1. Degradation of diclofenac as a function of time in the absence of buffer at various O_3 doses; (●) O_3:110 mg/L; (○) O_3:60 mg/L; (▼) O_3:20 mg/L. Experimental conditions: pH_0=5.2.

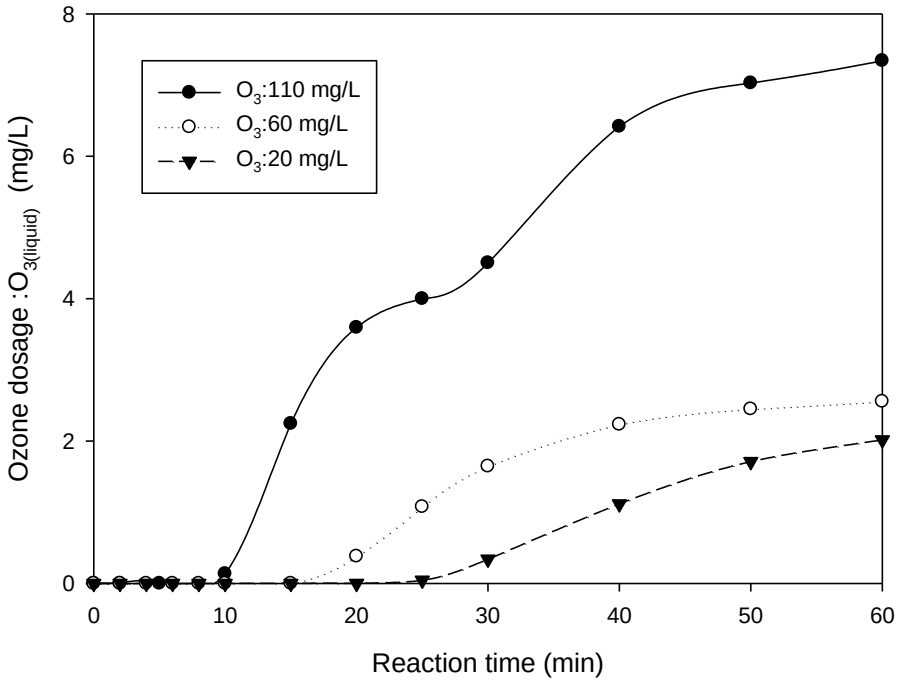


Fig. 4-2. Ozone concentration in the solution in the absence of buffer at various O_3 doses; (●) O_3:110 mg/L; (○) O_3:60 mg/L; (▼) O_3:20 mg/L. Experimental conditions: pH_0=5.2.

4-1-2 Degradation of total organic carbon (TOC)

Figure 4-3 shows the TOC removal rate of ozonation of diclofenac at three different ozone doses and without pH adjustment via phosphate buffer. For the highest ozone dose, the TOC removal was 41.59%, the best as expected. However, for the other two ozone doses, the removal efficiency were 32% and 33.74% respectively at ozone dose of 60 and 20 mg/L, respectively.

The TOC removal percentage at distinctive ozone inputs were supposed to be higher as the ozone dose increased. Although the best TOC removal efficiency occurred at the highest ozone dose, the other two ozone doses also yielded percentage TOC removal as expected. The TOC removal efficiency at other ozone doses varied slightly while one was twice of the other. The difference in TOC removal was likely brought by

the complex self-reaction of ozone. As ozone was introduced into the reactor, it would either soon decomposed into free radicals, such as OH radical, or maintained in its original molecular form, which will attack the chemical species in the solution. As for the high ozone dose, the concentration of radicals formed increased. Because free radical is reactive, the diclofenac decomposed easily, formed low-molecular-weight intermediates, and finally becomes mineralized. Therefore, as the ozone dose increased, the TOC removal increased. The two irregular results needed further investigation, which will be discussed in the following sections. This phenomenon perhaps indicates the low ozone dose might be beneficial to decompose diclofenac into short-chain organic compounds which are easily mineralized. In order to discuss more about the results and find the possible correlation, the last two ozone doses were taken as the main operative conditions with fixed pH values, which would be shown in section 4-2.

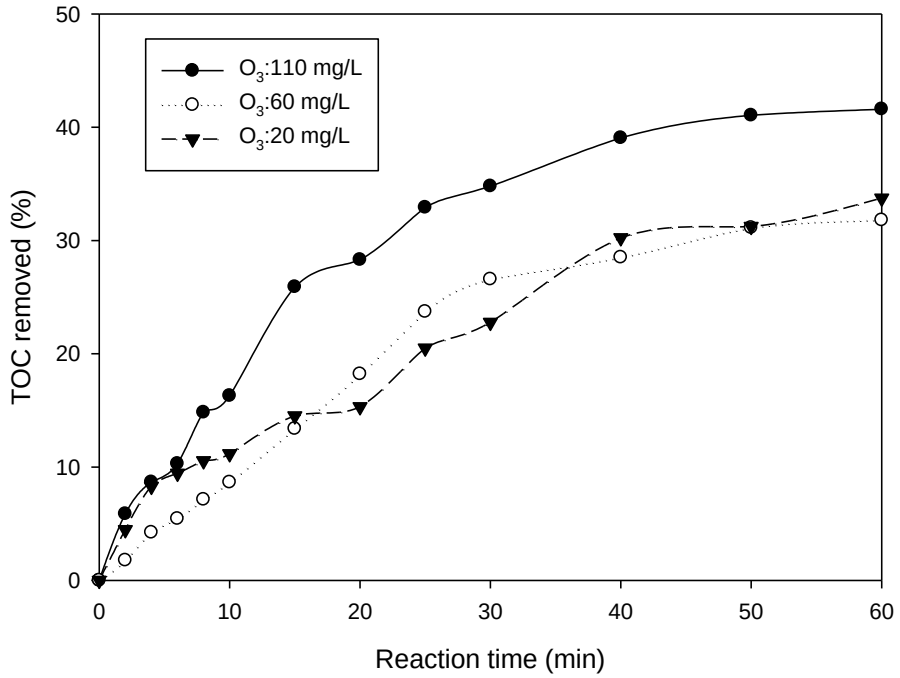


Fig. 4-3. Degradation of TOC removal as a function of time in the absence of buffer at various O_3 doses; (●) O_3:110 mg/L; (○) O_3:60 mg/L; (▼) O_3:20 mg/L. Experimental conditions: pH_0=5.2.

4-1-3 Formation of chloride

Figure 4-4 shows the concentration of chloride formed during ozonation. The chloride was released consistently at the highest concentration of about 2.2 mg/L in the first 20 - 25 min, and then remained constant or slightly decreased with the last 40 - 35 min respectively at the two higher ozone doses. For the lowest one, the chloride continued to form during the whole process and reached about 2 mg/L finally.

The theoretical amount of chloride released during ozonation was predicted at a maximum of about 2.4 mg/L. It could be seen that the observed results were close to the maximal concentration, which indicated that the oxidation of diclofenac were almost completed in terms of dechlorination. Table 4-1 shows the percentage of chloride formation at the three ozone doses. The percentage of chloride formation was expressed in two terms, the maximum and the final concentration with respect to the theoretical value. In the present s study, the maximal concentration of chloride under one ozone dose was used to calculate the estimated percentage versus theoretical maximum concentration.

In Figure 4-4, the ozone doses seemed to show little correlation with the concentration of chloride formation. But the variance between the theoretical value and experimental data could still infer that ozone dose could affect the level of detected chloride concentration. The delayed time of maximum concentration of chloride and the lower concentration of chloride formation could indicate the minor ozone dose effect of chloride formation. It could be concluded that the lower ozone dose could render diclofenac degraded by various ways.

The chloride was formed as the ozone attacked the diclofenac, and this step was taken as the possible reaction pathway in the beginning. According to some studies, the formation of chloride somehow seems to have the connection with the TOC removal.

The chloride, as the first step of the ozonation of diclofenac, was supposed to be totally released since the diclofenac had been disappeared in the semi-batch reaction. The above results indicated the lower ozone dose could probably produce the intermediates which might have contained chloride and have strong structure. These intermediates could not be decomposed or oxidized easily and contribute to the residual TOC.

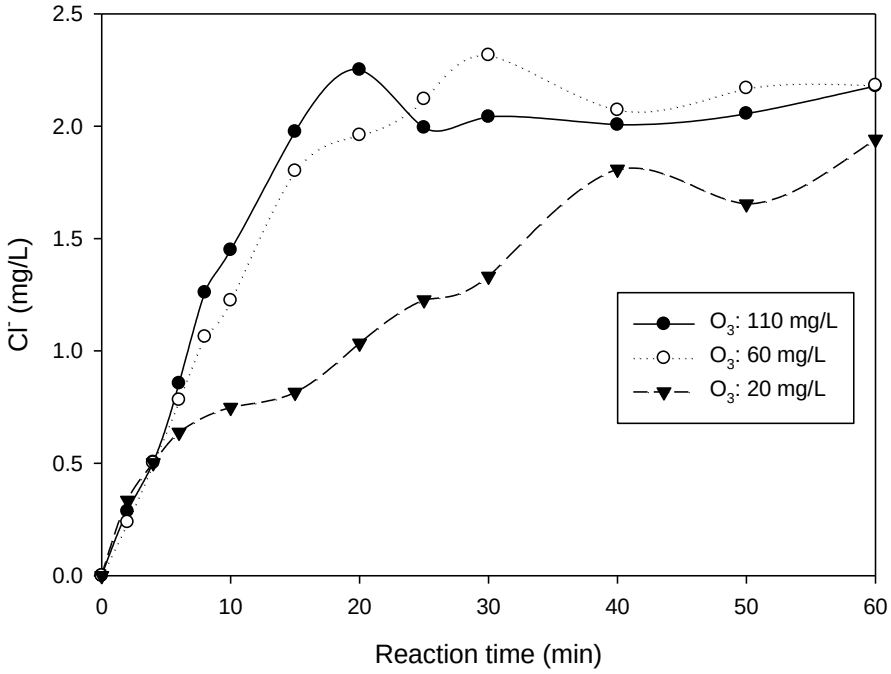


Fig. 4-4. Evolution of Cl^- as a function of time during ozonation in the absence of buffer at various O_3 doses; (●) O_3:110 mg/L; (○) O_3:60 mg/L; (▼) O_3:20 mg/L. Experimental conditions: pH_0=5.2.

4-1-4 Formation of ammonia

The possible forms of nitrogen compounds produced during the ozonation of diclofenac were monitored under each operational condition. Due to the detection limit of the ion chromatography technique, the nitrite and nitrate were not found in the reaction. Therefore, the ammonia formed from nitrogen of the diclofenac was detected and estimated as the main product.

The presence of ammonia indicated the ability of the oxidation of the nitrogen compounds. Under the condition of various pH values, as shown in Figure 4-5, the concentration of ammonia would reach approximately 0.122 mg/L after 40 minutes of ozonation even at different ozone doses. After 40 minutes of reaction, the decreasing concentration of ammonia at the highest ozone dose showed the better tendency of the oxidation of ammonia, while other two ozone doses showed almost the same results at the end of reaction. The results showed that the ozone dose had little effect on the oxidation of nitrogen in diclofenac when the pH values were not buffered.

The theoretical amount of nitrogen was about 0.47 mg/L in the ozonation of diclofenac. The percentage of ammonia formation was determined in two terms, the maximum and the final concentration with respect to the theoretical value. Moreover, the ozone dose showed little effect on the formation of ammonia. It could be concluded that the ozone dose could not control the pathway of the C-N cleavage.

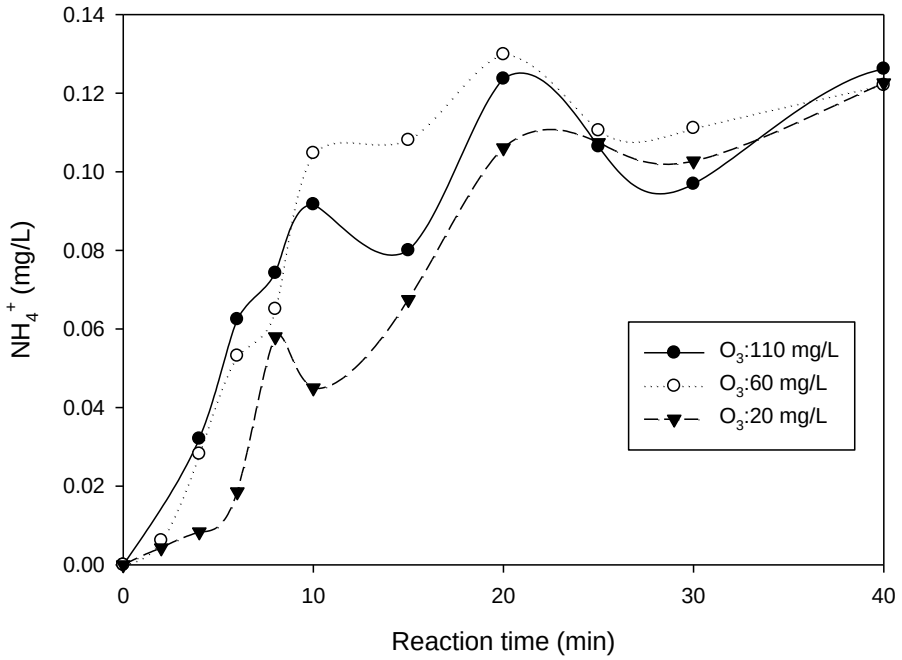


Fig. 4-5. Evolution of NH_4^+ as a function of time during ozonation in the absence of buffer at various O_3 doses; (●) O_3:110 mg/L; (○) O_3:60 mg/L; (▼) O_3:20 mg/L. Experimental conditions: pH_0=5.2.

4-1-5 Summary

Table 4-1 compares results of ozone doses at various pH values on diclorfenac degradation. Due to the excess ozone injection, the removal all reached over 99%. The different level of ozone dose caused the time of the same removal at each curve increased by times. As a result, it could be inferred that the ozone dose increased the removal of diclofenac. For TOC degradation, the level of ozone dose showed insignificant effects. Though the highest ozone dose (110 mg/L) presented the best performance, the other ozone doses (60 and 20 mg/L) presented almost the same effectiveness. This phenomenon could also be demonstrated by the results of chloride release. For chloride formation, the results of ozone doses at 110 and 60 mg/L showed

the same trend that the concentration of chloride reached the maximum at specific time then decreased. However, the concentration of chloride at the lowest ozone dose (20 mg/L) continued to increase during the reaction. It could be concluded that the low ozone dose could render diclofenac degraded into specific intermediates. These intermediates might have smaller structure as their parent compound, contain chloride, and difficult to degrade even after the breakdown of diclofenac. The occurrence of ammonia at three levels of ozone doses showed almost the same trend and reached the highest value at the same time. This may be concluded that the ozone dose barely affected the C-N cleavage, and it also was unrelated to the TOC degradation.

Table 4-1 Comparison of removal rate of DFC and TOC, and formation of chloride and ammonia during ozonation in different operational conditions.

		O_3:110 mg/L	O_3:60 mg/L	O_3:20 mg/L
DFC removal rate (%)		>99	>99	>99
TOC removal rate (%)		41.5	32	33.7
Chloride formation rate (%)	C_{max}/C_{the}(%)	93.9	96.6	80.9
	C_{60}/C_{the} (%)	90.8	91.0	80.9
Ammonia formation rate (%)	C_{max}/C_{the}(%)	26.7	29.7	31.9
	C_{60}/C_{the} (%)	15.9	29.7	28.0

C_{max}: The maxima concentration occurred in the reaction
C_{the}: The theoretical release concentration
C_{60}: The concentration detected in the end of 60 min reaction

4-2 Ozonation at fixed pH values

According to the results in the previous section, the ozone doses at 60 and 20 mg/L were chosen to investigate the effect of pH on the ozonation of diclofenac. Due to the large amount of residual ozone being introduced into the reactor at the ozone dose 110 mg/L, it was not taken into consideration as one suitable factor in experimental design of evaluating effect of adjusted-pH systems.

To maintain the stability of pH value, the buffer, in combination of monosodium and disodium phosphate, was used to adjust pH to specific values. The pH values were fixed at 5.5, 7.4, and 8.9, respectively. Two levels of ozone dose were also used to conduct the experiments for the degradation and formation of organic and inorganic by-products. The degradation of diclofenac and TOC, and the formation of chloride and ammonia were also detected.

4-2-1 Degradation of diclofenac

The degradation of diclofenac at fixed pH values (5.5, 7.4, and 8.9) at two levels of ozone dose (60 and 20 mg/L) is shown in Figures 4-6 and 4-7, respectively. At the higher ozone dose (60 mg/L), diclofenac degradation reached over 98% between 20 to 25 minutes at three pH values. For diclofenac removal at pH 5.5, 7.4 and 8.9, the results showed almost similar trend, especially at pH 5.5 and 8.9. Although it is insignificant, the diclofenac degradation at pH 7.4 was slightly faster than the other cases.

For the lower ozone dose (20 mg/L), the diclofenac removal reached over 99% at about 40 minutes under all three pH values. The diclofenac degradation obviously differed from 0 to 15 minutes more than the other ozone dose. As it can be seen that diclofenac degraded more rapidly at pH 7.4, and then followed by pH 8.9 and pH 5.5 in a decreasing order.

According to the previous studies (Vogna et al, 2004; Coelho et al, 2009), the rate

constants would increase as the pH increased (5.0 to 7.0). Lower pH values inhibited the production of OH radical, which is considered as an active reactant that can undergo a series of fast reactions with target compound. Since the OH radical can be produced more extensively at higher pH values, the diclofenac degradation should be better than other lower pH values. For the pH 5.5 and 7.4, the results showed similar trend. However, the results at pH 8.9 disagreed with what would be predicted.

The different ozone doses affected the diclofenac degradation even at the same pH values. For the delay of time of the turning points in the curves, it can be inferred that larger ozone dose could enhance the diclofenac removal. Besides, the result at larger ozone dose indicated the different levels of pH value got minor effect on the performance of diclofenac removal via ozonation.

Based on the observation mentioned above, it could be inferred that the larger ozone dose bring about more complicated reaction of ozone self-decomposition. Moreover, the presence of phosphate buffer seemed to interfere more with the reaction of diclofenac at pH 8.9.

The effect of pH on diclofenac degradation

The effects of the presence of phosphate buffer on the degradation of diclofenac can be seen from the results shown in Figures 4-6, 4-7 and Figure 4-1. At the same ozone dose, the presence of phosphate buffer seemed to play a role as inhibitor of diclofenac degradation due to the time delay in reaching the same concentration. The result indicated that the control of pH in semi-batch would caused the diclofenac degrade slower than variable pH condition.

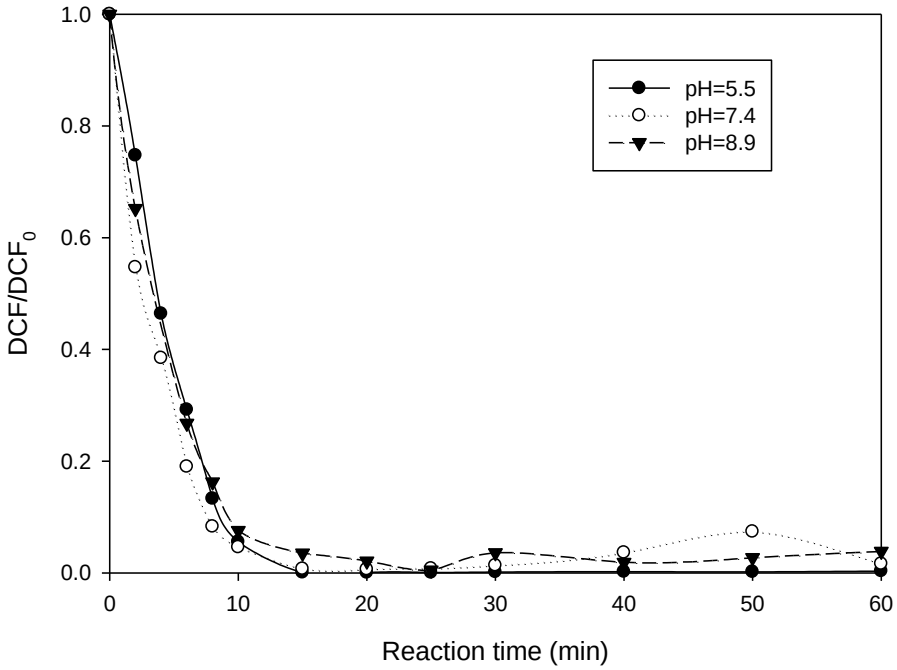


Fig. 4-6. Degradation profile of diclofenac as a function of time in the presence of buffer at O_3 doses 60 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

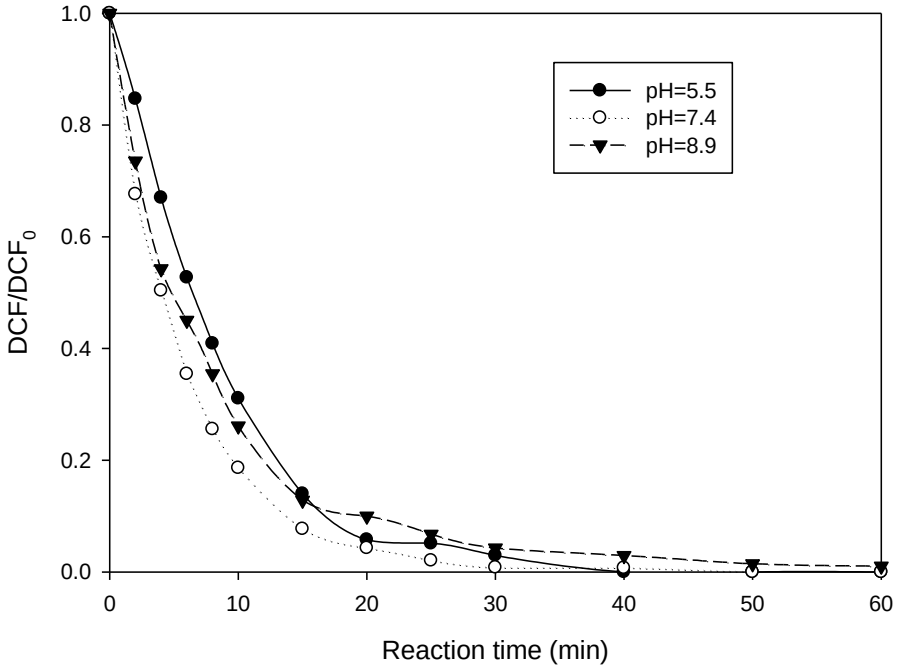


Fig. 4-7. Degradation profile of diclofenac as a function of time in the presence of buffer at O_3 doses 20 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

4-2-2 Degradation of total organic carbon (TOC)

The degradation of TOC at fixed pH values (5.5, 7.4, and 8.9) at two levels of ozone dose (60 and 20 mg/L) is shown in Figures 4-8 and 4-9, respectively. At the higher ozone dose (60 mg/L), TOC removal reached 43.6, 44.46, and 35.18% at pH values 5.5, 7.4, and 8.9, respectively. For TOC removal at pH 5.5 and 7.4 were almost similar in the first 10 minutes. As for the pH 8.9, the TOC degradation was the lowest and quite different from the other conditions.

For the lower ozone dose (20 mg/L), the TOC removal reached 25.97, 28.81, and 25.41% at pH 5.5, 7.4, and 8.9, respectively. The TOC removal at pH 5.5 was almost the same as at 8.9, while the TOC removal at pH 7.4 was slightly higher. Furthermore, the TOC degradation profiles at three levels of pH values were same, especially in the first 6 minutes.

Comparing the results of two ozone doses at the same pH value, the extent of TOC degraded apparently was more at higher ozone dose. On the other hand, different pH values affected TOC removal, significantly at larger ozone dose. Since the OH radical plays the major role in TOC degradation, the TOC removed should be greater under higher pH. However, the TOC degradation at pH 8.9 was relatively lower than that at other ozone doses, especially at 60 mg/L. This indicated that the OH radical contributed less to TOC degradation at higher ozone dose.

The profile of TOC degradation could be related to the diclofenac degradation in section 4-2-1. All in all, the best TOC removal and diclofenac degradation both occurred at pH 7.4 and two ozone doses. As for pH 5.5, the TOC removal was consistent with diclofenac degradation. For the smaller ozone dose, the TOC removal was consistent with that of diclofenac at pH 8.9. However, at pH 8.9 and larger ozone dose, although the profile of diclofenac degradation was similar that at pH 5.5, the TOC removal was

lower than that of diclofenac by 8%. It could be concluded that the indirect reaction of OH radicals produced non-degradable intermediates that increased TOC degradation.

The effect of pH on TOC degradation

At ozone dose of 60 mg/L, the presence of phosphate buffer seemed to enhance the TOC removal. It could be inferred that pH control might prevent the indirect reaction and enhance the production of intermediates with smaller molecular weight or simple structure. Therefore, the extent of TOC degradation was greater at pH-controlled than that of pH-uncontrolled condition.

At ozone dose of 20 mg/L, the presence of phosphate exhibited contradictory results. The TOC removal was lower with pH control than that without pH control. This could be attributed to insufficient ozone dose. Since the ozone dose was small, the amount of OH radical formed was decreased due to the presence of phosphate buffer. Therefore, the contribution of OH radical to TOC removal was reduced.

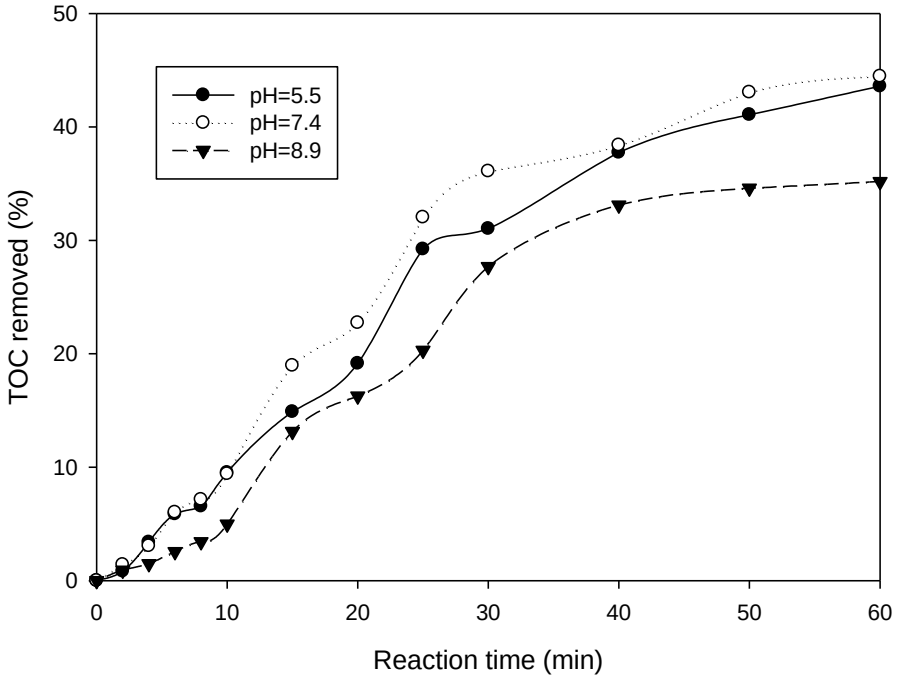


Fig. 4-8. Degradation profile of TOC as a function of time in the presence of buffer at O_3 doses 60 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

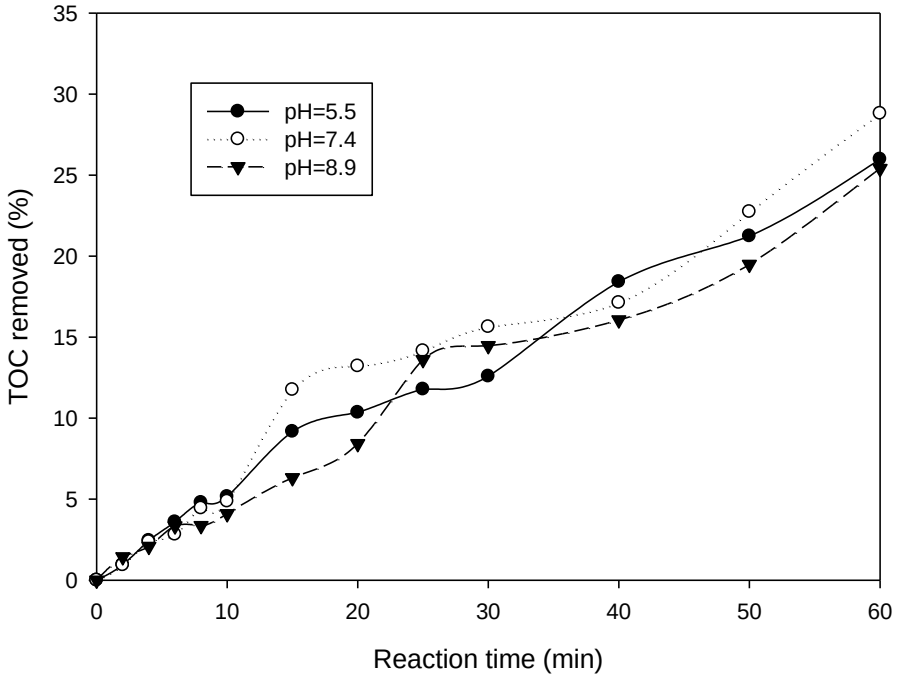


Fig. 4-9. Degradation profile of TOC as a function of time in the presence of buffer at O_3 doses 20 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

4-2-3 Formation of chloride

The formation of chloride at fixed pH values (5.5, 7.4, and 8.9) at ozone dose of 60 and 20 mg/L) is shown in Figures 4-10 and 4-11, respectively. At the higher ozone dose of 60 mg/L, chloride concentration reached about 1.9, 2.0 and 0.65 mg/L at pH values 5.5, 7.4, and 8.9, respectively. The chloride was continuously formed at a faster pace within the first 30 minutes, and then occurred at slower pace after 30 minutes. The amount of chloride formation at pH 5.5 and 7.4, were almost of the same value at about 2.0 mg/L. At pH 8.9, the chloride formation was the lowest comparing to that at the other pH values.

At the lower ozone dose of 20 mg/L studied, chloride concentration reached about 1.4, 1.6, and 0.8 mg/L at pH 5.5, 7.4, and 8.9, respectively. The chloride was formed continuously throughout the course of reaction. The chloride formation profile at pH 5.5 and 7.4 were similar and were relatively lower at pH 8.9.

Due to the high percentage of diclofenac degradation, the amount of chloride released was likely to be the theoretical value of 2.4 mg/L. The incomplete release of chloride indicated the abundant amount of intermediates formed, which was concident with the low TOC degradation. On the other hand, since pH 5.5 was an unfavorable for the formation of OH radical, the amount of chloride formation was small due to the higher chloride concentration at pH 5.5.

At pH 5.5 and 7.4, as the ozone dose decreased, the concentration of chloride decreased, too. In contrast, at pH 8.9, the concentration of chloride increased as the ozone dose decreased. Results demonstrated that ozone dose barely affected the chloride formation at higher pH values.

The effect of pH on chloride formation

Previously, Sein et al. (2008) investigated the presence of OH radical scavenger on

chloride release. Since phosphate buffer was a weaker OH radical scavenger, the concentration of chloride should decrease with the presence of phosphate buffer at the same ozone dose. The results verified our hypothesis that phosphate buffer was OH scavenger. The chloride release between the controlled and uncontrolled pH conditions was likely the same at 0.2 mg/L.

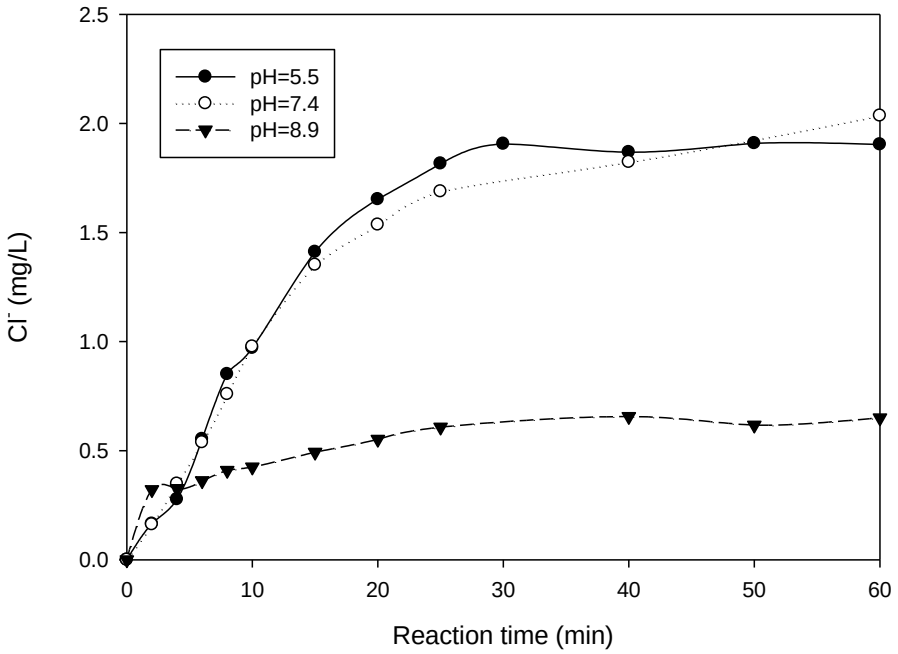


Fig. 4-10. Evolution profile of chloride as a function of time in the presence of buffer at O_3 doses 60 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

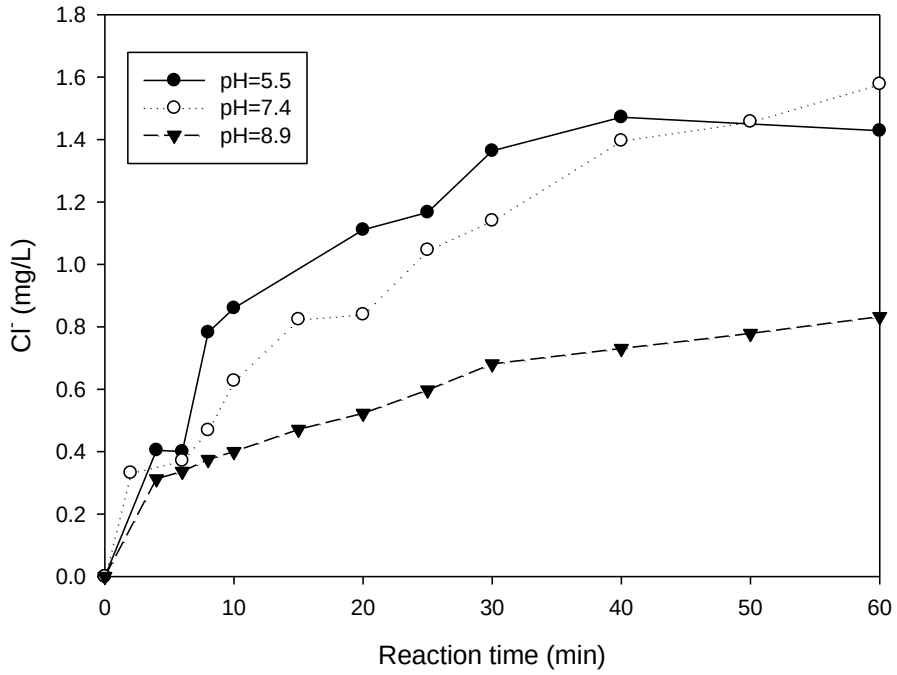


Fig. 4-11. Evolution profile of chloride as a function of time in the presence of buffer at O_3 doses 20 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

4-2-4 Formation of ammonia

Figures 4-12 and 4-13 show the formation of ammonia at fixed pH values (5.5, 7.4, and 8.9) at two levels of ozone dose (60 and 20 mg/L),respectively. At higher ozone dose of 60 mg/L, the concentration of ammonia increased continuously. At pH 5.5, the formation of ammonia was rapid and apparently was greater than that at other pH values. At lower ozone dose (e.g., 20 mg/L), although the ammonia- versus- time curves at different pH values were irregular in shape, it still could be seen that the concentration of ammonia was still insignificantly increasing.

The theoretical amount of nitrogen was about 0.47 mg/L in the ozonation of diclofenac. Results showed that pH had important influence on the formation of ammonia. The unique distribution of ammonia at pH 8.9 and the approximate

distribution of formation of ammonia at the other pH values probably implied the direct reaction of ozone contributed more to the destruction of C-N cleavage at low ozone dose. For the middle scale of ozone dose, the pH values also showed effect on the formation of ammonia. However, the distribution of ammonia was different from the results of the lowest ozone dose. The possible explanation was as the ozone dose enhanced, the effect of OH radical reaction would increase. Therefore, the OH radical dedicated significantly to ammonia formation when the pH was more acidic, which leaded to the better extent of ammonia release. The results indicated that the ozone dose would partly affect the formation of ammonia, and the higher-level oxidation of ammonia underwent at the highest and lowest ozone dose.

The effect of pH on ammonia formation

When the pH value was fixed, the acidic condition dedicated more to the release of ammonia, and the concentration of ammonia increased significantly as the ozone dose increased. At value pH 7.4, the ozone dose did not change the formation of ammonia much. The results showed that in more alkaline solution, ozone dosage played greater role in ammonia formation which implied the more complex oxidation reaction. In short, the results were consistent with the hypothesis that the ozone tended to attack the C-N cleavage side when the pH value was low.

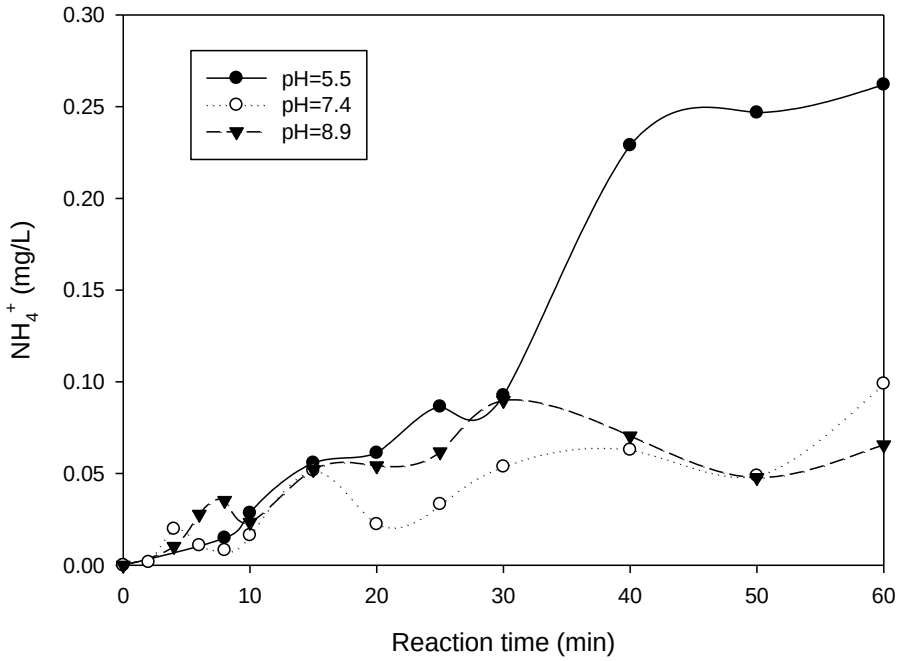


Fig. 4-12. Evolution profile of ammonia as a function of time in the presence of buffer at O_3 doses 60 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

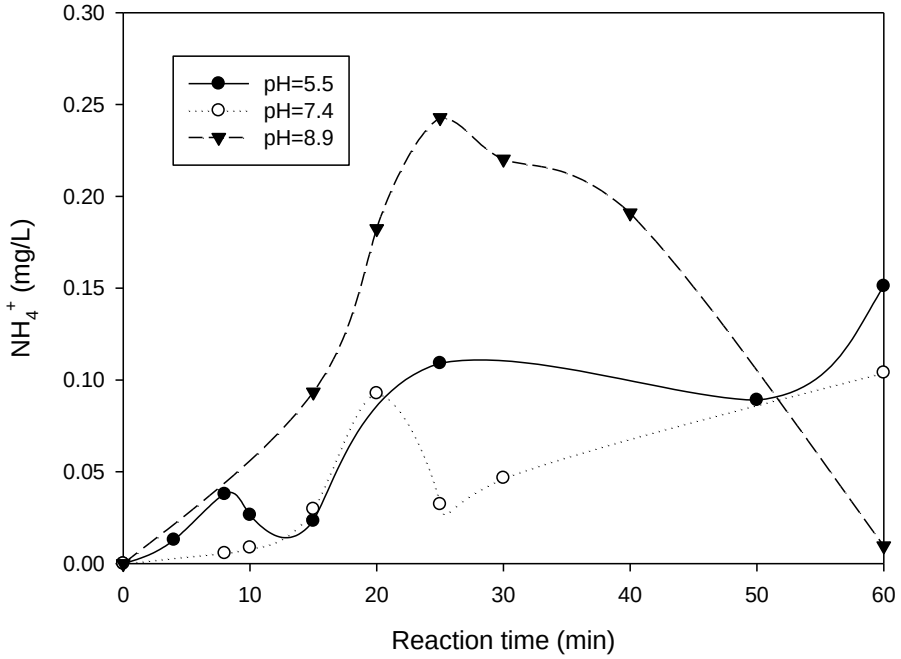


Fig. 4-13. Evolution profile of ammonia as a function of time in the presence of buffer at O_3 doses 60 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

4-2-5 Summary

Table 4-2 compares the results of ozone doses at fixed pH values of 5.5, 7.4, and 8.9 on diclofenac degradation. At both two levels of ozone dose (60 mg/L), diclofenac was almost degraded at three levels of pH values. It indicated that pH values might affect the degradation of diclofenac insignificantly in semi-batch reactor. On the other hand, pH values obviously affected the degradation of TOC, and formation of chloride as well as ammonia. The TOC removal rate and formation rate of chloride as well as ammonia showed relatively lower at pH 8.9.

To compare the results with others shown in section 4-1, it can be concluded that the presence of phosphate buffer affected the efficiency significantly. The results showed that the presence of phosphate buffer can make the diclofenac degraded slower and decrease the TOC removal rate. The consequences can be supported by the decreasing amount of chloride and ammonia formation concentration in the presence of phosphate buffer. This might indicate that the more efficient removal process of diclofenac by ozonation would be in the condition without pH control.

Table 4-2 Comparison of ozonation of diclofenac in different operational conditions

		O_3:60 mg/L			O_3:20 mg/L		
		pH=5.5	pH=7.4	pH=8.9	pH=5.5	pH=7.4	pH=8.9
DFC removal rate (%)		98.4	98.7	98.12	>99	>99	>99
TOC removal rate (%)		43.6	44.5	35.5	26.0	28.8	25.4
Chloride formation rate (%)	C_{60}/C_{the} (%)	79.4	84.8	27.1	59.5	65.8	34.7
	C_{max}/C_{the} (%)	79.4	84.8	27.1	59.5	65.8	34.7
Ammonia formation rate (%)	C_{60}/C_{the} (%)	55.4	20.9	13.9	31.9	22.0	2.04
	C_{max}/C_{the} (%)	55.4	20.9	19.0	31.9	22.0	51.3

C_{max}: The maxima concentration occurred in the reaction
C_{the}: The theoretical release concentration
C_{60}: The concentration detected in the end of 60 min reaction

4-3 Ozonation By-Products

4-3-1 Formation of ozonation by-products

In general, the formation of the typical ozonation by-products includes aldehydes carboxylic acids, and ketones (Richardson et al., 1999; Huang et al., 2005). Aldehyde has been concerned as hazardous material that may form during ozonation with large-molecular- weight compounds. The method of derivation to detect aldehyde is described in Chapter 3. From the experimental results, formaldehyde was the only ozonation by-products detected by GC-MS. In this study, the principal ozonation by-products considered was aldehyde. Figures 4-14 and 4-15 show the formation profile of formaldehyde at different pH and ozone doses (60 and 20 mg/L) during reaction.

From the Figures 4-14 and 4-15, it can be seen that the formaldehyde formation curves at pH 7.4 and 8.9 were identical at ozone dose of 60 and 20 mg/L, increased first then decreased. The formaldehyde formation at pH 5.5 was all the same at low concentration during the whole reaction.

According to Chang et al. (2007), there was a greater amount of hydroxyl radical formed at pH 9 which could decompose organic compounds and generate shorter chain by-products such as formaldehyde. Basically, the results of pH 5.5 agreed with Chang et al. (2007). On the other hand, the results revealed that the formaldehyde would be generated more with higher ozone dose at pH 5.5 and 8.9. Figure 4-16 shows the results of formaldehyde formation at pH 7.4 and two different ozone doses. It could be concluded that this phenomenon might be contributed to the highest diclofenac degradation and TOC removal might produce more formaldehyde.

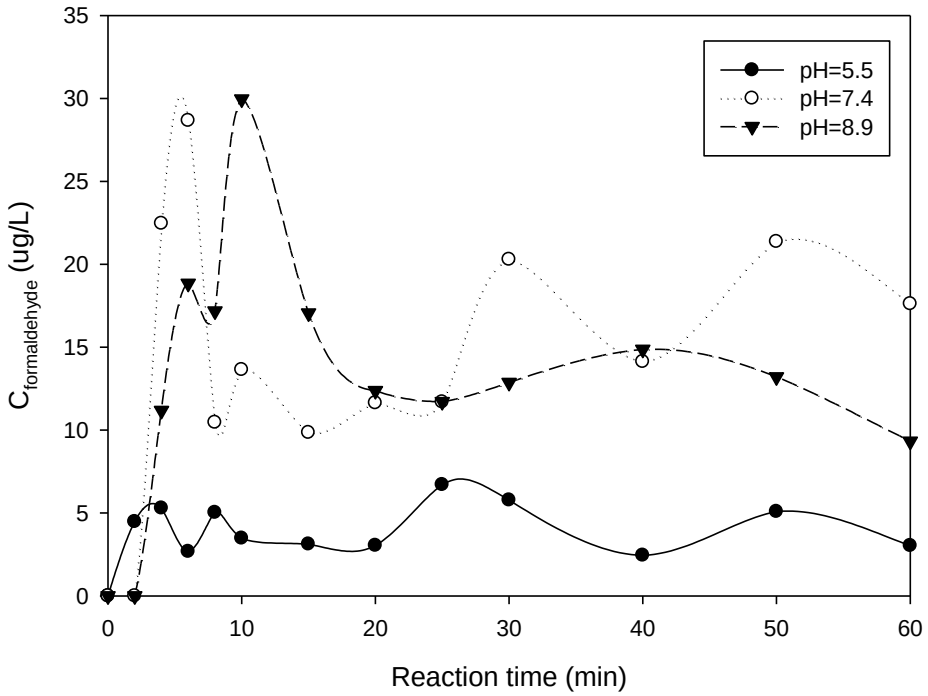


Fig. 4-14. Evolution of formaldehyde as a function of time in the presence of buffer at O_3 dose 60 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

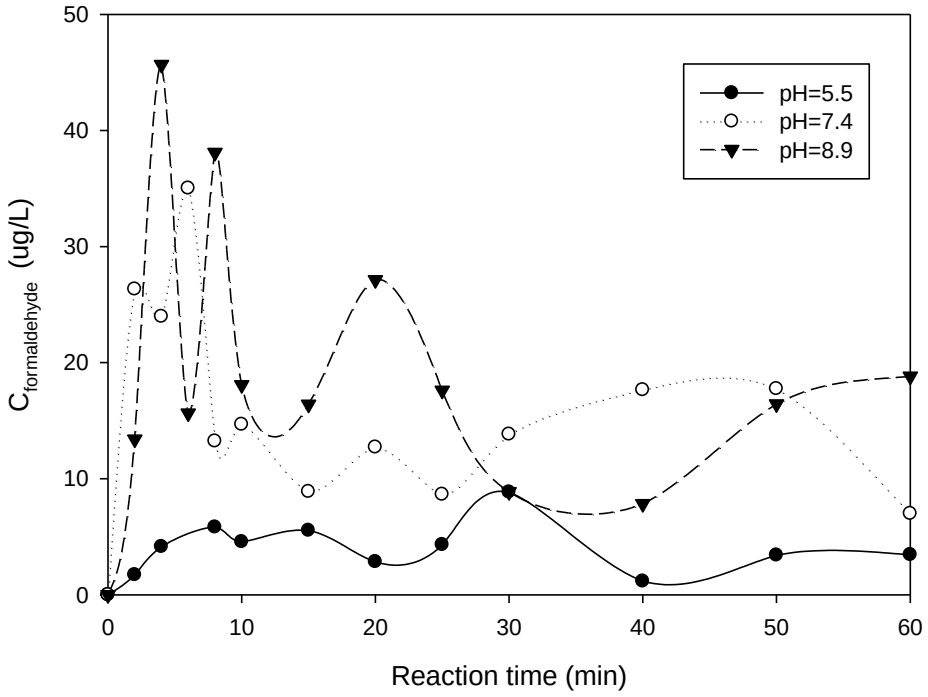


Fig. 4-15. Evolution of formaldehyde as a function of time in the presence of buffer at O_3 dose 20 mg/L at different levels of pH values; (●) pH=5.5; (○) pH=7.4; (▼) pH=8.9.

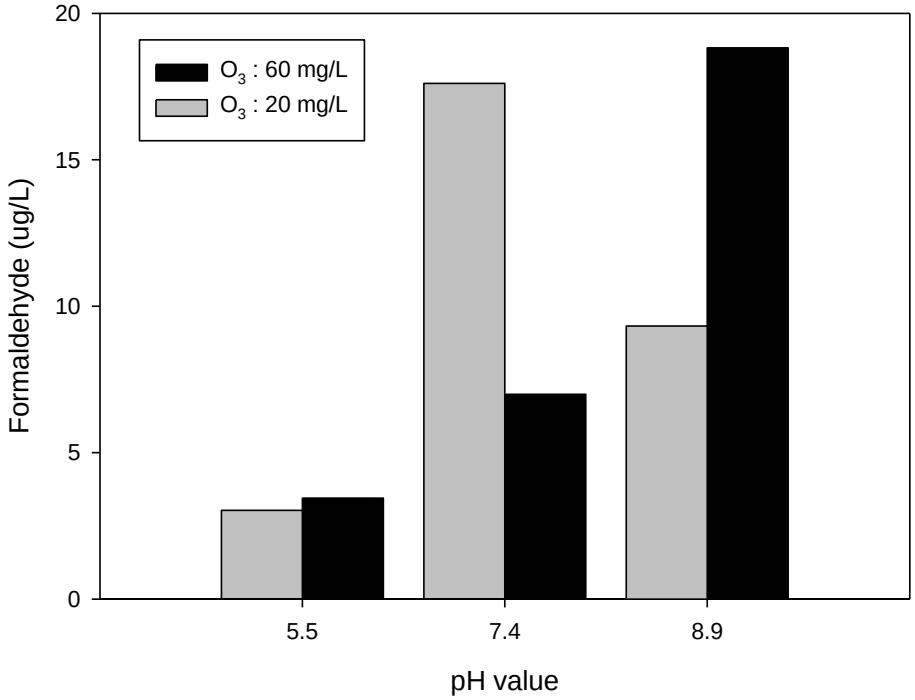


Fig. 4-16. The formation of formaldehyde for diclofenac at different levels of pH and at different ozone doses in the ozonation process.

Table 4-3 Ozonation by-products formation in different operational conditions

Organic compound	Applied O_3 (mg/L)	pH	Formaldehyde ($\mu g\ L^{-1}$)
DFC	110	-	1.0
	60	-	1.9
	20	-	1.3
DFC	60	5.5	3.4
		7.4	7.0
		8.9	18.8
DFC	20	5.5	3.0
		7.4	17.6
		8.9	9.3

Formation of formaldehyde at variable pH values

Figure 4-17 provides the results of the formation of formaldehyde in the absence of phosphate buffer at different ozone doses. It can be seen that the absence of phosphate buffer would increase the generation of formaldehyde. Results also show the higher ozone dose may generate more formaldehyde. Although the increase in formaldehyde between the two ozone doses was small, the difference was conspicuous.

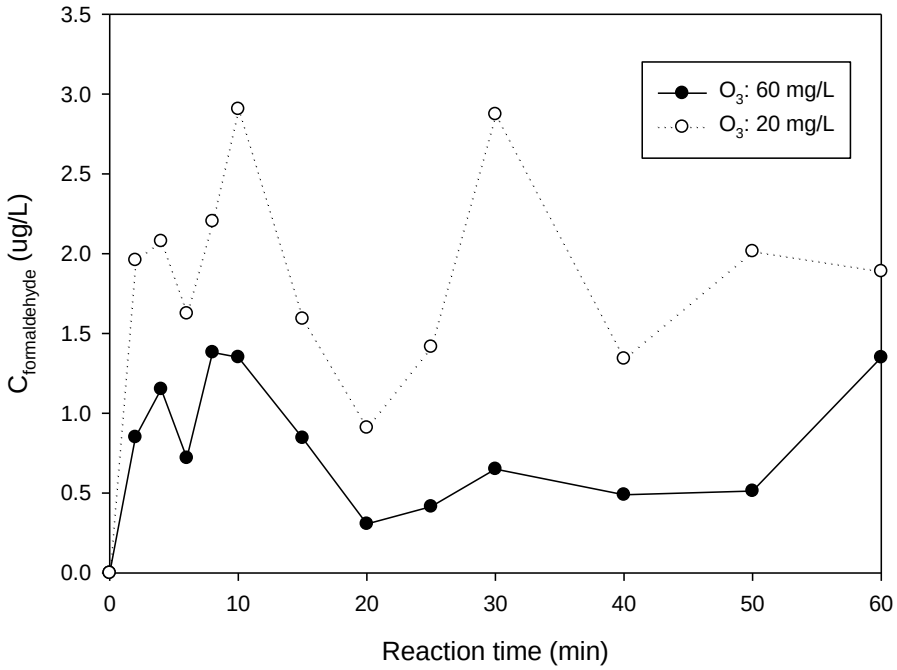


Fig. 4-17. Evolution of formaldehyde as a function of time in the absence of buffer at different O_3 dose at; (●) 60 mg/L ; (○) 20 mg/L.

4-3-2 Risk Assessment

Since formaldehyde would occur in the ozonation of diclorfenac, a risk assessment should be studied to design the appropriate treatment method. The formaldehyde is a carcinogenic substance by USEPA, and its carcinogenic risk can be determined by the following equation:

$$Carcinogen\,ic \quad risk = Exposure \quad dose \times Slope \quad factor \qquad \text{Eq. (4-3-1)}$$

Where exposure dose (ED) is the quantity of ingestion (mg/kg-day), and slope factor (SF) is the carcinogenic slope $(mg/kg\text{-}day)^{-1}$. The value of ED is calculated base on the assumption that one person drinks 2 liters of water per day with an average body weight of 70 kg, exposure time, relative source contribution and concentration in water. According to toxicity data of formaldehyde proposed by USEPA and OEHAA, the value of SF is $2.1\times10^{-2}\,(mg/kg/day)^{-1}$. The final carcinogenetic risk was determined and listed in Table 4-4, which indicates that the lowest carcinogenetic risk in ozonation was at

ozone dosage of 20 mg /L and pH of 5.5, which is considered the appropriate treatment for reducing formaldehyde formation. The highest carcinogenetic risk was at ozone dosage of 60 mg/L and pH of 8.9.

Table 4-4 The carcinogenetic risk in different operational conditions

Organic compound	Applied O_3 (mg/L)	pH	Formaldehyde ($\mu g\ L^{-1}$)	Carcinogenetic risk
DFC	110	-	1.0	6.0×10^{-7}
	60	-	1.9	1.1×10^{-6}
	20	-	1.3	7.8×10^{-7}
DFC	60	5.5	3.4	2.0×10^{-6}
		7.4	7.0	4.2×10^{-6}
		8.9	18.8	1.1×10^{-5}
DFC	20	5.5	3.0	1.8×10^{-6}
		7.4	17.6	1.1×10^{-5}
		8.9	9.3	1.7×10^{-6}

4-4 Mass Balance

4-4-1 Mass balance of elemental carbon

In this study, carbon was used to calculate the mass balance relationship with respect to the formation of intermediates and the degree of mineralization. Calculation of mass balance for carbon during diclofenac ozonation was described as following:

- $(\text{Intermediates})_c = (\text{TOC})_t - (\text{DFC})_c$
- $(CO_2) = (\text{DFC})_{\text{initial c}} - (\text{TOC})_t$

Where $(\text{TOC})_t$, $(\text{DFC})_c$, and $(\text{DFC})_{\text{initial c}}$ are TOC at time t, diclorfenac concentration at time t, and at initial time, respectively.

Figure 4-18 shows the results of mass balance of carbon with time in the absence of phosphate buffer at variable ozone doses which indicated that the amount of intermediates increased first and then degraded gradually for all three ozone doses. It appears that at the higher ozone dose generated less intermediates at the end.

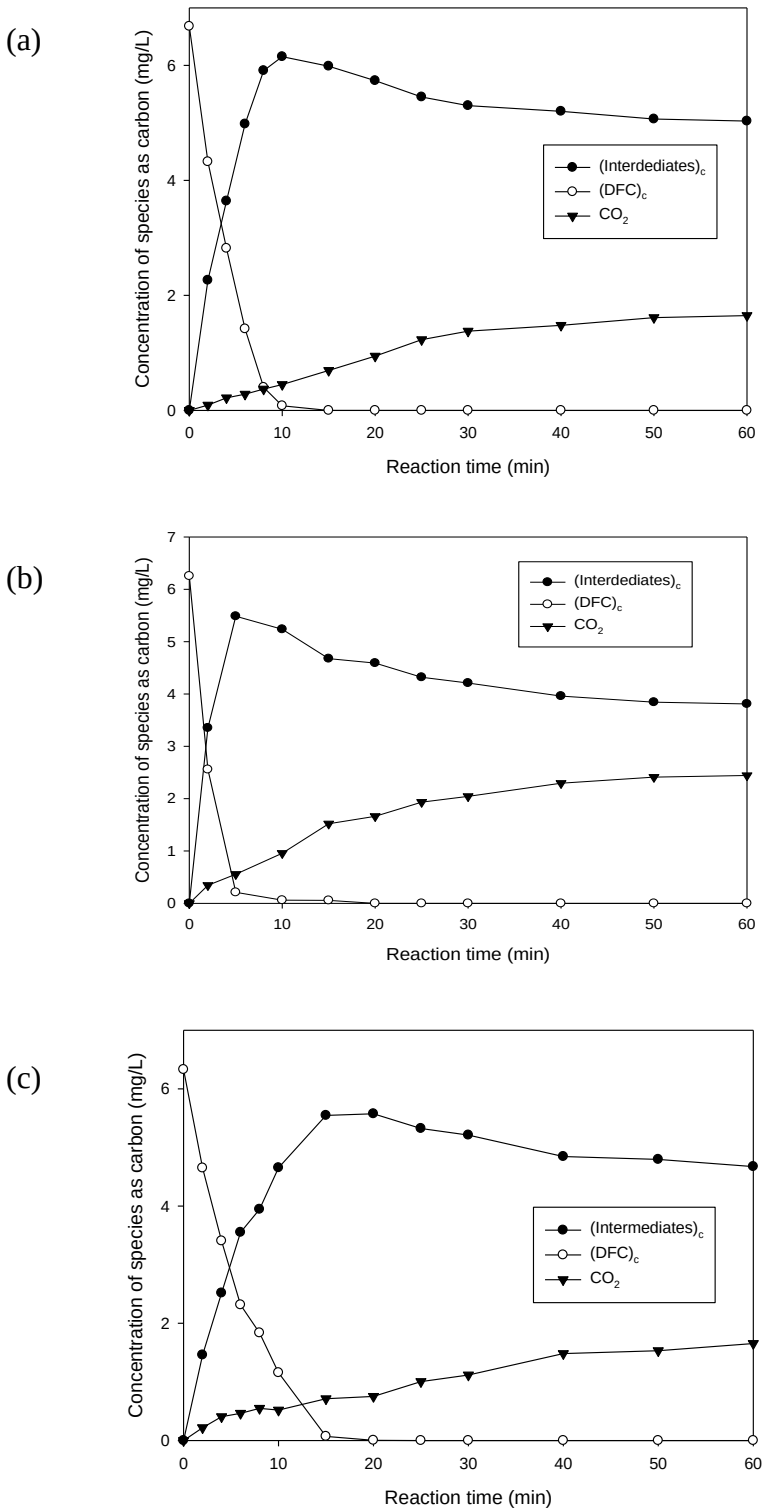
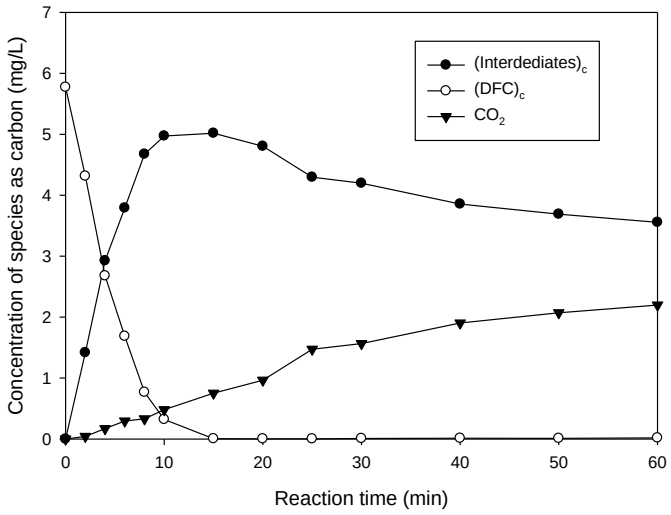


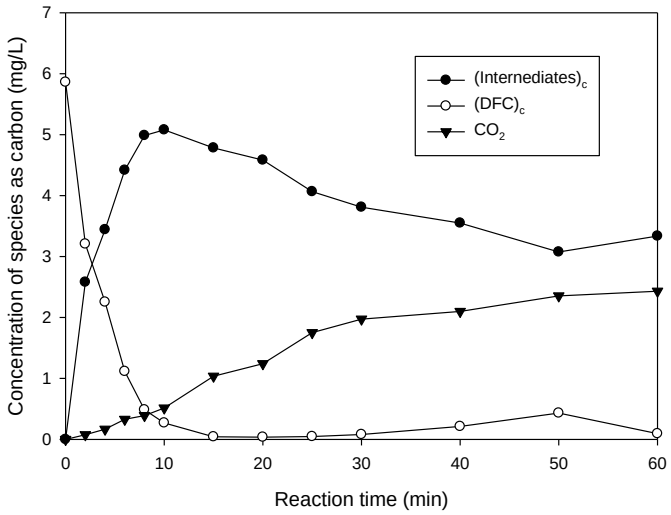
Fig. 4-18. Temporal distribution of carbon-containing species for the decomposition of diclofenac in the absence of phosphate buffer at ozone doses (a) 110 mg/L; (b) 60 mg/L; (c) 20 mg/L; (●) $(Intermediates)_c$; (○) $(DFC)_c$; (▼) CO_2. Experimental conditions: pH_0=5.2.

Figures 4-19 and 4-20 show carbon mass balance at pH 5.5, 7.4, and 8.9 with ozone doses of 60 mg/L and 20 mg/L, respectively. At ozone dose of 60 mg/L, the intermediates was generated first then steadily decomposed. However, at ozone dose of 20 mg/L, the intermediates was generated first then almost remained unchanged afterward. This result could be demonstrated by the higher CO_2 formation rates at ozone dose of 60 mg/L as shown in Table 4-5 which indicates that the formation rate constants rise as the pH value increases from 5.5 to 7.4, and then decreases as pH value increases from 7.4 to 8.9. This revealed that the pH could enhance the CO_2 formation and the decomposition of intermediates. Figure 4-21 shows the trend of carbon formation rate constants at different levels of pH values. Moreover, the different levels of ozone dose exhibits no effects on the distribution of constants of various pH values, although the higher ozone dose still contributes to higher CO_2 formation rate constants. This result also indicated that the higher mineralization would occur at pH 7.4, which was consistent with the results of TOC degradation presented in section 4-2-2.

(a)



(b)



(c)

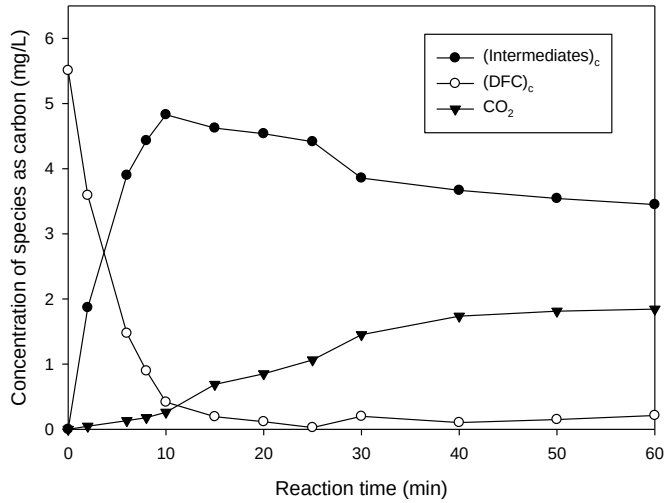
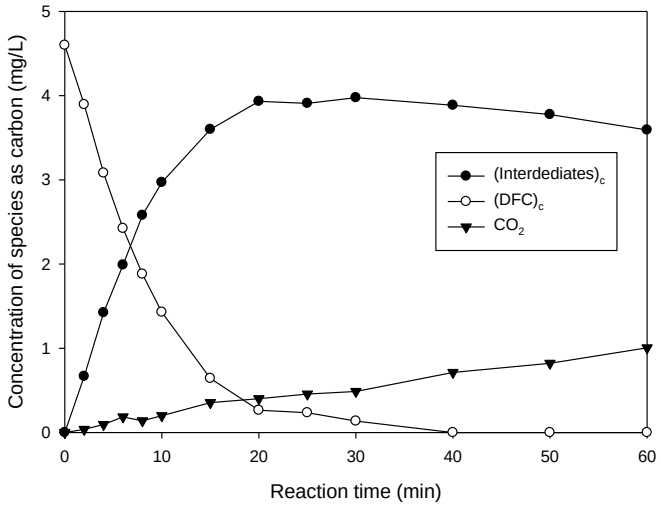
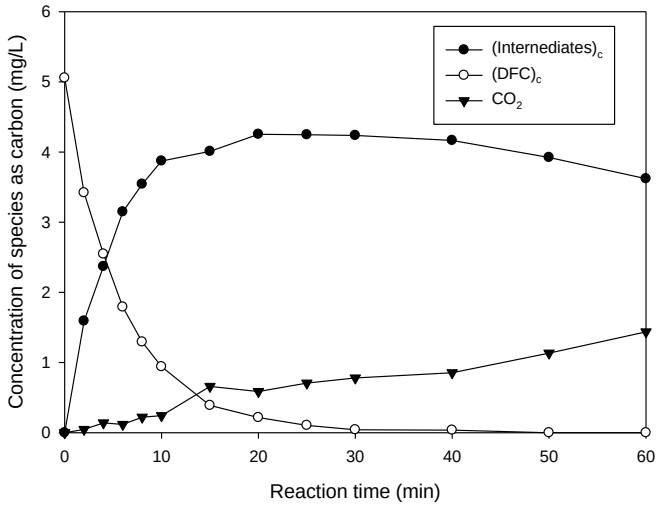


Fig. 4-19. Temporal distribution of carbon-containing species for the decomposition of diclofenac at (a) pH 5.5, (b) pH 7.4, (c) pH 8.9 at ozone doses 60 mg/L; (●) $(Intermediates)_c$; (○) $(DFC)_c$; (▼) CO_2.

(a)



(b)



(c)

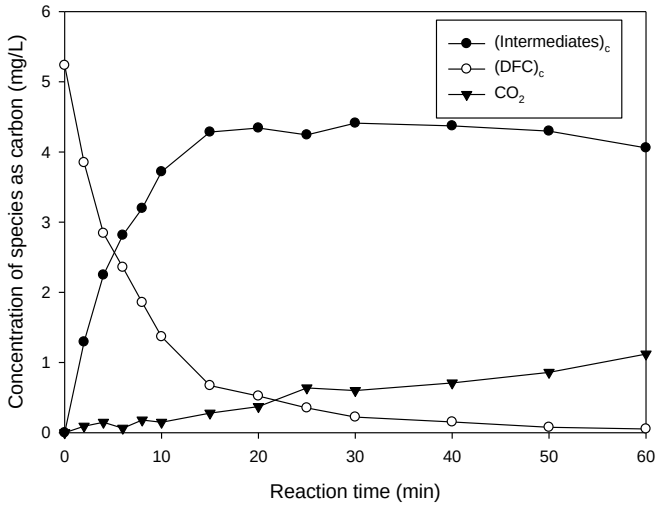


Fig. 4-20. Temporal distribution of carbon-containing species for the decomposition of diclofenac at (a) pH 5.5, (b) pH 7.4, (c) pH 8.9 at ozone doses 20 mg/L; (●) $(Intermediates)_c$; (○) $(DFC)_c$; (▼) CO_2.

Table 4-5 The CO_2 formation rate constant k_c (min^{-1}) determined at different levels of ozone dose and pH value

Ozone dose (mg/L)	pH value		
	5.5	7.4	8.9
60	3.95×10^{-3}	1.64×10^{-2}	7.93×10^{-3}
20	1.23×10^{-3}	5.85×10^{-3}	3.32×10^{-3}

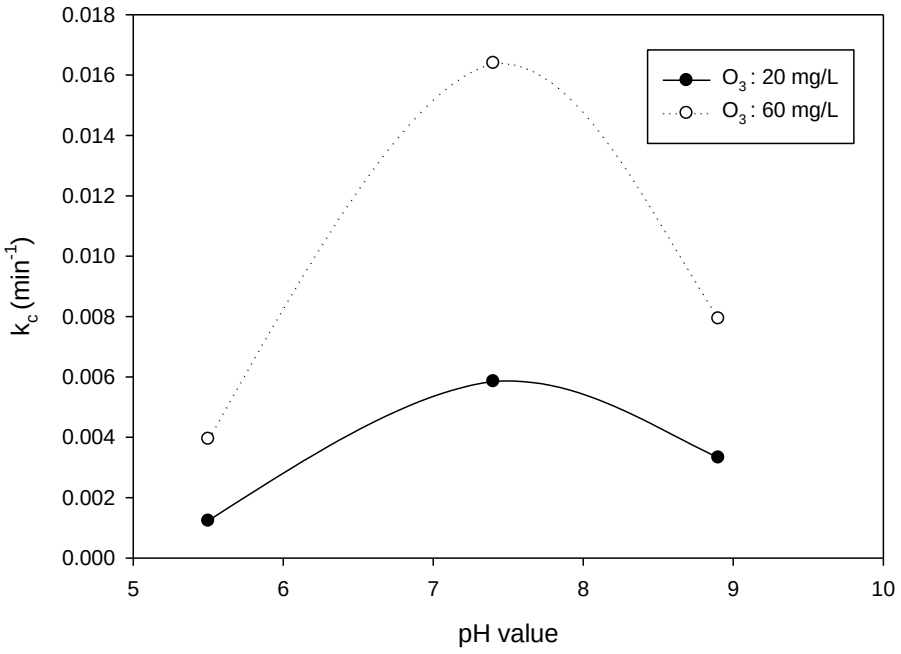


Fig. 4-21. The CO_2 formation rate constants at pH 5.5, 7.4, and 8.9 at ozone doses 20, and 60 mg/L; (●) O_3 : 20 mg/L; (○) O_3: 60 mg/L.

4-4-2 Mass balance of elemental chlorine

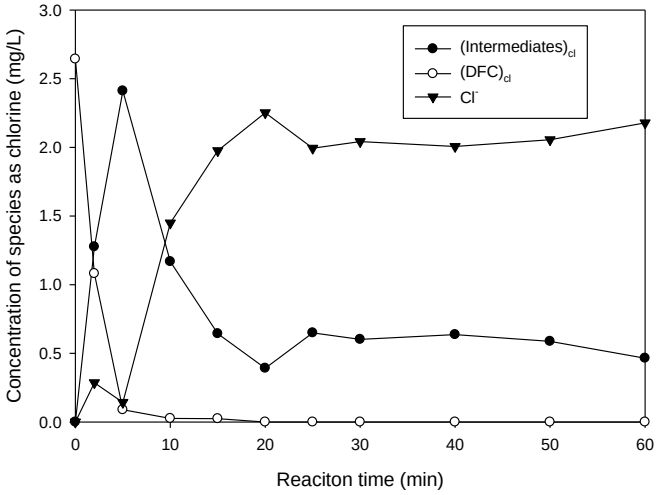
In this study, the chlorine mass balance was calculated as to gain insight into the reaction pathway. Calculation of mass balance for chlorine during diclofenac ozonation was described as following:

- $(\text{Intermediates})_{cl} = (DFC)_{\text{initial cl}} - (DFC)_c - (Cl^-)_t$

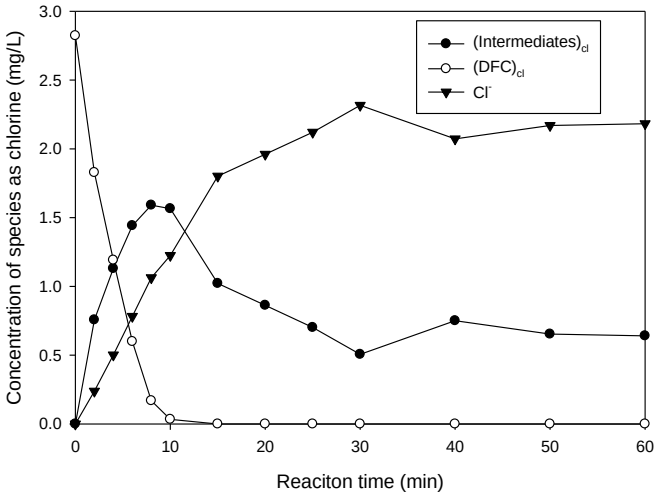
Where $(DFC)_{\text{initial Cl}}$ and $(Cl)_t$ were the initial Cl and the Cl at time time, t, respectively.

Figures 4-22 showed the chlorine mass balance relationship with time in the absence of phosphate buffer at various ozone doses. Intermediates containing chlorine were decomposed relatively rapidly than those contain carbon. The results indicated that the amount of intermediates increased first and then decreased gradually at the three ozone doses. Furthermore, the higher ozone dose generated less chlorine containing intermediates at the end.

(a)



(b)



(c)

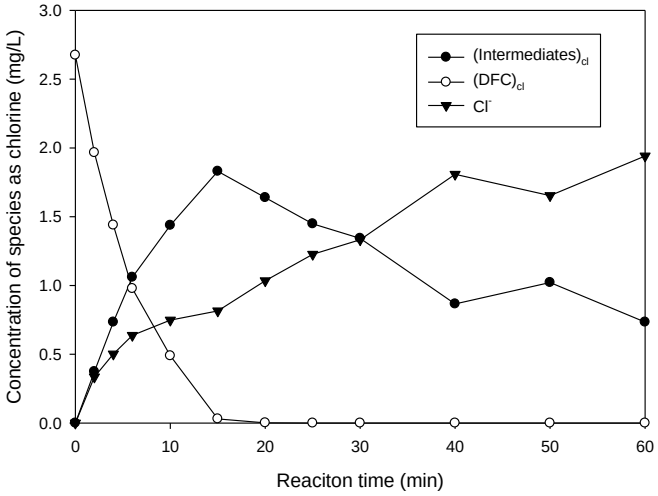
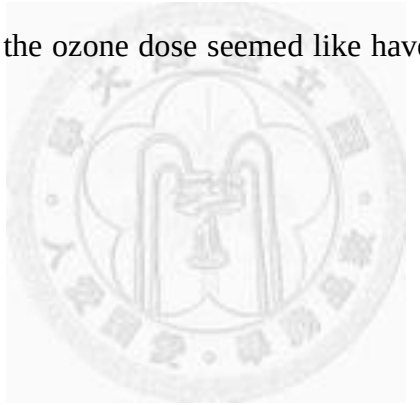
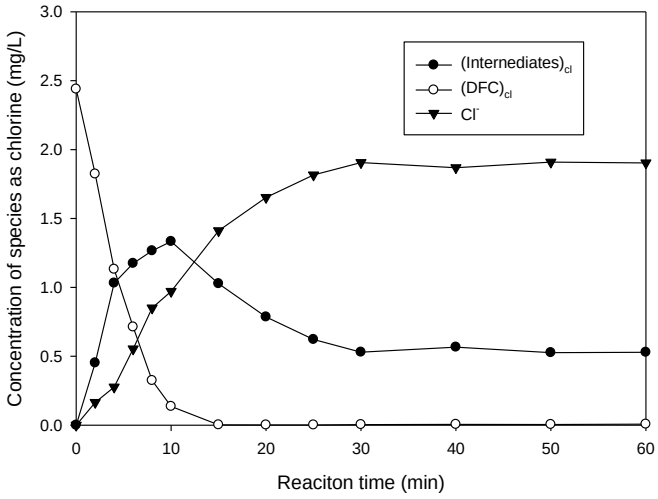


Fig. 4-22. Temporal distribution of chlorine-containing species for the decomposition of diclofenac in the absence of phosphate buffer at ozone doses (a) 110 mg/L; (b) 60 mg/L; (c) 20 mg/L; (●) $(Intermediates)_{cl}$; (○) $(DFC)_{cl}$; (▼) Cl^-.

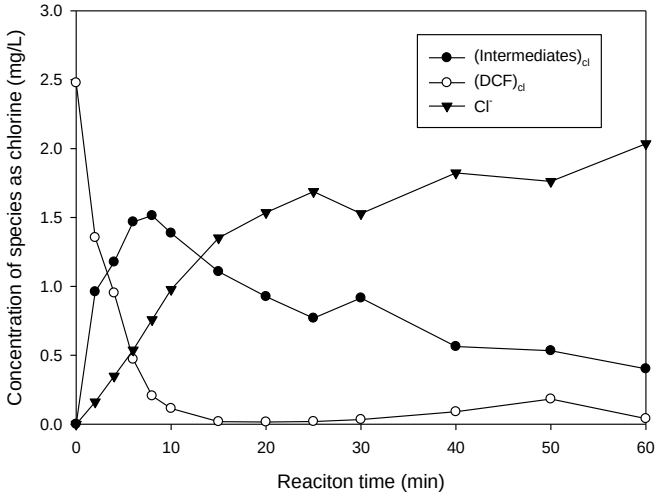
Figures 4-23 and 4-24 show chlorine mass balance at pH 5.5, 7.4, and 8.9, with ozone doses of 60 mg/L and 20 mg/L, respectively. In Figures 4-23 and 4-24, the intermediates containing elemental chlorine generated first then steadily decomposed or became stable at two levels of ozone doses. Table 4-6 and Figure 4-25 depict the effect of different levels of pH value and ozone dose on chloride formation rate constants. At both two levels of ozone dose, the rate constants increased then decreased as the pH increased from 5.5 to 7.4, then to 8.9. The distribution of chloride formation rate constants is the same with the CO_2. This trend also showed similarity to the results of chloride formation in the same conditions described in section 4-2-3. Furthermore, the ozone dose 60 mg/L showed the enhancement of chloride formation rate constants at pH 5.5 and 7.4. As for pH 8.9, the ozone dose seemed like have insignificant influence on the constants at pH 8.9.



(a)



(b)



(c)

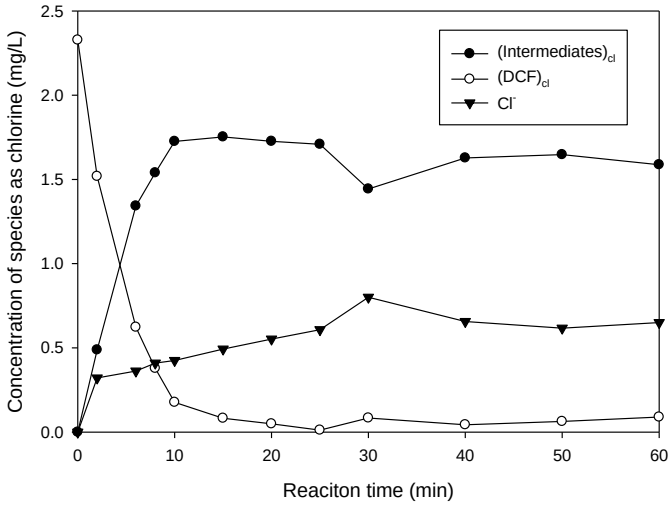
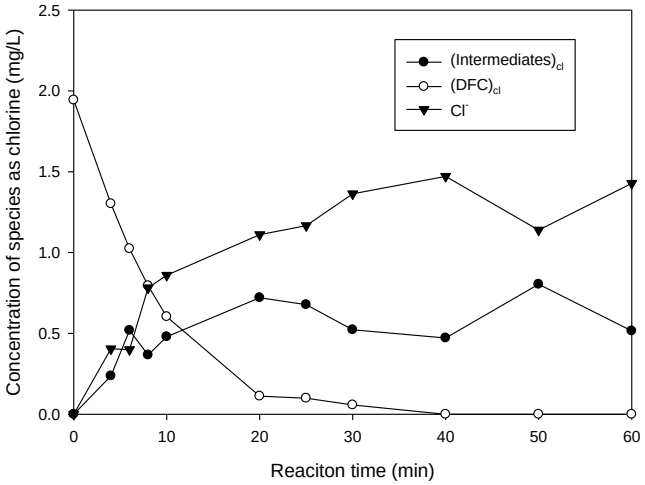
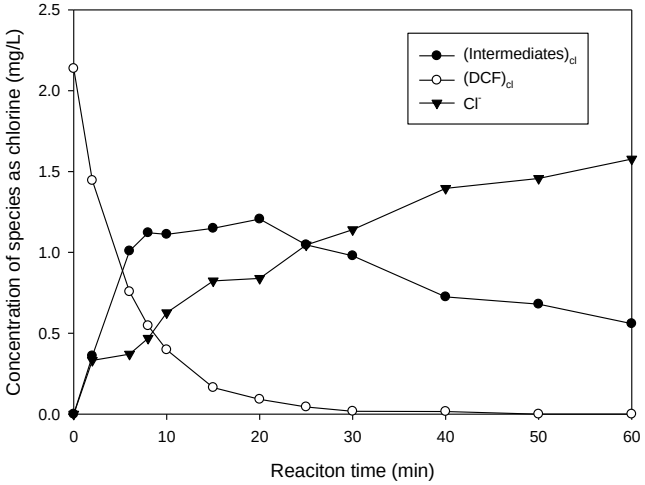


Fig. 4-23. Temporal distribution of chlorine-containing species for the decomposition of diclofenac at (a) pH 5.5; (b) pH 7.4; (c) pH 8.9 at ozone doses 60 mg/L; (●) $(Intermediates)_{cl}$; (○) $(DFC)_{cl}$; (▼) Cl^-.

(a)



(b)



(c)

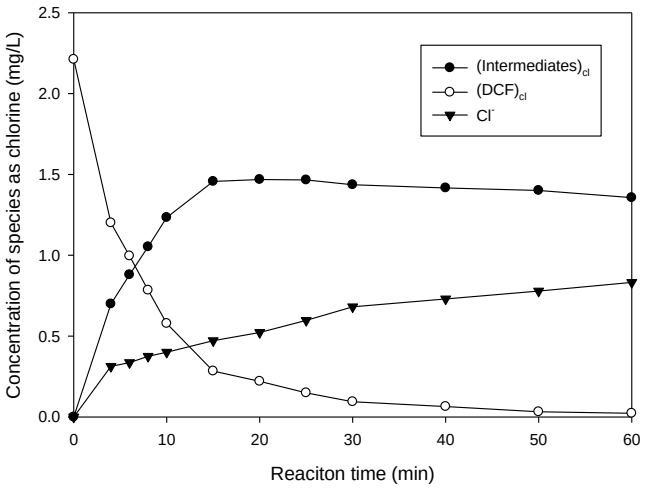


Fig. 4-24. Temporal distribution of chlorine-containing species for the decomposition of diclofenac at (a) pH 5.5; (b) pH 7.4; (c) pH 8.9 at ozone doses 20 mg/L; (●) $(Intermediates)_{cl}$; (○) $(DFC)_{cl}$; (▼) Cl^-.

Table 4-6 The chloride formation rate constant k_{cl} (min^{-1}) determined at different levels of ozone dose and pH value

Ozone dose (mg/L)	pH value		
	5.5	7.4	8.9
60	5.93×10^{-2}	1.21×10^{-1}	2.71×10^{-2}
20	3.72×10^{-2}	4.92×10^{-2}	3.35×10^{-2}

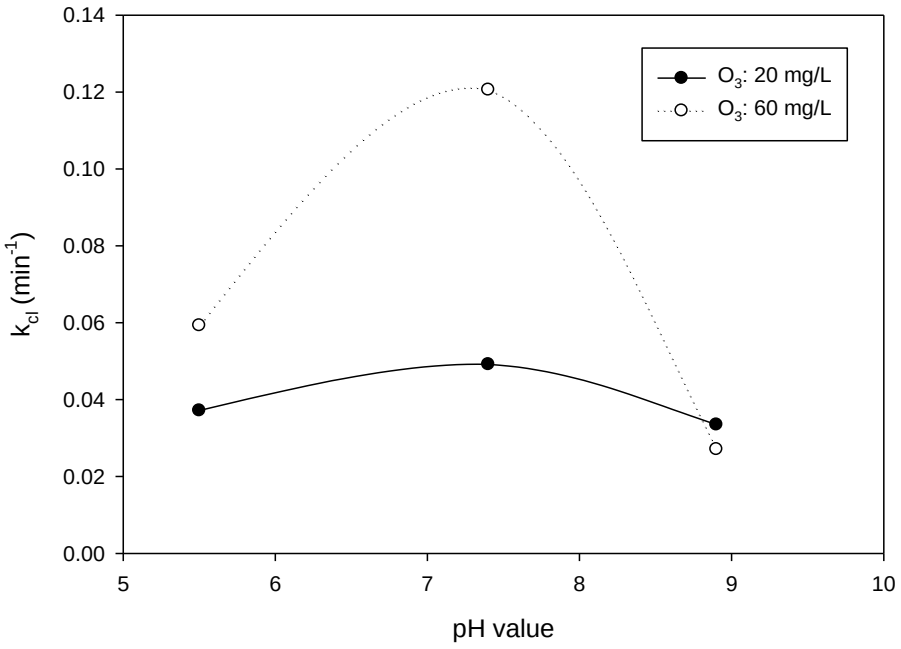


Fig. 4-25. The chloride formation rate constants at pH 5.5, 7.4, and 8.9 at ozone doses 20, and 60 mg/L; (●) O_3 : 20 mg/L; (○) O_3: 60 mg/L.

4-4-3 Mass balance of elemental nitrogen

In this study, the amount of elemental nitrogen mass balance was calculated. The form of nitrogen release during oxidation includes the intermediates containing organic nitrogen, which occurred in the form of intermediates or by-products, and inorganic nitrogen, like nitrate, nitrite, and ammonia. According to previous studies (Coelho et al, 2009), the forms of nitrogen release during ozonation of diclofenac are mainly ammonia but minor nitrate. In this study, the formation of nitrate did not detected by the IC. Therefore, the concentration of ammonia measured with time in different conditions was used to evaluate the mass balance of elemental nitrogen. Calculation of mass balance for elemental nitrogen during diclofenac ozonation was described as following:

- $(\text{Intermediates})_N = (\text{DFC})_{\text{initial N}} - (\text{DFC})_N - (NH_4^+)_t$

Where $(\text{DFC})_{\text{initial N}}$, $(\text{DFC})_N$ and $(NH_4^+)_t$ were initial nitrogen content, nitrogen content at time t and ammonia content at time t, respectively.

Figure 4-26 shows the results of calculation of mass balance of nitrogen with time in the reaction in the absence of phosphate buffer at variable ozone doses. Intermediates containing nitrogen decomposed relatively slower than containing chlorine. The results indicated that the amount of intermediates increased first and then degraded gradually for all three ozone doses. Furthermore, the higher ozone dose made the intermediates generated less in the end.

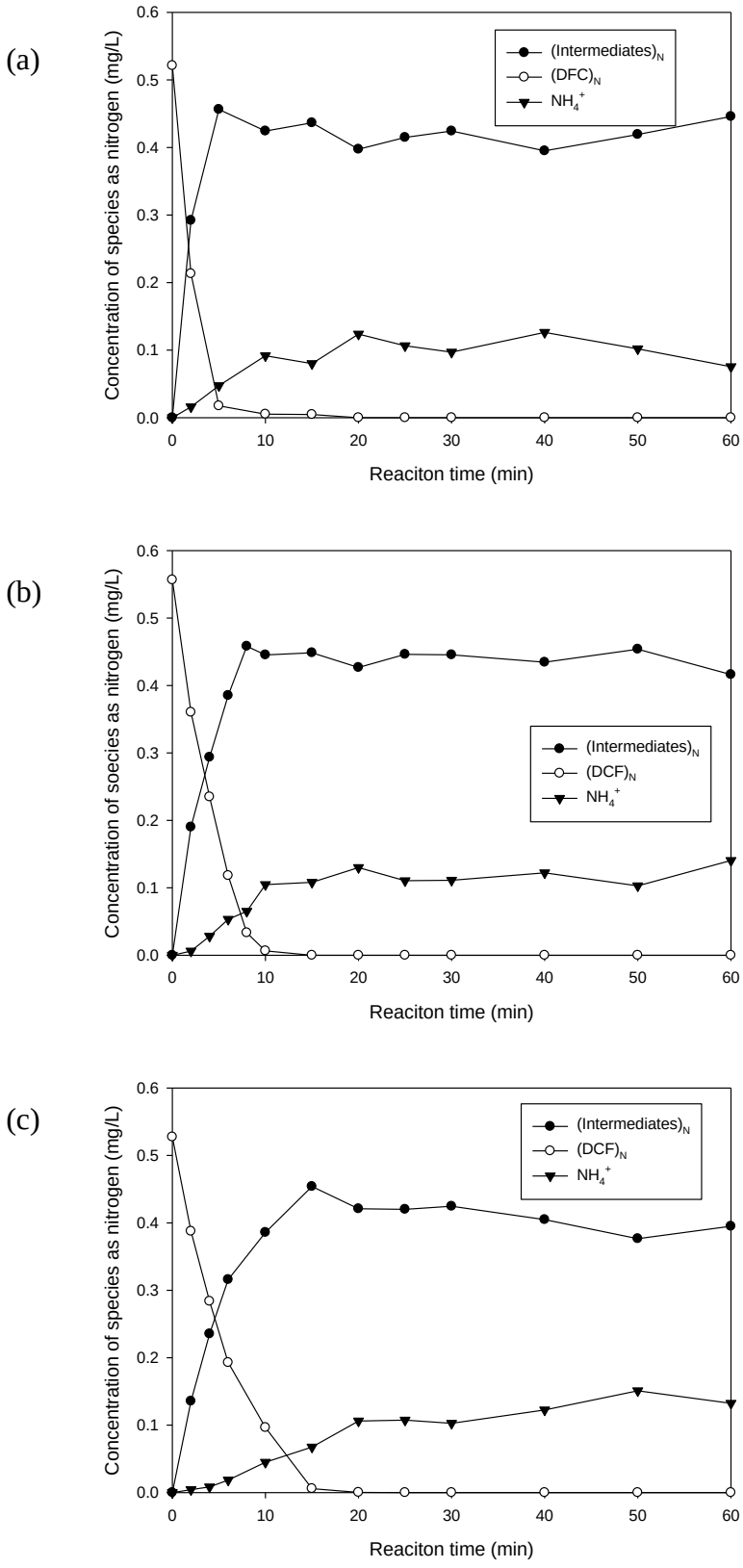
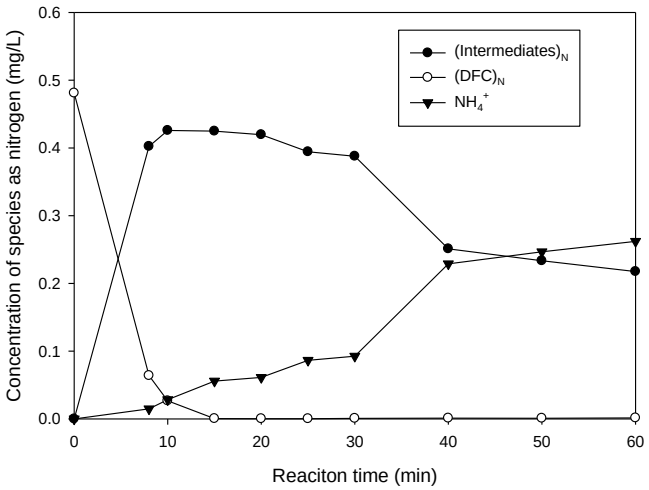


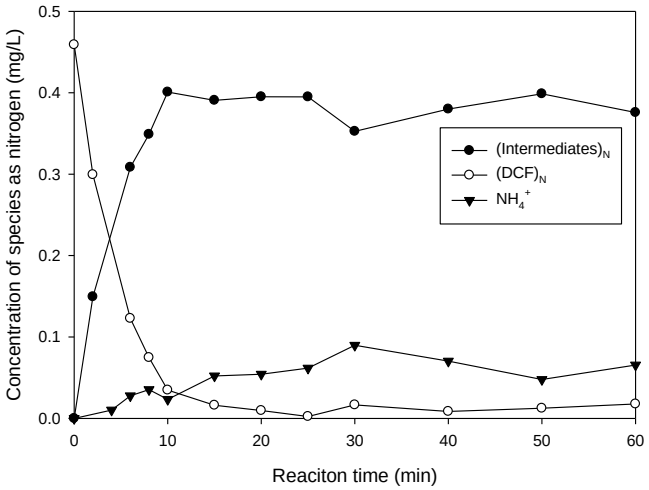
Fig. 4-26. Temporal distribution of nitrogen-containing species for the decomposition of diclofenac in the absence of phosphate buffer at ozone doses (a) 110 mg/L; (b) 60 mg/L; (c) 20 mg/L; (●) $(Intermediates)_N$; (○) $(DFC)_N$; (▼)NH_4^+.

The results of mass balance of ammonia are shlown in Figure 4-27 and 4-28 for three pH values of 5.5, 7.4, and 8.9 with ozone doses of 60 and 20 mg/L. At ozone dose 60 and 20 mg/L, the intermediates generated first then steadily decomposed. This trend of intermediates containing nitrogen decomposition showed similarity with intermediates containing chlorine discussed in previous subsection. In Table 4-7 and Figure 4-29, the ammonia rate constants show various trend at different levels of pH. At low ozone dose, the rate constants increased with the increasing pH values. However, at high ozone dose, the constants decreased from pH 5.5 to 7.4, and increased slightly from pH 7.4 to 8.9. This result is quietly coherent with the results of formation of ammonia in section 4-2-4. On the other hand, this result indicated that the enhancement of ozone dose could not enhance the ammonia formation. The increasing ozone dose might decrease the formation rate constants on the contrary. If the assumption of proportional relationship between the TOC degradation and ammonia formation is correct; the ozone dose might have possibility to enhance the amount of intermediates with nitrogen, and even partly inhibit the degradation of C-N cleavage.

(a)



(b)



(c)

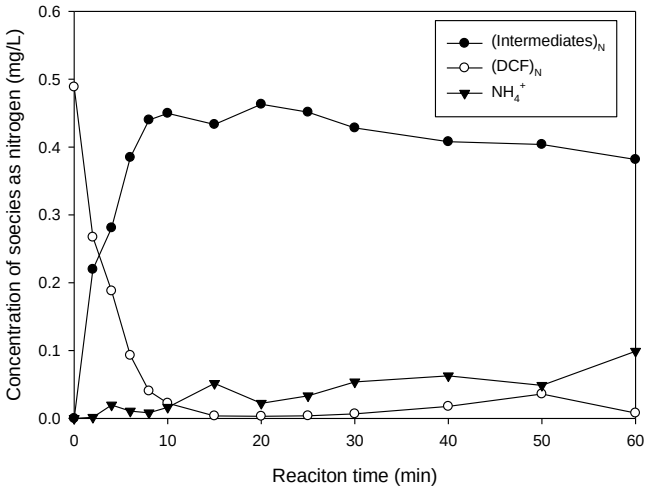


Fig. 4-27. Temporal distribution of nitrogen-containing species for the decomposition of diclofenac at (a) pH 5.5; (b) pH 7.4; (c) pH 8.9 at ozone doses 60 mg/L; (●) $(Intermediates)_N$; (○) $(DFC)_N$; (▼)NH_4^+.

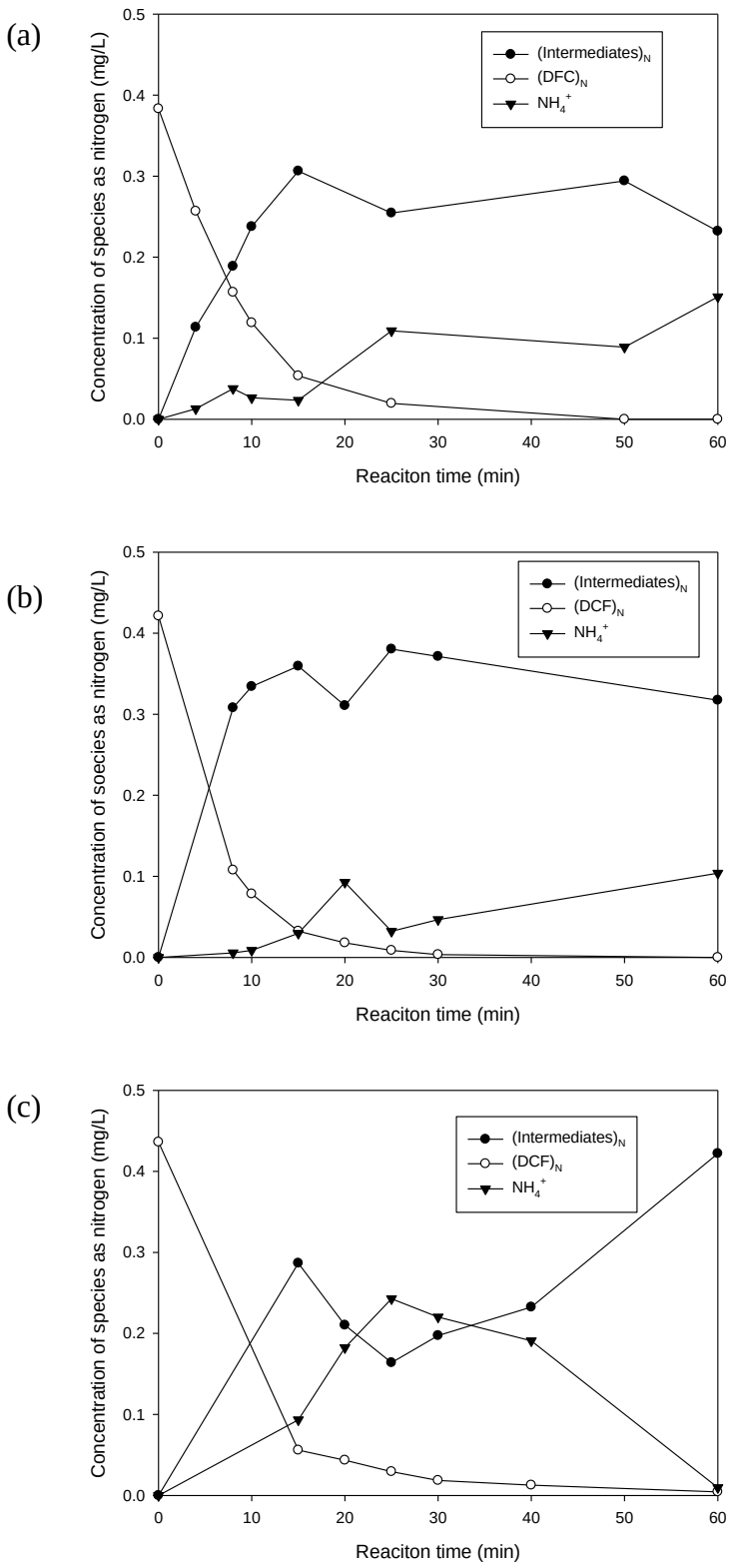


Fig. 4-28. Temporal distribution of nitrogen-containing species for the decomposition of diclofenac at (a) pH 5.5; (b) pH 7.4 (c) pH 8.9 at ozone doses 20 mg/L; (●) $(Intermediates)_N$; (○) $(DFC)_N$; (▼)NH_4^+.

Table 4-7 The ammonia formation rate constant k_N (min^{-1}) determined at different levels of ozone dose and pH value

Ozone dose (mg/L)	pH value		
	5.5	7.4	8.9
60	7.04×10^{-3}	2.75×10^{-2}	3.31×10^{-2}
20	1.2×10^{-2}	1.25×10^{-1}	2.74×10^{-1}

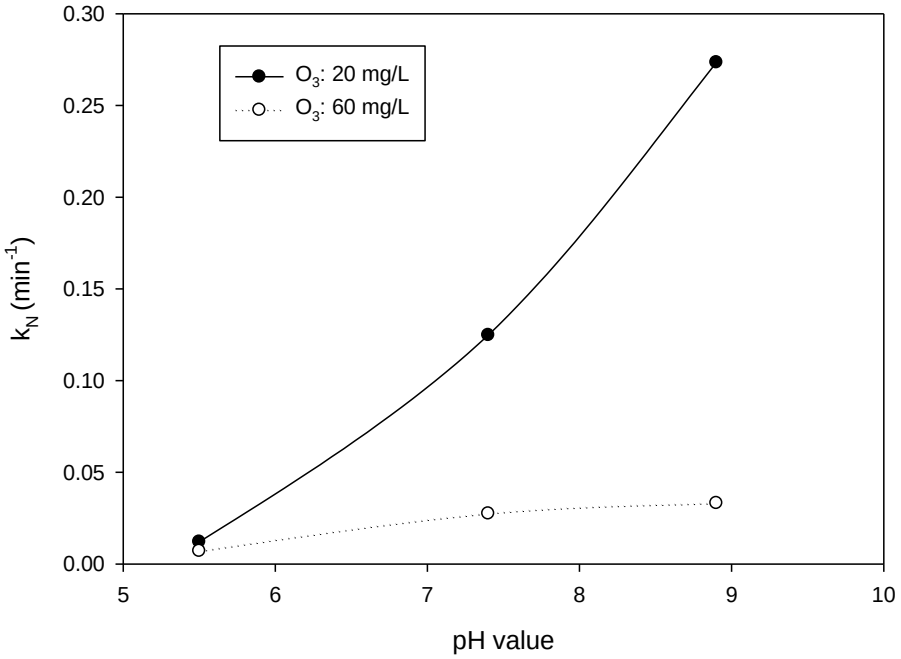


Fig. 4-29. The ammonia formation rate constants at pH 5.5, 7.4, and 8.9 at ozone doses 20, and 60 mg/L; (●) O_3 : 20 mg/L; (◯) O_3: 60 mg/L.

4-5 Elucidation of the degradation pattern during ozonation

4-5-1 Kinetic Studies

According to the previous studies (Vogna et al, 2004; Coelho et al, 2009; Sein et al, 2008), the method of developing kinetic constants include model simulation and the competition method. Due to the discrepancy of the reported values of ozone rate constant, the redetermination established by an independent method was important. However, to use the competition method for kinetic constants determination needs to add competed reagent and OH radical scavenger. The added compounds in the matrix of solution might become obstacle in observing the formation of the organic or inorganic compounds. Therefore, another calculation done by the following assumption and equation was developed in this investigation

To consider that diclofenac was almost removed in the early ozonation stage in all the operational conditions in this study. A suitable kinetic model was developed to describe the consumption of diclofenac in early ozonation stage. The assumption is that the ozone gas introduced into the solution could undergo a fast mass transfer regime and react soon with the target compounds or others in reactor. To try to investigate the conceive ozone dose that really react with diclofenac, a fluid-dynamic submodel (Andreozzi et al, 1995) was introduced and the ozone concentration in the freeboard, inlet gas, and soluble ozone in the solution were monitored on-line to fit in the mass balance equation described as follows:

$$\frac{d[O_3]_B}{dt} = \frac{Q}{V_B}([O_3]_{in} - [O_3]_B) - \frac{k_L^0 aE([O_3]_B \alpha - [O_3]_L)}{V_B} V_L \qquad \text{(Eq. 4-5-1)}$$

$$\frac{d[O_3]_F}{dt} = \frac{Q}{V_B}([O_3]_B - [O_3]_F) \qquad \text{(Eq. 4-5-2)}$$

$$\frac{d[O_3]_L}{dt} = k_L^0 aE([O_3]_B \alpha - [O_3]_L) - z\gamma_{diclofenac} \qquad \text{(Eq. 4-5-3)}$$

However, because of the disappearance of soluble ozone in the solution ($[O_3]_L$) in the early stage of ozonation, the model needed to be modified. Since the soluble ozone concentration is zero, the difference between the concentrations of ozone gas at inlet and freeboard could be assumed to adsorb and react with target compounds. Thus, the ozone concentration was determined as follows:

$$ozone \quad dose = \frac{\int_t G(C_{O3(g)}^{in} - C_{O3(g)}^{out})dt}{V_L} \qquad \text{(Eq. 4-5-4)}$$

where $C_{O3(g)}^{in}$ and $C_{O3(g)}^{out}$ (mg/L) are the values of the ozone concentrations in the gas stream in the inlet and outlet of the reactor, G (L/s) is the volumetric flow rate of the gas stream, V (L) the ozonation reactor volume and t (s) the time of ozonation.

The reaction of diclofenac and ozone was simplified as:

$$\begin{aligned} DFC + zO_3 &\xrightarrow{k_{O_3},\beta} products + Cl^- (path1) \\ DFC + zO_3 &\xrightarrow{k_{O_3},\alpha} products + NH_4^+ (path2) \\ DFC + zO_3 &\xrightarrow{k_{O_3},1-\alpha-\beta} products (path3) \end{aligned} \qquad \text{(Eq. 4-5-5)}$$

where β and α parameter indicates the selectivity of the oxidation for pathway 1 and pathway 2, z indicated the stoichiometric coefficient.

The overall diclofenac consumption, chloride and ammonia ion production rates are given by the following:

$$\frac{d[S]}{dt} = -\frac{1}{z} K_{O_3}[S][O_3]_L = \gamma_{diclofenac} \qquad \text{(Eq. 4-5-6)}$$

$$\frac{d[Cl]}{dt} = \beta K_{O_3}[S][O_3]_L \qquad \text{(Eq. 4-5-7)}$$

$$\frac{d[NH_4^+]}{dt} = \alpha K_{O_3}[S][O_3]_L \qquad \text{(Eq. 4-5-8)}$$

The α, β, z, and k_{O3} were determined by the experimental data. The selectivity of

chloride β and α varies from the pH value, and the stoichiometric coefficient z equal to 6.0, and K_{O3} were summarized in table 4-8.

Table 4-8 Kinetic constants for DFC degradation determined by kinetic model

pH value	pH 5.5	pH 7.4	pH 8.9
$k_{O3}(M^{-1}S^{-1})$	3.91×10^4	7.60×10^4	6.25×10^4
α	0.14	0.12	0.09
β	0.35	0.40	0.26

Table 4-9 Comparison of DFC degradation rate constant, k_{DFC} $(M^{-1}s^{-1})$

pH value			Method	Reference
5.0	5.5	6.0	Simulation	Vogna et al, 2004
1.76×10^4	1.69×10^4	1.84×10^4		
5.5	7.4	8.9	Eq. 4-5-6	This study
3.91×10^4	7.60×10^4	6.25×10^4		

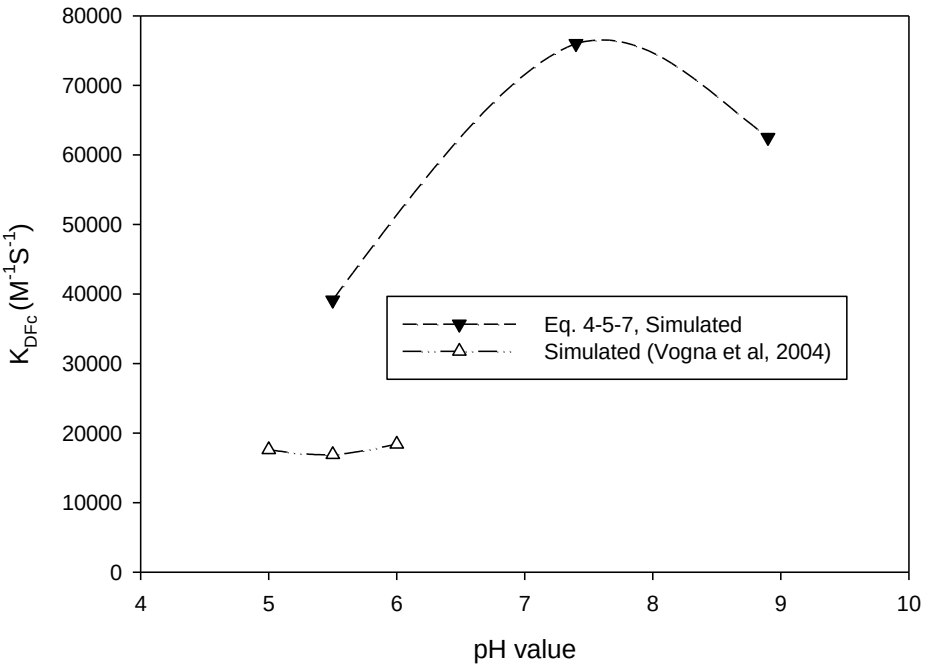


Fig. 4-30. The DFC reaction rate constants at pH 5.5, 7.4, and 8.9 at ozone doses 20, and 60 mg/L; (▼) Eq. 4-5-7, Model simulation; (Δ) Simulation, Vogna et al, 2004.

From the above results, it could be inferred that the model simulated the same trend reaching the maxima value at pH 7.4, increasing from pH 5.5 to 7.4, decreasing from 7.4 to 8.9. It also could be estimated that one mole of diclofenac consumed 6 mole ozone; moreover, the pH value could affect the degradation pathway due to the different selectivity α, β calculated. The highest selectivity of chloride and ammonia formation was at pH 7.4, which was consistent with the pattern of the kinetic constants. The results also could indicate that the pH value showed insignificant effect on C-N cleavage, but significant effect on C-Cl cleavage. On the other hand, combining with the result of TOC removal, it could indicate that the diclofenac preferred to lead to C-C cleavage at pH 5.5 and 8.9, and formed other intermediates with complex structure which could be hardly oxidized further.

4-5-2 Predictive pathway and mechanism of diclofenac in ozonation

Figures 4-32 to 4-34 show the speculated intermediates containing carbon, chlorine, and nitrogen with various reaction time. It could be inferred that in the early stage of ozonation, the organic carbon degraded rapidly at ozone dose of 60 mg/L. However, after 30 min, the intermediates with carbon generation at 20 mg/L exceeded 60 mg/L, and the difference became more significant as the pH value increased. Therefore, the intermediates formed at pH 5.5 were difficult to decompose or the rate of decay of intermediates could not satisfy the rate of generation of intermediates.

For intermediates containing chloride and ammonia, it was observed at pH 8.9, the degradation rates remained steady after 10 min. The result also demonstrated that a lower TOC removal rate and CO_2 formation constants could be observed. In comparison of the results at pH of 5.5 and 7.4, in which the degradation rates at pH 5.5 remained stable after 30 min whereas remained steadily degraded within 60 min at pH 7.7, it could be speculated the pathway of diclofenac by ozonation was significantly affected by pH values. Moreover, the degradation of intermediates with chloride occurred as the concentration of intermediates while nitrogen remained stable. It could then be concluded that the intermediates with nitrogen might not contain chloride, and the remaining ones were well-structured and resulted in the C-N cleavage and TOC degradation barely.

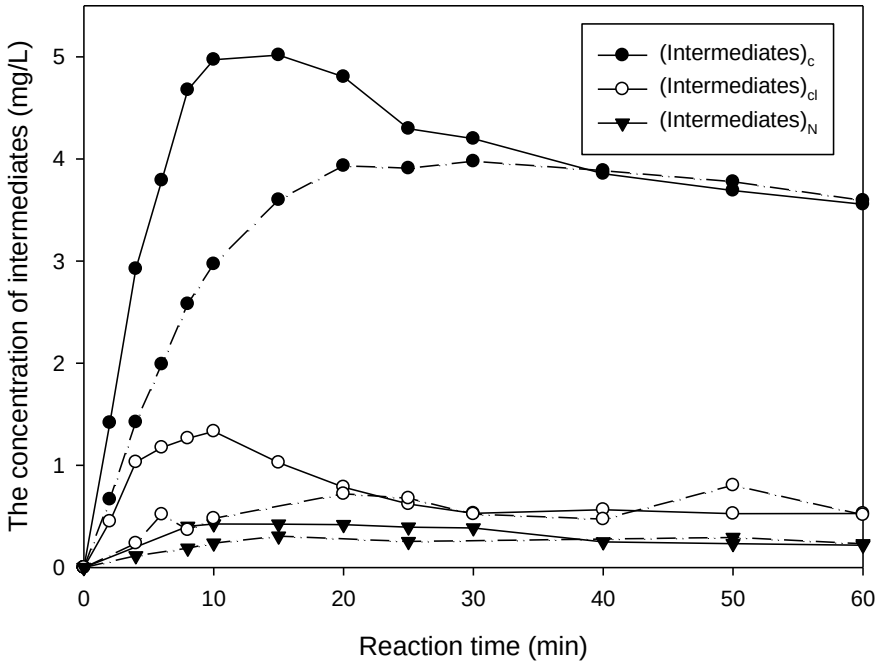


Fig. 4-31. Temporal distribution of carbon, chlorine, and nitrogen-containing species for the decomposition of diclofenac at pH 5.5 at O_3: 60 mg/L (solid line), and 20 mg/L (spot-dash line); (●) $(Intermediates)_C$; (○) $(Intermediates)_{Cl}$; (▼) $(Intermediates)_N$.

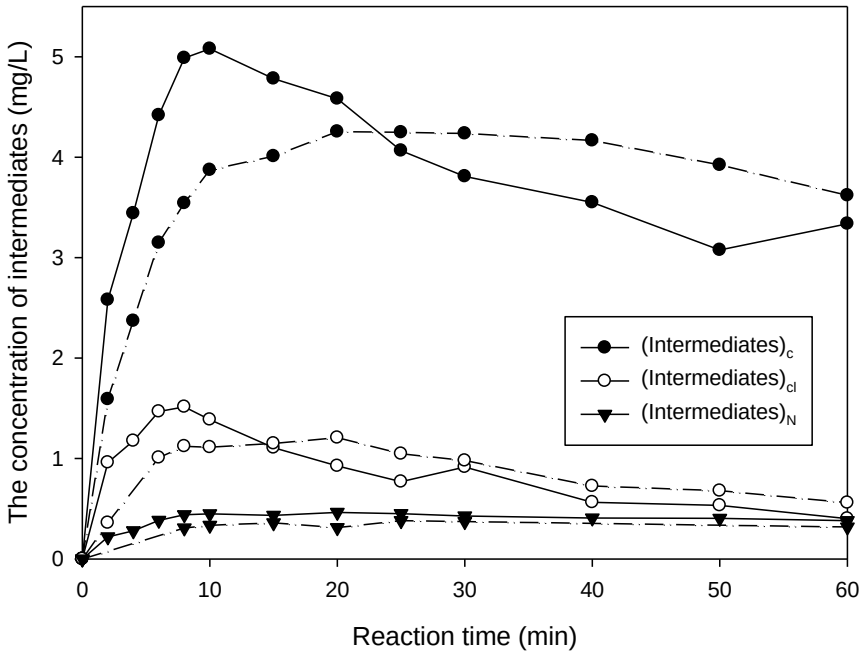


Fig. 4-32. Temporal distribution of carbon, chlorine, and nitrogen-containing species for the decomposition of diclofenac at pH 7.4 at O_3: 60 mg/L (solid line), and 20 mg/L (spot-dash line); (●) $(Intermediates)_C$; (○) $(Intermediates)_{Cl}$; (▼) $(Intermediates)_N$.

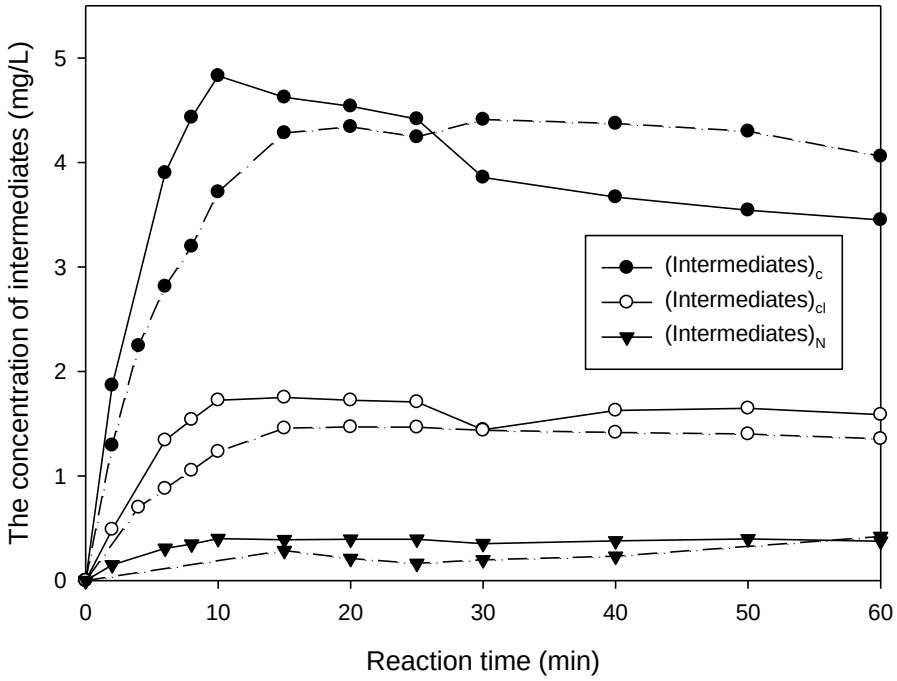


Fig. 4-33. Temporal distribution of carbon, chlorine, and nitrogen-containing species for the decomposition of diclofenac at pH 8.9 at ozone doses 60 (solid line), and 20 (spot-dash line) mg/L; (●) $(Intermediates)_C$; (○) $(Intermediates)_{Cl}$; (▼) $(Intermediates)_N$.

The proposed pathway and mechanism of diclofenac during ozonation were assessed by other studies (Vogna et al, 2004; Sein et al, 2008; Coelho et al, 2009) and the analytical result of GC-MS. The reaction was likely followed three competitive routes. One leaded to hydroxylated intermediates and the possible main product might be 5-hydroxydiclofenac. The other leaded to C-N cleavage broken and the possible main product might be 2,6-dicloroaniline.

The hydroxylated intermediates were less found in the early ozonation of diclofenac solution at variable pH values, because the pH value was so small that the OH radicals were less active. On the other hand, the 2,6-dicloroaniline was observed in the early stage. Ozone is an electrophile, it would attack the nucleophilic site, which is amino group in the reaction of diclofenac, and probably make the aminyl redical formed.

Therefore, the C-N cleavage was likely to break and form 2,6-dicloroaniline, or other group of compound might add on to the amino group to from an ring or other compounds.

To investigate the formation of hydroxylated intermediates, the pH value was adjusted to 8.9 to observe the hydroxylated compounds. The OH radicals, due to its electrophilic nature, would attack the active site on aromatic rings. Because of the nucleophilic characteristic of amino group, the *ipso*-position would be the favorable site for OH radical to add. Thus, the 5-hydroxydiclofenac was supposed to be the main products.

Chlorination also occurred at times as the ozonation of diclofenac. It almost contains the HCl elimination during ozonation. Therefore, the low efficiency of chloride formation constants at pH 5.5 would be demonstrated.

The pathway was predicted by the kinetic model used above. The degradation of diclofenac could be divided into more than three steps: hydroxylation, C-Cl cleavage, C-N cleavage, and others, such as ring opening. From Figures 4-31 to 33, the intermediates formed quickly at the early stage of ozonation, and then started to decay at different paces.

In Figure 4-34, the reaction from DFC to D7 would be considered to be the main reaction of C-N cleavage and formation of ammonia. Furthermore, the reaction between these compounds would contribute to the chloride formation as they mineralized. The diclofenac aminyl radical (D5) is considered to be the first compound formed initially in ozonation process with diclofenac, and then it would react with other radicals or ozone into D1 and D2. The chloride would be released after 12 minutes since the D9 and D3 were detected at the time. From the conclusions in section 4-1 and 4-2, there might be some compounds with strong structures and chlorine that hardly decomposed and

released chloride. Therefore, D11, which were detected and identified by GC-MS in 24 minutes, would be considered as the possible compounds make the formation of chloride incompletely.

Table 4-10 Corresponding chemical structure of intermediates in previous references and this study.

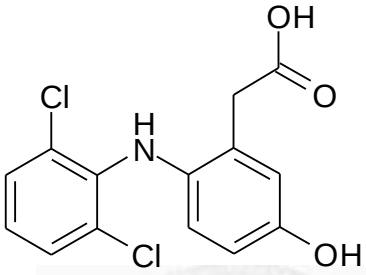
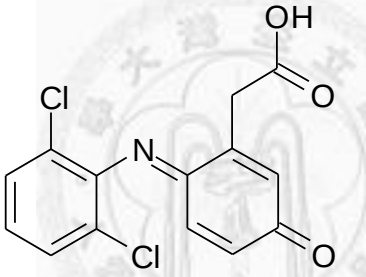
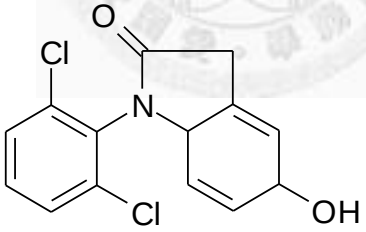
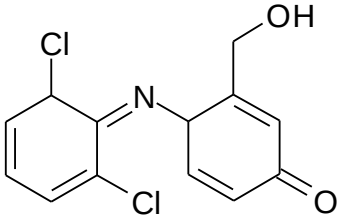
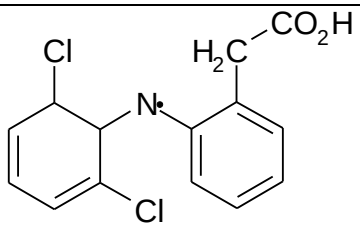
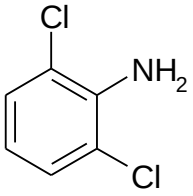
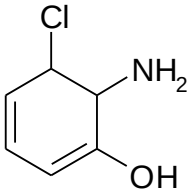
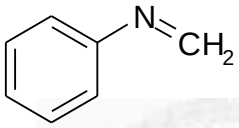
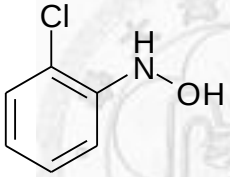
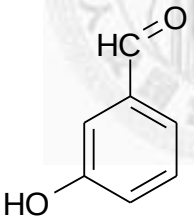
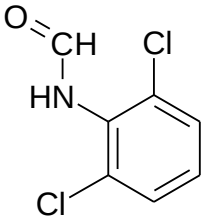
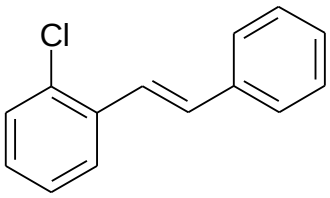
Number	Chemical structure	Previous identification
(D1)		Vogna et al, 2004 Perez-Estrada et al, 2005b Calza et al, 2006
(D2)		Calza et al, 2006
(D3)		Perez-Estrada et al, 2005b Calza et al, 2006
(D4)		Perez-Estrada et al, 2005b
(D5)		Sein et al, 2008

Table 4-10 Corresponding chemical structure of intermediates in previous references and this study. (Continues)

Number	Chemical structure	Previous identification
(D6)		Vogna et al, 2004 Perez-Estrada et al, 2005b Bartels and Von Tumpling, 2007 Hohmann et al, 2007
(D7)		Coelho et al, 2009
(D8)		Coelho et al, 2009
(D9)		Perez-Estrada et al, 2005b
(D10)		Coelho et al, 2009
(D11)		Coelho et al, 2009
(D12)		Analyzed by GC-MS.

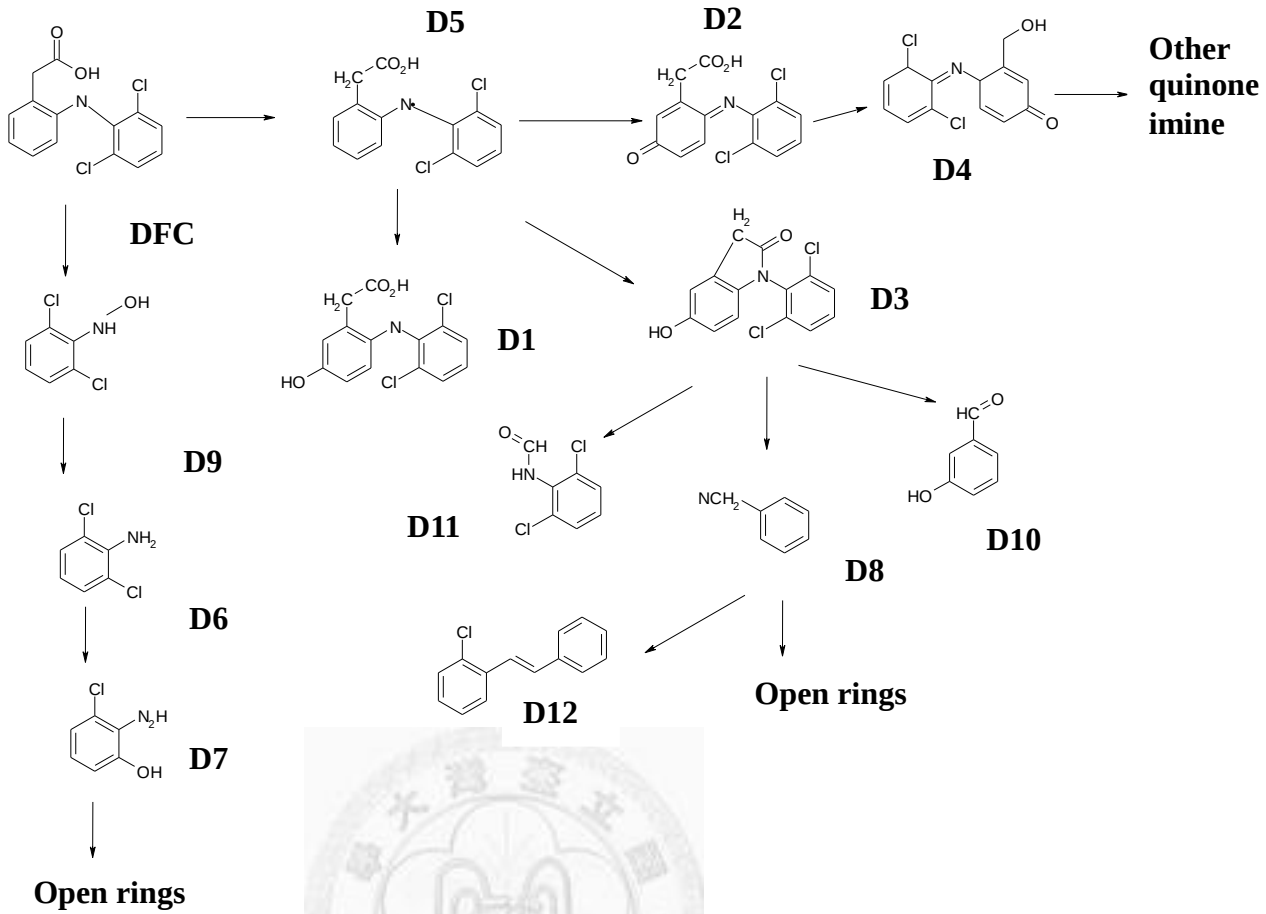


Fig. 4-34 Proposed pathway of ozonation of diclofenac

From the kinetic studies, the level of pH value could partly affect the degradation pathway. The selectivity of chloride-releasing pathway at pH 7.4 showed the same pattern with the temporal profile of chloride-releasing as shown previously, and so did the other to pH levels. For the selectivity of ammonia, the levels of pH exhibited a lower relationship with it, which was partly consistent with the temporal profile of ammonia-releasing.

As the attack of OH radical is considered nonselective, previous studies suggested that hydroxylation at C-5 as the most possible way. The hydroxylation was caused by the OH radical attack, and the first and main product of hydroxylation was possibly 5-hydroxy diclofenac, which would lead to the formation of

diclofenac-2,5-iminoquinone (Pérez-Estrada et al, 2005; Sein et al, 2008). Furthermore, OH radical would also attack the halogenated site and result in the releasing of chloride by replacement of OH group. Therefore, this reaction showed the pathway of chloride formation and could be represented as selectivity β. At pH 8.9, in which more OH radical could be formed, the amount of chloride formation was the least one. This pattern could be explained by the inhibition of phosphate buffer, and indicated that the OH radical would not only lead to the formation of chloride. It would undergo other reaction such as hydroxylation or decarboxylation at other sites. In summary, the increasing amount of OH radical could probably enhance the amount of chloride formation due to the comparison of pH 5.5 and 7.4, but as the OH radical increased over a limitation, the OH radical reaction might become nonselective and form other complex intermediates containing chlorine.

Another important reaction during oxidation of diclofenac was considered as the C-N cleavage, which might lead to the formation of ammonia. This reaction was somehow regarded as the alternative pathway of degradation of diclofenac compared to the quinine imine derivatives. (Pérez-Estrada et al, 2005) This direct attack to the aliphatic chain was caused by OH radical. (Sein et al, 2008) However, with the similar selectivity of reaction of ammonia formation at different levels of pH value, it could be concluded that the broken of C-N cleavage might be caused by the ozone direct attack or other free radicals instead of OH radicals. This speculation was consistent with the results shown previous in this study. The reason could be stated that with the continuously injected ozone, the excess amount of ozone was able to lead the reaction of formation of ammonia. Moreover, from the previous results showing the high percentage of the yield ratio of chloride, it could thus be concluded that the chloride formation not only caused by the competitive reaction of quinone imine, but also

contributed by the nonchlorinated products generated from the reaction of C-N cleavage. Compared to the other studies, Vogna et al (2004) and Pérez-Estrada et al (2005) showed the evidences that after forming 2,6-dichloroaniline, one of the two-NH bearing positions (C-1') would not easily activated by OH radical attack. Therefore, it was inferred that the further reaction of 2,6-dichloroaniline would probably undergo the decarboxylation reaction or ring-opened reaction that caused the chloride and carbon dioxide released.

In conclusion, the chloride releasing would be caused by OH radical attack, and degradation of 2,6-dichloroaniline or other chlorine-containing compounds. At first, the OH radical reaction could be taken as the major one to release the first chlorine, and HCl elimination reaction with a fast kinetic constant would occur. As for the formation of ammonia, the C-N cleavage would break and 2,6-dichloroaniline would form as the major product. After a few minutes, the chloride releasing concentration enhanced as the structure of chlorine-containing organic compounds had been eliminated. However, due to some chlorine-containing and well structure organic compounds, the chloride formation could not reach the theoretical amount. For nitrogen-containing target compounds, according to the small amount of ammonia releasing, it could be indicated that once the C-N cleavage broken did not occur in the beginning, the nitrogen-containing compounds would form complex and strong structure that hard to release ammonia, which cause the TOC removal could not increase.

4-5-3 Optimum control for reducing diclofenac

In this study, many kinetic constants were presented. Furthermore, the risk assessment was determined. Therefore, as long as the relationship between each parameter is reasonable speculated or identified, the optimization could be inferred by several figures. Form the hypothesis, the chloride and ammonia formation indicated the TOC degradation, which represented the real organic carbon or possible hazardous materials existing in the water. Thus, the optimized condition was conducted by following Figures comparison.

From the Figures, it could be seen that at ozone dose 20 mg/L, the carcinogenetic risk would be low, the DFC kinetic constants and nitrogen formation rate constants are high. As for ozone dose 60 mg/L, including the carbon dioxide formation rate, and chloride formation rate constants are high. From the parameters derived from model, the formation of nitrogen only account for a minor part of diclofenac ozonation. Therefore, the chloride formation should be the significant part on degradation of diclofenac via ozonation.

As for pH value, it is obviously that the most of the kinetic constants reach maxima value at pH 7.4. Moreover, even the constants or pH or carcinogenetic risk is not the highest value at pH 7.4, the difference would not be too far. Consequently, the lowest carcinogenetic risk was found to be at ozone dosage of 20 mg/L and pH 5.5. If the focus was put on the removal of carbon and diclofenac,

On the other hand, since diclofenac removal rate, carbon formation rate, and carcinogenetic risk are more important in ozonation of diclofenac removal, the optimum control would be taken these three values into considerations. For ozone dose 60 mg/L, because the DFC rate constants were slightly lower than 20 mg/L, while the differences of carbon dioxide formation rate constants were larger than 20 mg/L. From Figures, it

was observed that at pH 7.4 the kinetic constants were almost the highest one at both two ozone doses. Although the carcinogenetic risk at pH 7.4 was higher than pH 5.5, the difference between the two values still showed the same pattern with DFC rate constants. In general, the optimum control of ozonation for diclofenac removal was at pH of 7.4 and at ozone dose 60 mg/L.

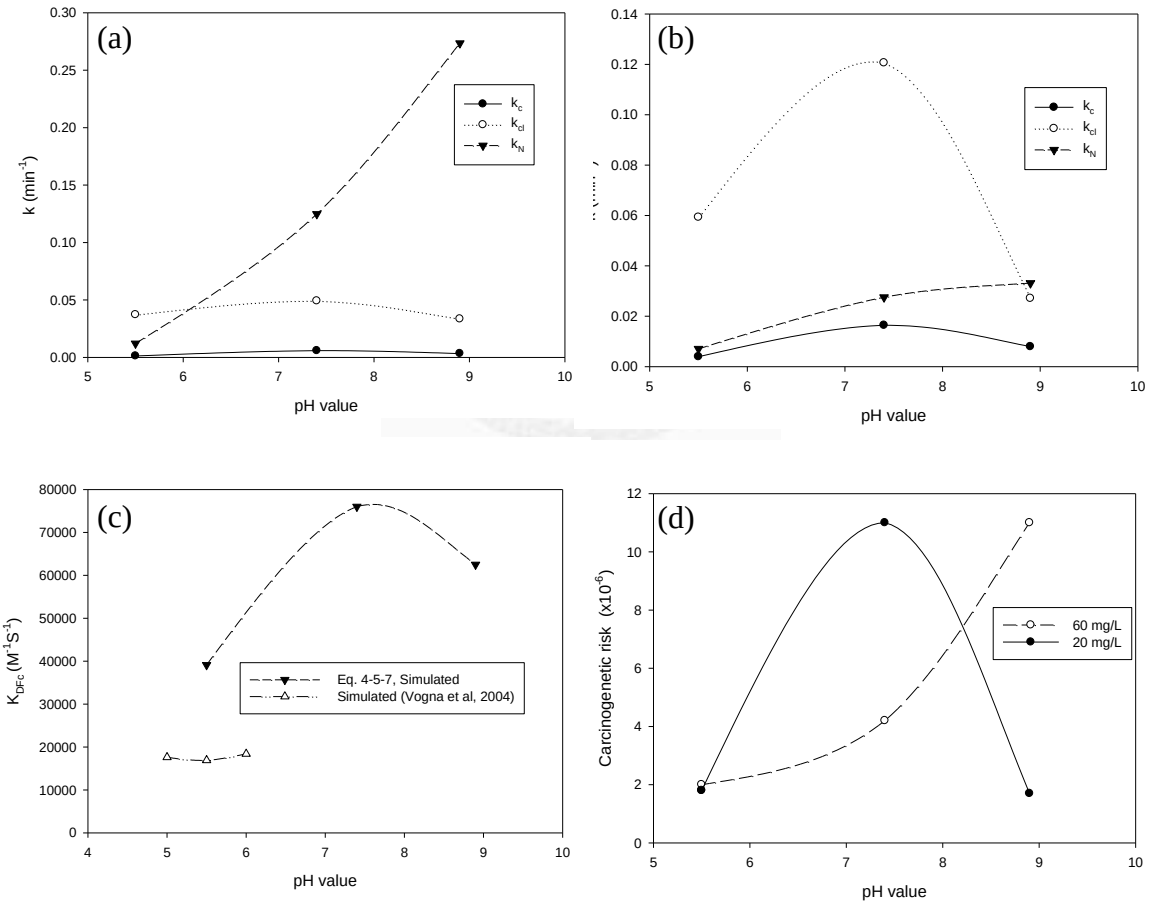


Fig. 4-35.The different rate constants of carbon, chloride, ammonia at pH 5.5, 7.4 and 8.9 at ozone dose (a) 20 mg/L, (b) 60 mg/L, (c) rate constants of diclofenac at two levels of ozone doses, and (d) carcinogenetic risk ; (●) 20 mg/L; (◯)60 mg/L.

Chapter 5 Conclusions and Recommendations

5-1 Conclusions

This study demonstrated that ozonation process can be an effective method to remove diclofenac from water. At variable pH condition, diclofenac as well as TOC were degraded very quickly by ozonation. The inorganic by-products, e.g., chloride, reached to a maximum concentration rapidly under high ozone dose. On the contrary, the effect of ozone dose on TOC removal was insignificant, and the extent of chloride formation decreased significantly with a low ozone dose, which implied that ozone dose played an important role on the degradation and mineralization of diclofenac.

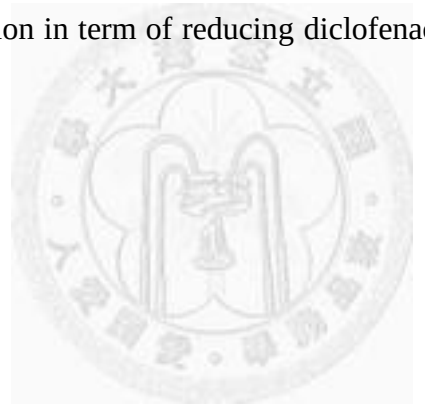
At fixed pH condition, i.e., controlled by adding phosphate buffer, the diclofenac degradation was slower. In addition, phosphate buffer also enhanced the extent of TOC degradation as ozone dose increased. The amount of chloride formation decreased as the phosphate buffer was added, but the formation of ammonia was insignificantly affected by adding phosphate buffer. In summary, the most effective condition for TOC degradation was determined at pH of 7.4..

The formation rates of CO_2, chloride and ammonia were calculated to determine based on the mass balance to determine the corresponding rate constant. The rate constant for carbon dioxide formation increased as pH increased from 5.5 to 7.4, and then decreased as pH from 7.4 to 8.9. The rate constant for chloride formation was in the same pattern as carbon dioxide formation. The rate constant for ammonia formation increased as pH increased at a lower ozone dose, whereas it decreased then increased at a higher ozone dose.

The kinetic constant, derived from the assumption of pseudo-first order reaction, increased as the pH increased, which followed the same pattern as carbon and chloride formations. In the kinetic model, the selectivity of chloride releasing and

ammonia releasing were 0.35 and 0.13, respectively. From the results, it can be concluded that ozonation of diclofenac tended to favor the oxidation of chloride ions than C-N bond cleavage.

The ozone attacked the amino group and aromatic ring of diclofenac and resulted in generating ozonation by-products such as aldahydes. In this study, the formation of aldehyde increased with increasing pH. Regarding to human health, the lowest carcinogenetic risk was determined based on the lowest formation concentration of aldehyde at ozone dosage of 20 mg/L and pH 5.5 through the health assessment proposed by USEPA. Coupling the health risk assessment with the result of rate constant calculation, ozone dose of 60 mg/L and pH 7.4 would be considered as the optimum operation condition in term of reducing diclofenac, CO_2 formation rate, and carcinogenetic risk.



5-2 Recommendations

1 The formation of intermediates and the pathway for diclofenac degradation are still not well developed. It is suggested that further experiments be focused on the formation of intermediates as well as the pathway of degradation.

2 Besides aldehydes, carcinogenetic risk of other ozonation by-products should be further investigated to make the health risk assessment more comprehensive.

3 The input variables for executing ANOVA and RSM analyses should be more complete for optimizing the process in reducing diclofenac.

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Appendix

Appendix A-1

TOC

1. Method

   According to NIEA W532.51C, promulgated by EPA, Republic of China.

2. Apparatus

   Total organic carbon analyzer

3. Reagents

   a. Reagent water

      Use Milli-Q water as blank sample

   b. Phosphoric acid, H_3PO_4.

   c. Organic carbon stock solution:

      Dissolve 2.1254 g anhydrous potassium biphthalate, $C_8H_5KO_4$ (KHP), in carbon free water and dilute to 1000 mL.

   d. Carrier gas: Purified nitrogen

   e. Purging gas: Purified nitrogen

4. Procedure

   a. Add $Na_2S_2O_8$ (oxidizer) and H_3PO_4 (acidifier) to the containers of TOC analyzer.

   b. Before the analysis of samples, warm up the analyzer for 30 minutes; run blank for 60 minutes; run reagent water for 60 minutes.

   c. Preparation of standard curve: Prepare standard organic carbon series by diluting stock solution to cover the expected range in samples.

   d. Examine the samples

   e. Wash the analyzer after the examination for 60 minutes.

Appendix 2 Raw data

Table A-1 Concetration of diclofenac. TOC, chloride and ammonia in the absence of phosphate buffer during ozonation

Reaction time (min)	DFC concentration			TOC concentration			Chloride concentration			Ammonia concentration		
	O_3 (mg/L):20	O_3 (mg/L):60	O_3 (mg/L):110	O_3 (mg/L):20	O_3 (mg/L):60	O_3 (mg/L):110	O_3 (mg/L):20	O_3 (mg/L):60	O_3 (mg/L):110	O_3 (mg/L):20	O_3 (mg/L):60	O_3 (mg/L):110
0	11.15	11.77	11.02	4.91	5.18	5.87	0	0	0	0	0	0
2	8.19	7.62	4.51	4.69	5.09	5.53	0.34	0.24	0.29	4.28E-03	6.17E-03	0.01
4	5.99	4.97	1.06	4.50	4.96	5.36	0.50	0.50	0.51	8.35E-03	0.03	0.03
6	4.08	2.50	0.37	4.44	4.90	5.27	0.64	0.78	0.86	0.02	0.05	0.06
8	3.24	0.71	0.23	4.36	4.81	5.00	0.75	1.06	1.26	0.06	0.07	0.07
10	2.04	0.14	0.11	4.39	4.74	4.92	0.77	1.22	1.45	0.04	0.10	0.09
15	0.12	0.11	0.09	4.19	4.49	4.35	0.82	1.80	1.98	0.07	0.11	0.08
20	0.007	0.002	0	4.15	4.24	4.21	1.03	1.96	2.25	0.11	0.13	0.12
25	0	0	0	3.90	3.95	3.94	1.23	2.12	1.99	0.11	0.11	0.11
30	0	0	0	3.79	3.81	3.83	1.33	2.31	2.04	0.10	0.11	0.10
40	0	0	0	3.42	3.71	3.58	1.81	2.07	2.01	0.12	0.12	0.13
50	0	0	0	3.37	3.57	3.46	1.65	2.17	2.06	0.15	0.10	0.10
60	0	0	0	3.25	3.53	3.43	1.94	2.18	2.18	0.13	0.14	0.08

Experimental condition: semi-batch reacion

Table A-2 Temporal profile of pH value and residual ozone dose during ozonation in the absence of phosphate buffer

Reaction time (min)	pH value			Residual ozone dose		
	O_3 (mg/ L):20	O_3 (mg/ L):60	O_3 (mg/ L):110	O_3 (mg/ L):20	O_3 (mg/ L):60	O_3 (mg/ L):110
0	5.36	5	5.13	0	0	0
2	5.26	4.4	4.99	0	0	0
4	5.1	4.12	4.06	0	0	0
6	4.91	3.77	3.95	0	0	0
8	4.73	3.73	3.83	0	0	0
10	4.53	3.66	3.8	0	0	0.135
15	3.97	3.48	3.65	0	0	2.243
20	3.41	3.4	3.62	0.086	0.381	3.593
25	3.41	3.34	3.65	0.422	1.077	3.998
30	3.41	3.34	3.59	1.11	1.646	4.502
40	3.41	3.38	3.52	1.73	2.233	6.419
50	3.41	3.38	3.52	1.95	2.448	7.027
60	3.41	3.38	3.52	2.05	2.554	7.341

Table A-3 Concetration of diclofenac. TOC, chloride and ammonia in the presence of phosphate buffer at ozone dose 60 mg/L during ozonation

Reaction time (min)	DFC concentration			TOC concentration			Chloride concentration			Ammonia concentration		
	pH 5.5	pH 7.4	pH 8.9	pH 5.5	pH 7.4	pH 8.9	pH 5.5	pH 7.4	pH 8.9	pH 5.5	pH 7.4	pH 8.9
0	10.17	10.33	9.70	5.04	5.47	5.24	0	0	0	0	0	0
2	7.60	5.65	6.33	5.00	5.39	5.20	0.16	0.16	0.32	-	1.62E-03	0.0102
4	4.72	3.97	2.60	4.87	5.30	5.11	0.28	0.35	0.33	-	0.0197	-
6	2.97	1.96	1.58	4.75	5.14	5.07	0.55	0.54	0.36	-	0.0108	0.0277
8	1.35	0.85	0.74	4.71	5.08	4.98	0.85	0.76	0.40	0.0149	8.16E-03	0.0353
10	0.57	0.47	0.34	4.56	4.95	4.56	0.97	0.98	0.42	0.0284	0.0163	0.0233
15	0.007	0.075	0.21	4.29	4.43	4.39	1.41	1.35	0.49	0.0558	0.0516	0.0521
20	0.006	0.065	0.05	4.08	4.22	4.18	1.65	1.54	0.55	0.0612	0.0223	0.0542
25	0.005	0	0	3.57	3.72	3.79	1.82	1.69	0.61	0.0864	0.0333	0.0618
30	0	0	0	3.48	3.50	3.51	1.91	1.53	0.80	0.0925	0.0537	0.0898
40	0	0	0	3.14	3.37	3.43	1.87	1.82	0.66	0.2289	0.0628	0.0704
50	0	0	0	2.97	3.11	3.40	1.91	1.76	0.62	0.2467	0.0487	0.0477
60	0	0	0	2.85	3.04	5.24	1.90	2.04	0.65	0.262	0.0989	0.0656

Table A-4 Concetration of diclofenac. TOC, chloride and ammonia in the presence of phosphate buffer at ozone dose 20 mg/L during ozonation

Reaction time (min)	DFC concentration			TOC concentration			Chloride concentration			Ammonia concentration		
	pH 5.5	pH 7.4	pH 8.9	pH 5.5	pH 7.4	pH 8.9	pH 5.5	pH 7.4	pH 8.9	pH 5.5	pH 7.4	pH 8.9
0	8.10	8.91	9.22	3.87	4.99	4.41	0	0	0	0	0	0
2	5.43	6.02	5.00	3.84	4.94	4.35	-	0.33	0.30	-	1.62E-03	0.0102
4	4.27	3.16	4.15	3.78	4.85	4.32	0.40	0.34	0.31	-	5.60E-03	-
6	3.31	2.28	3.27	3.73	4.87	4.27	0.39	0.37	0.33	0.0129	8.64E-03	0.0277
8	2.52	1.66	2.41	3.69	4.77	4.26	0.78	0.46	0.37	0.0378	-	0.0353
10	0.47	0.68	1.18	3.67	4.75	4.23	0.86	0.62	0.40	0.0264	0.0197	0.0233
15	0.41	0.38	0.92	3.52	4.33	4.13	-	0.82	0.47	0.0233	0.0108	-
20	0.24	0.18	0.62	3.47	4.40	4.04	1.11	0.83	0.52	0.1091	0.0297	0.0934
25	0	0.07	0.39	3.41	4.28	3.77	1.16	1.04	0.59	0.089	0.0927	0.1824
30	0	0.06	0.27	3.38	4.21	3.81	1.36	1.14	0.68	0.1511	0.0323	0.2428
40	0	0	0.13	3.16	4.13	3.70	1.47	1.39	0.73	0.1052	0.0466	0.2202
50	0	0	0.09	3.05	3.85	3.55	1.14	1.45	0.77	0.1126	0.104	0.1909
60	0	0	0	2.87	3.55	3.29	1.42	1.57	0.83	0.1511	0.104	0.0196

Table A-5 Concentration of formaldehyde during ozonation (μg/L)

Reaction time (min)	O_3 (mg/ L):60			O_3 (mg/ L):20		
	pH 5.5	pH 7.4	pH 8.9	pH 5.5	pH 7.4	pH 8.9
0	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
2	-	26.3216	13.3932	0.8503	4.4714	0.0000
4	1.7210	23.9737	45.6762	1.1513	5.2855	22.4563
6	4.1354	35.0144	15.6504	0.7195	2.6676	28.6595
8	5.8213	13.2297	38.0985	1.3812	5.0204	10.4524
10	4.5711	14.6633	18.0805	1.3514	3.4705	13.6407
15	5.5413	8.8844	16.4069	0.8451	3.1186	9.8459
20	2.8441	12.7086	27.1302	0.3069	3.0377	11.6309
25	4.3049	8.6483	17.6056	0.4155	6.6997	11.6933
30	8.8344	13.8180	8.8658	0.6501	5.7713	20.2835
40	1.1674	17.6524	7.8360	0.4892	2.4473	14.1235
50	3.4099	17.7414	16.4271	0.5130	5.0860	21.3577
60	3.4453	6.9940	18.8207	1.3495	3.0258	17.6094