Decomposition of some pharmaceuticals by Advanced Oxidation Processes

Rita Katalin Szabó

Supervisors:
Dr. Krisztina Gajda Schrantz - University of Szeged
Prof. András Dombi - University of Szeged
Prof. Patrick Mazellier - University of Poitiers / University of Bordeaux
Prof. Bernard Legube - University of Poitiers

University of Szeged
Doctoral School of Environmental Sciences

Université de Poitiers
Ecole Doctorale Science pour l'Environnement Gay Lussac

Szeged
2010

To my family

Contents

Introduction **1**
1. Review of literature **2**
1.1. Pharmaceutical compounds **2**
1.1.1. Sources 3
1.1.2. Fate of the pharmaceuticals in the environment 3
1.2. Characteristics of the selected compounds **5**
1.2.1. Non Steroidal Anti Inflammatory Drugs (NSAIDs) 5
1.2.2. Pharmaco-chemical behaviour of the investigated compounds 6
1.2.3. Effect on human and animal health and living organisms 7
1.2.4. Occurrence and removal of the investigated pharmaceuticals 7
1.2.5. Toxicity of the investigated pharmaceuticals 11
1.3. Advanced Oxidation Processes **12**
1.3.1. Photochemistry 13
1.3.2. Fundamental parameters in the photochemical processes 14
1.3.3. VUV photolysis by Xe-excimer lamp 16
1.4. Degradation of the target compounds by Advanced Oxidation Processes (AOPs) **16**
1.4.1. Ibuprofen 17
1.4.2. Ketoprofen 17
1.4.3. Naproxen 18
2. Objectives **20**
3. Materials and Methods **21**
3.1. Materials **21**
3.2. Photochemical reactors and light sources **21**
3.2.1. UV and UV/VUV photolysis of the selected compounds 21
3.2.2. The VUV photolysis of the selected compounds by Xe-excimer lamp 24
3.3. Analytical methods **25**
3.3.1. High Performance Liquid Chromatography 25
3.3.2. Gas Chromatography 26
3.3.3. Total Organic Carbon (TOC) determination 26
3.3.4. Electron spin resonance (ESR) spectroscopy 26
4. Results and Discussion **27**
4.1. Determination of the photophysical properties of the investigated compounds **27**
4.1.1. Characterisation of the UV spectrum of the investigated compounds 27
4.1.2. Determination of the fluorescence quantum yield of the target compounds 28
4.2. Ultraviolet, ultraviolet/vacuum-ultraviolet and vacuum-ultraviolet photolysis of ibuprofen and ketoprofen, separately **28**
4.2.1. Decomposition of ibuprofen and ketoprofen by UV (254 nm) light 28
4.2.2. Decomposition of ibuprofen and ketoprofen by UV/VUV (254/185 nm) light 33
4.2.3. VUV (Xenon excimer, 172 nm) photolysis of ibuprofen and ketoprofen 37
4.3. Ultraviolet, ultraviolet/vacuum-ultraviolet and vacuum-ultraviolet photolysis of the mixture of ibuprofen and ketoprofen **39**
4.3.1. Photodecomposition by UV photolysis (254 nm) 40
4.3.2. Photodecomposition by UV/VUV (254 nm+185 nm) photolysis 44
4.3.3. VUV degradation of the mixture solution of ibuprofen and ketoprofen 47
4.4. Ultraviolet, ultraviolet/vacuum-ultraviolet and vacuum-ultraviolet photolysis of naproxen **49**
4.4.1. Decomposition of naproxen by UV (254 nm) light 49

4.4.2. Decomposition of naproxen by UV/VUV (254/185 nm) irradiation 52
4.4.3. VUV photolysis of naproxen..... 54
4.4.4. VUV degradation of the mixture solution of naproxen and ketoprofen..... 55
4.5. Photoproducts identification 56
4.5.1. By-products in the decomposition of ibuprofen and ketoprofen..... 56
4.5.2. By-products of naproxen decomposition 60
4.6. Distinction of photolytic and radical reaction pathways 61
4.6.1. The effect of methanol on the decomposition of ketoprofen 61
4.6.2. The effect of sodium azide on the photolytic decomposition 66
4.6.3. Detection of other radicals generated during the degradation of ketoprofen 67
4.6.4. The effect of methanol on the UV degradation of ibuprofen 68
4.6.5. Investigation of the effect of methanol on the UV and UV/VUV degradation of ibuprofen in the presence of ketoprofen..... 70
4.7. Mineralisation of the target compounds during UV, UV/VUV and VUV photolysis 71
4.7.1. Mineralization of ibuprofen and ketoprofen 71
4.7.2. Mineralization of naproxen 73
5. Summary 74
6. Résumé..... 78
7. Összefoglalás 82
8. References 86
List of publications..... 89
Acknowledgement 92

Introduction

During the last three decades the pollution of the aquatic environment has become an important issue. The attention of the society and researchers was focused almost exclusively on the conventional "priority" pollutants listed in the EU Water Framework. Beside these recognised pollutants however, numerous other chemicals are released into the environment with unforeseen consequences. This group, classified as so-called emerging contaminants, is mainly composed of products used in everyday life, such as surfactants, pharmaceuticals and personal care products, as well as gasoline additives, fire retardants, plasticizers etc. This work is focused on pharmaceuticals. Although some of them are not persistent, they can still cause negative effects to living organisms, due to their continuous introduction into the environment. Pharmaceuticals are released not only from production facilities and hospitals, but households as well, due to the improper disposal of the unused drugs. Since wastewater treatment plants are not able to remove most of them completely from wastewaters, they can reach surface waters. There are even some reports about their presence in drinking water. Although they are found in these waters in very low concentrations, in the lower ppb range, they can represent a risk to the non target organisms and even to humans, due to the long-term exposure. There are already reports on the mutagenic effects of some hormones and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in trace concentrations on fishes, causing dysfunction of the reproductive organs. In Europe, the three most often prescribed non steroidal anti-inflammatory drugs are ibuprofen, ketoprofen and naproxen. They are widely used as antipyretics and analgesics. In Hungary in the period between 2004 and 2008 the amount of ketoprofen sold has been increased by 45%, the quantity of naproxen by 30% and the sale of ibuprofen became almost 3 times higher. Due to the increase of their consumed quantity there is a high possibility that they are present in our waste and surface waters, too.

One group of the intensively studied procedures to remove the emerging contaminants and other organic pollutants from water are the Advanced Oxidation Processes (AOPs), mostly based on the generation of the hydroxyl radicals. OH-radicals are one of the most reactive and non selective species which can react very rapidly with almost every organic substances. Among others, these processes include direct ultraviolet photolysis, ultraviolet photolysis combined with vacuum-ultraviolet photolysis and vacuum-ultraviolet photolysis, which are available methods for removing contaminants from drinking water, without the addition of other reagents.

1. Review of literature

1.1. Pharmaceutical compounds

Until the 1990's, some specific contaminants were already in the focus of interest and awareness of the public and the government. These are aromatics, halogenated aromatics, polyaromatics, pesticides, organotin (IV) compounds, heavy metals (lead, mercury) and their derivatives. These contaminants are included in regulation 2455/2001/EC of the European Parliament.

However, in the last decades the release of the so-called emerging contaminants has become an environmental problem too. Legislations are available only for some specific pollutants [1]. This group mainly comprises products used in large quantities in everyday life, such as human and veterinary pharmaceuticals, personal care products, surfactants and surfactant residues, plasticizers and various industrial additives [1-6].

Table 1-1 shows the annual use of some anti-inflammatory drugs, antibiotics and hormones in some European countries.

Table 1-1 Annual consume of pharmaceuticals in some countries (the values are in tonnes)

Therapeutic class	Compounds	Denmark 1997/1998 (a, b)	United Kingdom 2000 (c)	Sweden 2002 (d)	Germany 1995 (e)	France 1998 (f)	Hungary 2008 (g)
Anti-inflammatory drugs	Acetylsalicylic acid	213	18			880.4	
	Ketoprofen			62			0.11
	Ibuprofen	34	162	68	105	166.5	38.5
	Naproxen		35	14		39	9.2
	Diclofenac		26	4	75		6.8
Antibiotics	Amoxicillin		71		127.5	438.2	
	Penicillin V				140		
	Erythromycin		26		19.8		
Hormones	Ethinyloestradiol		0.029	0.006			
	Estradiol	0.119					
	Oestradiol			0.153			

(a) [7], (b) [8], (c) [9], (d) [10], (e) [11], (f) [12], (g) [13].

Before the 90s, only a few studies on the environmental effects of pharmaceutical compounds were published. The interest on the presence of pharmaceuticals in the environment increased as the number of reports and reviews on the detectable concentrations of pharmaceuticals in authentic samples grew [14-24].

Pharmaceuticals can be divided into numerous therapeutic classes such as antibiotics, analgesics, anti-inflammatory drugs, anti-epileptics, beta-blockings, anti-depressing drugs, natural and synthetic hormones, lipid regulators *etc.* [25].

Pharmaceutical compounds were developed with the intention of performing a biological effect; therefore, most of them are bio-accumulative [26-29,] and can provoke unpredictable effects in the aquatic ecosystems [30].

Most xenobiotics, as pharmaceuticals, occur in the environment at very low concentrations, but can still have harmful effects on the living organisms [31] due to their bio-accumulative [32] properties. Therefore, their long-term effects have to be taken into consideration. As pharmaceuticals are present as a mixture in the waste and surface waters, synergistic or antagonistic effects can occur as well [33].

1.1.1. Sources

The pollution of the environment by pharmaceuticals originates from the improper discharge of the unused and expired medicines and from the effluents of Waste Water Treatment Plants (WWTPs).

Actually, pharmaceuticals are excreted without any structural change from human bodies [34-36] or in form of their metabolites. In case of veterinary use, the main difference is that pharmaceutical compounds can be directly discharged onto the soil and into waters [23, 31-37].

1.1.2. Fate of the pharmaceuticals in the environment

The behaviour of pharmaceutical compounds and their metabolites in the aquatic environment depends on the interaction with either the naturally present compounds (sediments, organic matters, microorganism *etc.*) or those added during the water treatment (active sludge, activated carbon, ion exchange resins, coagulants, disinfectants *etc.*).

The formation of complexes or precipitates increases the probability of elimination. The strong interaction with dissolved organic matter can increase their mobility in the environment. The physico-chemical (pH, salinity, oxygen content) and biological characteristics (microorganisms) of these compounds also have an important impact on the fate of the pharmaceuticals. Furthermore, the detectable concentrations in the environment depend on their pharmacokinetic behaviour (half life, metabolism *etc.*).

Certain pharmaceutics are slightly soluble in water; their partition (K_{ow}) and adsorption coefficient (K_{oc}) are high, showing that these compounds have a capacity for adsorption on solid particles and on organic matter. These properties permit their bioaccumulation [19-21, 23, 32, 33]. The relation between the bioaccumulation and the effect of these products means a threat to the proper functioning of aquatic ecosystems, as well as to the human health.

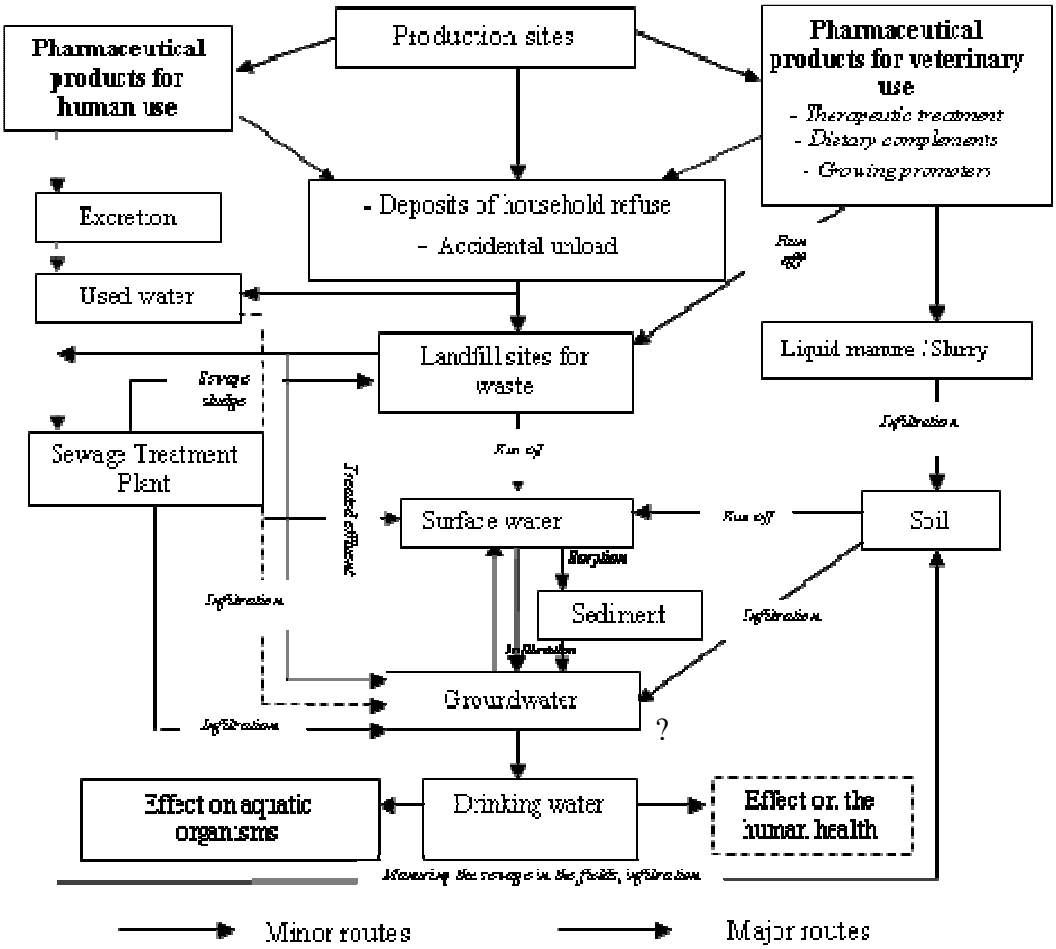


Figure 1-1 Possible introduction pathways of the human and veterinary use pharmaceuticals to the environment, from Halling-Sørensen [23]

Streaming and leaching are processes conditioning the introduction and distribution of pharmaceuticals and their degradation by-products.

Pharmaceutical substances can be metabolized in humans and animals, transformed in the environment and in wastewater treatment plants by different chemical (photolysis, hydrolysis *etc.*) and biological (mineralization, bio-transformation/degradation) mechanisms. In the environment certain compounds which can absorb the light in the UV-A ($\lambda > 315$ nm) or in the visible domain can undergo a solar induced transformation. The degradation rate can be increased by the presence of sensitizers [38, 39]. The total degradation corresponds to a

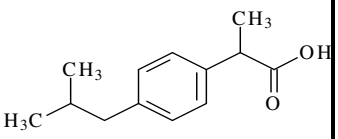
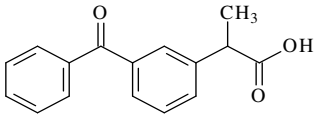
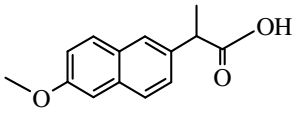
complete mineralization generating only carbon-monoxide, water and inorganic ions. However, in most of the cases the degradation is only partial, leading to the formation of by-products in function of the environmental conditions. Health and environmental impacts related to the presence of by-products, at low concentrations and in mixtures are still unknown [40].

1.2. Characteristics of the selected compounds

1.2.1. Non Steroidal Anti Inflammatory Drugs (NSAIDs)

Three NSAIDs were selected for this study: ibuprofen, ketoprofen and naproxen. Their structure and some physico-chemical characteristics are presented in **Table 1-2**.

Table 1-2 Some properties of the selected pharmaceutical compounds

Compound	Molar weight ($g.mol^{-1}$)	Water solubility (25 °C) ($mg.dm^{-3}$)	Log K_{ow}[c]	pK_a[c]	Henry constant[c] ($atm.m^3.mol^{-1}$)
Ibuprofen (IBU)  (S)-2-(p-isobutyl phenyl) propionic acid	206.28	21[a]	4.13-4.91	4.91	1.5×10^{-7}
Ketoprofen (KET)  (*S*)-2-(3-Benzoylphenyl) propionic acid	254.3	12.5[b]	3.12-3.16	4.45	2.12×10^{-11}
Naproxen (NAP)  (S)-(+)-6-Methoxy-α-methyl-2-naphthalene-acetic acid	230.27	15.9[a]	3.18-3.24	4.15	$3.39\ 10^{-10}$

[a][41], [b][42], [c][19].

1.2.2. Pharmaco-chemical behaviour of the investigated compounds

More than 3000 active molecules for human use and 300 for veterinary use are currently available on the European market. These are selected molecules, produced and employed for their biological effects, are characterized by a large diversity of chemical structures. They have been in use for a long time. In 1899 Hoffmann synthetized the acetyl-salicylic acid, which is known as Aspirin. Since then, several similar pharmaceutical compounds have been commercialized (ibuprofen, diclofenac, naproxen, ketoprofen *etc.*) and these products rule the huge part of the pharmaceutical market [43].

These substances are not steroid type compounds and their effect is not linked to the steroid hormone (glucocorticoid) receptors. They are used by humans as analgesics, antipyretics, anti-arthritics and anti-rheumatics, but are also present in the veterinary medicine as well [44].

The mechanism of action of the NSAIDs in the organisms is still a subject of debate. Meanwhile, the most probable hypothesis is the inhibition of the cyclo-oxygenase enzyme (COX), which is the main active enzyme during the biosynthesis of prostaglandins, responsible for pain manifestation and inflammation [45, 46]. Prostaglandins are also capable of inducing the contraction and atony of muscles with an effect on blood circulation and pressure. Some prostaglandins protect cells in the gastro-intestinal region (stomach, kidney, liver). The inhibition of these enzymes can lead to several secondary effects, such as bleeding (one of the most important negative effects of these compounds). Beside that, gastric ulcer and, mostly for older people, liver and kidney troubles can be induced by NSAIDs [47].

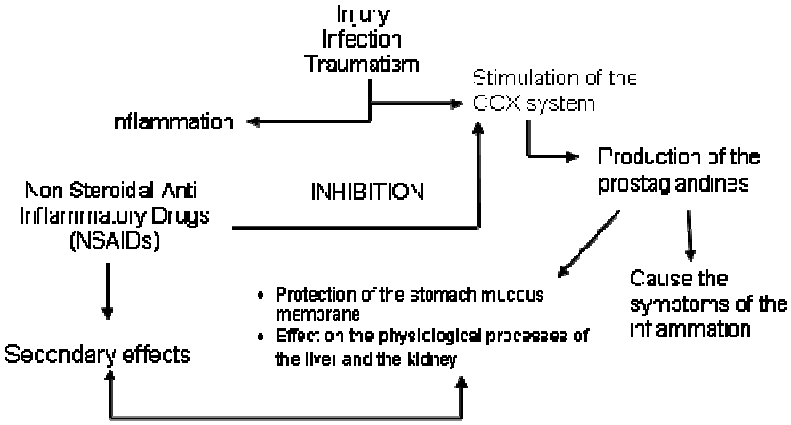


Figure 1-2. Schema of the functioning development of the NSAIDs

1.2.3. Effect on human and animal health and living organisms

To our knowledge only a few studies dealing with the effect of these pharmaceuticals on human and animal health have been published. They mainly investigate the effect on living organism with a special focus on acute and chronicle toxicological test with low-grade organisms such as algae, daphnia and bacteria [41, 48]. According to the results these compounds can have negative effects in the environment even in low concentrations [7-14, 16, 27].

1.2.4. Occurrence and removal of the investigated pharmaceuticals

Due to the widespread and high concentration use of the NSAIDs, their occurrence in waters is an important issue in the field of environmental sciences. A lot of researchers investigate the presence of pharmaceuticals in rivers, groundwater, WWTP effluents and also the performances of several treatment processes for their elimination.

Huber [49] reported some hundred nanogramm active component content in the investigated rivers.

Table 1-3 The average (and in the brackets the maximal) concentration of some pharmaceutical compounds in German Sewage Treatment Plants (STPs) influent, effluent and in rivers as well as the removal efficiencies [49]

Compound	Influent (µg/ dm^3)	Effluent (µg/ dm^3)	Removal (%)	Rivers (µg/ dm^3)
Bezafibrate	4.9 (7.5)	2.2 (4.6)	55.1 (39)	0.35 (3.1)
Carbamazepine	2.2 (3.0)	2.1 (6.3)	4.5 (-)	0.25 (1.1)
Diclofenac	3.5 (28.0)	0.81 (2.1)	76.9 (92.5)	0.15 (1.2)
Ibuprofen	5.0 (14.0)	0.37 (3.4)	92.6 (76)	0.07 (0.53)
Iopromide	13.0 (22.0)	0.75 (11.0)	94.2 (50)	0.01 (0.91)

As it can be seen, the selected pharmaceuticals are only partly eliminated by STPs (they are still present in the effluent). It demonstrates that classical sewage treatment processes are not suitable for the total elimination of these compounds [50].

Due to their polar structure, some pharmaceuticals are only very slightly adsorbed in the subsoil and they can migrate into the groundwater and from there to the surface water [50].

Kosjec *at al.* [51] investigated nine tap waters, two wells and sixteen rivers in Slovenia. Naproxen, ketoprofen, ibuprofen, diclofenac have not been detected in the tap waters and wells while 11 out of 16 river samples contained naproxen (17–80 ng dm^{-3}) and diclofenac

(9–49 ng dm^{-3}). One sample taken from the river downstream of a pharmaceutical factory showed a concentration approximately four to five times higher than the rest of the tested compounds: naproxen: 313 ng dm^{-3} and diclofenac: 282 ng dm^{-3}. Ketoprofen have been also detected but was under the limit of quantification.

A Finnish research group [52] investigated the five most frequent pharmaceutical compounds in the Finnish pharmaceutical industry (ibuprofen, naproxen, ketoprofen, diclofenac and bezafibrate). Due to their results the concentrations of the investigated compounds are significant only near the STPs, 3.5-64 ng dm^{-3}. A few kilometres from the factory they are under the limit of detection, so the Authors do not consider these substances as environmentally harmful.

Table 1-4 The removal rates by the investigated Finnish STPs [52]

Compound	Influent(µg/ dm^3)	Effluent (µg/ dm^3)	Removal rates (%)
Ibuprofen	13.1	1.3	92
Naproxen	4.9	0.84	83
Ketoprofen	2	0.45	78
Diclofenac	0.35	0.26	26
Bezafibrate	0.42	0.21	50

In the classical activated sludge process, microbiological treatment takes place. In case of pharmaceutical compounds, this process is not effective enough. These compounds are relatively polar, and have small volatility. The elimination of the pharmaceuticals with medium or high polarity by these techniques is not complete and is around 60-90% [43].

Jones *et al.* [36] showed that in certain cases these active sludge techniques can work with a good elimination rate. Depending on the process and the substance the 80-95% of the contaminants can be eliminated in 40 days.

There are an increasing number of compounds that cannot be eliminated by classical methods. Therefore, beside the classical sewage treatment processes, the development of new modern techniques is important and their use is necessary. NSAIDs are partially-or non-biodegradable. During the treatment of the sewage water other compounds harmful to health and environment can be generated. For example, the chlorination of waters is known as an imperishable method for disinfection. Nowadays it is known also that during the chlorination chlorinated hydrocarbons can be generated, which are mutagenic and responsible for the

emergence of different types of cancer. The pharmaceutical compounds can serve as the basis for chlorinated hydrocarbons [53].

1.2.4.1. Ibuprofen

Although only the S enantiomer has a pharmacological effect, a racemic mixture is used commercially. It has been shown that the inactive R(-)-ibuprofen is transformed into the active S(+) enantiomer through a chiral inversion, after absorption. The major metabolites of ibuprofen are hydroxyl-ibuprofen (2-(4-hydroxyl-2-methylpropyl) phenyl) propionic acid), carboxy-ibuprofen (3-(4-(1-carboxyethyl) phenyl)-2-methyl-propionic acid) and carboxy-hidratropic acid (4-(1-carboxyethyl) benzoic acid) as described in **Figure 1-3**.

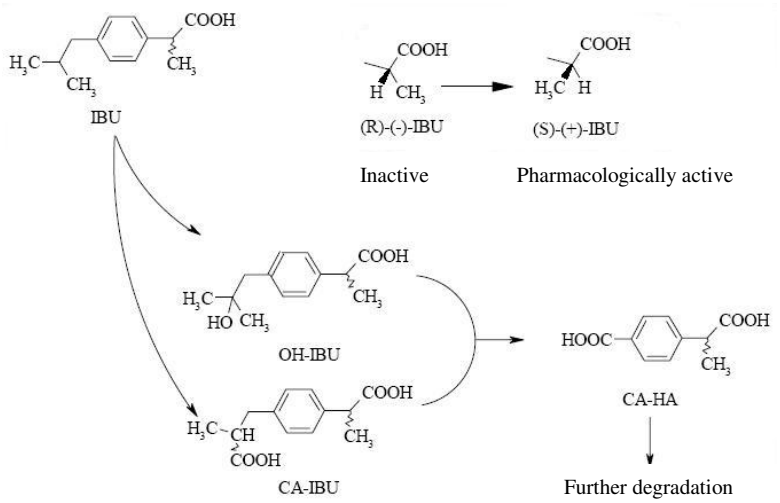


Figure 1-3. The ibuprofen and its human metabolites [45]

Ibuprofen has different kinetics of transformation within different conditions. Main transformations occurred during the biological treatment of the active sludge. Several metabolites of ibuprofen were determined and the carboxy-ibuprofen was quantified. However, at the influent and effluent of few wastewater treatment plants, hydroxy-ibuprofen was detected as the main component related to iburpofen. Therefore, it can be concluded that from the three identified degradation products, hydroxy-ibuprofen may be the most stable. Moreover, the authors also observed that hydroxy-ibuprofen was formed in the activated sludge in aerobic conditions whereas carboxy-hidratropic acid was formed under anaerobic conditions. These products never exceed the 10% of the initial concentration of ibuprofen [45].

Carballa *et al.* investigated the processes of coagulation and flocculation for the removal of ibuprofen and naproxen and they ascertained that the maximal elimination was 50-75% [37].

Several studies investigate the occurrence of ibuprofen in the Sewage Treatement Plants (STPs). The detected values are in ng dm^{-3} and µg dm^{-3} range depending on the STP [47, 52-55]. For example, in an STP near Frankfurt am Main (Germany), Ternes *et al.* determined an elimination efficiency of about 90% in the effluent containing 0.37 µg dm^{-3} of ibuprofen [56]. In another study, Brun *et al.* [57] investigated several STPs in two seasons. The measured concentrations of ibuprofen were very different: for example in summer the value was in the range of 2.2-690 ng dm^{-3} depending on the STP [57]. Rosal *et al.* investigated the elimination of several pollutants including the investigated pharmaceuticals by biodegradation followed with ozonation. In the case of ibuprofen the elimination efficiency was 95% [58].

1.2.4.2. Ketoprofen

The human metabolites of ketoprofen (racemic mixture) identified in urine are the 2-[3-(3-hydroxybenzoyl) phenyl]-propionic acid, 2-[3-(4-hydroxibenzoyl) phenyl]-propionic acid and 2-[3-(hydroxy (phenyl) methyl) phenyl]-propionic acid, which is formed later by the reduction of the ketone group of ketoprofen. More recently, two new metabolites have also been identified as the ether of the 2-[3-(3-hidroxibenzoil) phenyl]-propionic acid and the 2-[3-(4-hydroxybenzoyl) phenyl]-propionic acid [59].

Further, Brun *et al.* have detected concentrations ranging between 15 and 310 ng dm^{-3} in summer and 15 and 170 ng dm^{-3} in spring [57] in some STPs in Atlantic Canada. According to a Sweden study, in the Källby STP the ketoprofen content in the influent was 0.94 µg dm^{-3} and the removal efficiency was 65% [54].

The presence of ketoprofen in the STP has been determined by Rosal *et al.* The elimination efficiency was 11.2% with biodegradation and almost 100% after 15 minute ozonation [58]. Fernández *et al.* also investigated the presence of ketoprofen in the same environment as ibuprofen. The measured values were in the range of 0.3-991 ng dm^{-3} [60].

1.2.4.3. Naproxen

Naproxen is frequently detected in the aquatic environment at different concentration levels. Several studies investigated the possible ways of elimination of naproxen in Sewage Treatment Plants. The elimination rates were between 15 and 93% [36, 50 and 53].

The maximal naproxen content in the effluent of certain STPs was between 0.25 µg dm^{-3} and 5.22 µg dm^{-3} [45, 47, 52 and 60]. In the rivers and streams its concentration was around 0.39 µg dm^{-3} [9]. Boyd *et al.* detected 1.6 – 145 ng dm^{-3} naproxen concentration in the rain water collecting system of New Orleans [61]. Two Spanish research groups (already mentioned) investigated several pollutants in different Spanish STPs and in the Henares-Jarama-Tajo river [58, 60]. Concerning the naproxen the STP elimination rate was 60.9 % with biodegradation and 100% after 2 minutes ozonation and its presence in the investigated river was in the range of 1.8-640.4 ng dm^{-3} [60].

1.2.5. Toxicity of the investigated pharmaceuticals

Nowadays huge amount of pharmaceuticals is consumed. Due to their improper disposal and their low or non-biodegradability they can be present in the environment in their initial form or as in their metabolites. Due to their characteristics, the toxicity of the pharmaceutical compounds has been awakening the interest of several research groups.

1.2.5.1. Toxicity of ibuprofen and ketoprofen

Brun *et al.* investigated the pharmaceutical content of the STPs flowing to the Atlantic Ocean and stated that the concentrations of these compounds are in a very wide range. The naproxen, ibuprofen, salicylic acid etc. occurred in larger concentrations, while ketoprofen and other compounds had less environmental load. The toxicological impact of these pharmaceuticals with respect to Daphnia (*Daphnia magna, Ceriodaphnia dubio*), bacteria (*Vibrio fischeri*) and green algae (Selanastrum capricornutum) has been investigated. Toxicological impact occurred for all cases, with the most significant impact observed in the growth of the algae in the case of ibuprofen with the value of 10 µg dm^{-3} as No Observed Effect Concentration (NOEC) and 32 µg dm^{-3} as Lowest Observed Effect Concentration (LOEC) [57].

The ecotoxicity of the most common analgesics (acetylsalicylic acid, diclofenac, ibuprofen, naproxen) was also investigated using Daphnia and algal tests. Their toxicity was found to be relatively small. The median of the effective concentration (EC_{50}) causing immobilization for daphnids was between 68-166 mg dm^{-3} and for algae 72-626 mg dm^{-3}. Since the LOEC can rise to approximately 10 000 – 100 000 times of the value present in nature, it was concluded that no acute toxical effects are expected for these compounds [33].

1.2.5.2. Toxicity of naproxen

In the study carried out between 1995 and 1998 in Sweden, Ericson and Källen [62] observed the occurrence of congenital malformations and cardiovascular diseases in children whose mothers used anti-inflammatory drugs, including naproxen, during the first trimester of their pregnancies. Some NSAIDs may act as a photosensitizers when the patient was exposed to sunlight. Thus, in vitro photolysis (irradiation between 310 and 390 nm) showed that light excitation of naproxen leads to the formation of free radicals, solvated electrons, excited triplet forms of naproxen and reactive oxygen species, including singlet oxygen ($^1O_2$) and superoxide anion radical ($O_2^{\bullet -}$), which will react with cells' lipid components leading to their degradation [63, 64].

La Farré et al. performed toxicology tests by inhibition of bioluminescence of bacteria (Vibrio fischeri). The EC_{50} values of naproxen were respectively 21.2 µg dm^{-3} from the test ToxAlert and 35.6 µg dm^{-3} with the Microtox test [65]. Cleuvers also demonstrated the synergistic effect of an adverse mixture of naproxen with other NSAIDs (ibuprofen and acetylsalicylic acid) on algal growth and immobilization of Daphnia. The toxicity of the mixture was proportional to the sum of the concentration of each compound. Although used at higher concentrations than that which can be found in the aquatic environment, these results demonstrated the harmful effect of the investigated compounds. However, it can be assumed that prolonged exposure to levels appropriate to the environment would lead to weakening of the general state of health of aquatic organisms [33].

1.3. Advanced Oxidation Processes

Advanced Oxidation Processes are based on the generation of very reactive radicals, such as hydroxyl radicals, which are able to react with most organic and inorganic compounds and initiate their degradation. Pollutants and their by-products are therefore degraded during complex processes. In the first step, hydroxyl radicals react with organic compounds either by H abstraction, double bond addition, or electron transfer, leading to the formation of organic radicals. These latter species react with dissolved oxygen to form peroxyl radicals or later peroxide radicals which undergo to rapid decomposition. The overall process leads to a partial or total mineralization of organic pollutants. Radicals can be generated by [53, 66, 67]:

- Ultraviolet (UV) photolysis and the combination of UV with vacuum-ultraviolet (UV/VUV) photolysis

- Excimer VUV photolysis (ex. Xenon)
- Combination of UV irradiation and hydrogen peroxide (H_2O_2)
- Use of ozone (O_3)
- Combination of UV irradiation and O_3
- Combination of UV irradiation, H_2O_2 and O_3
- Fenton reaction (Fe ions, H_2O_2) and the photo-Fenton reaction
- Heterogeneous photocatalysis

In this work UV, UV/VUV and VUV photolysis methods were used.

1.3.1. Photochemistry

The general term of photochemistry is used to describe the chemical reactions induced by the absorption of photons (characterised by their energy or equivallent wavelength). Electronic, vibrational and rotational energy states of the molecule can be excited by the energy of the absorbed photon. The molecule in excited state can relax by several different ways [68], such as ionisation and light emission (fluorescence, phosphorescence). Due to the nature of the singlet-triplet transition the lifetime of the triplet excited state (10^{-7}-10^{2} s) can exceed the lifetime of the excited singlet state (10^{-12}-10^{-6} s) with several orders of magnitude [68]. During this lifetime, photosensitizing reactions [69-73] may occur.

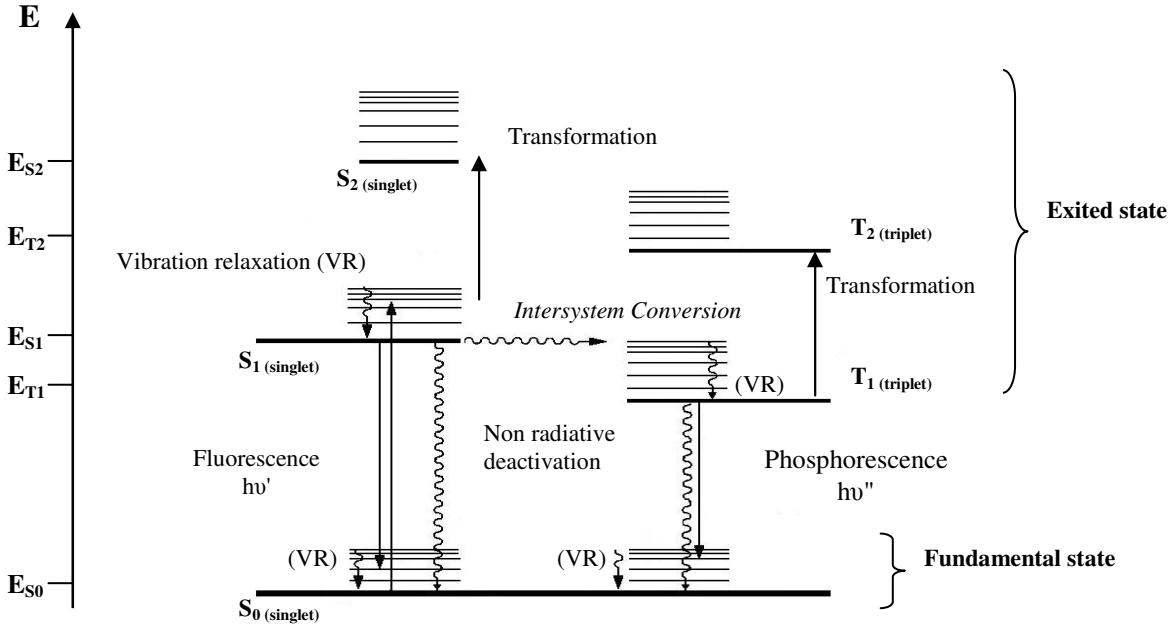


Figure 1-4. Jablonski scheme [74]

Most of the excited molecules lose their energy in non radiative processes, when the molecule transfers its energy to the vibrating, rotating, advancing movements of the molecules in its environment. The different modes of deactivation are summarized in the classical Jablonski scheme (**Figure 1-4**) [74].

Direct phototransformation is a process in which a compound reaches an unstable excited electronic state after absorbing a photon with sufficient energy. This phenomenon will partly lead to the degradation of the compound and to the formation of the by-products. The efficiency of this reaction in natural aquatic ecosystems is dependent on the rate of sunlight intensity absorption [75].

The indirect or sensitized phototransformation, occurs when the light is absorbed by another compound able to produce reactive radicals or to transfer the energy to the target molecule, generating in this way its degradation. Among these methods we can cite the techniques based on the activation of ozone [76-80] and/or hydrogen peroxide [76-86] by ultraviolet radiation. In natural aquatic environments, the sensitized photodegradation can involve various intermediate substances such as natural organic matter (humic acids, fulvic acids) [87-92] and some inorganic compounds such as NO^{2-}, $NO^{3-}$and Fe^{3+} ions [93-95]. They can transmit the energy received at the pollutant that will turn into an excited state and will be able to evolve to its chemical transformation. In addition, they can also undergo photolysis reactions and generate aqueous electrons (e^{-}_{aq}) or other reactive oxygen species ($^{1}O_2$, •OH, HO_2•, O_2•$^{-}$, ROO•, CO_3•$^{-}$ *etc.*) which will react with the organic pollutant.

1.3.2. Fundamental parameters in the photochemical processes

1.3.2.1. Photon flux

When the system receives irradiation, the incident flux (I_0) is absorbed (I_a), reflected (I_r) or transmitted (I):

$$I_o = I_a + I_r + I \qquad \text{eq. 1-1}$$

The ratio of the absorbed flux and the incident flux is called the absorption factor (α):

$$\alpha = \frac{I_a}{I_o} = 1 - 10^{A_\lambda} \qquad \text{eq. 1-2}$$

with A_λ: optical density at wavelength λ.

The radiation intensity of the lamp is measured by actinometry (eg. with hydrogen peroxide, potassium ferrioxalate, uranyl oxalate *etc.*)

1.3.2.2. Quantum yield

The efficiency of a photochemical reaction is determined by the quantum yield (ϕ). It is defined as the ratio of the transformed molecules (Δn) and the absorbed photons (N_a) during an irradiation time *t* at the wavelength of irradiation (λ_{exc}).

$$\phi = \frac{\Delta n}{N_a} \qquad \text{eq. 1-3}$$

1.3.2.3. Kinetic equations of photolysis

The rigorous determination of the quantum yield requires working in controlled conditions. If we consider the case of a simple monochromatic photochemical transformation C → D where C is the only substance that absorbs, the rate of photolysis of C may be related to the photon flux absorbed by the solution and the quantum yield [74, 96]:

$$-\frac{\mathrm{d}[C]}{\mathrm{dt}} = \phi I_a = \phi I_o (1 - 10^{A_\lambda}) \qquad \text{eq. 1-4}$$

Depending on the value of the optical density, this equation leads to different relationships shown in **Table 1-5**.

Table 1-5 Expression of kinetic equations of monochromatic photolysis (equations 1-5 – 1-10)

Conditions	Kinetical expressions	Integrated forms
General case	$-\frac{\mathrm{d}[C]}{\mathrm{dt}} = \phi I_o (1 - e^{-2,3A})$	$\ln(10^A - 1) = \ln(10^{A_o} - 1) - 2,3\varepsilon\ell\phi I_o \mathrm{t}$
A > 2 *complete absorption*	$-\frac{d[\mathrm{C}]}{dt} = \phi \mathrm{I_o}$	$[\mathrm{C}]_o - [\mathrm{C}] = \phi \mathrm{I_o} t$
A < 0,02 *low absorption*	$-\frac{\mathrm{d[C]}}{dt} = \phi \mathrm{I_o}(2,3\varepsilon\ell[\mathrm{C}])$	$\ln\frac{[C]}{[C]_o} = -2,303\varepsilon\ell\phi I_o \mathrm{t}$

1.3.3. VUV photolysis by Xe-excimer lamp

Xenon is an inert gas which can be excited with an alternating voltage (eq. 1-11). This atom can interact with another xenon atom and build an *exci*ted dim*mer* (*excimer*, eq. 1-12). These are extremely short-lived and energy-rich molecules, emitting 172 nm radiation during their decomposition (eq. 1-13) [67].

$$Xe^0 \xrightarrow{excitation} Xe^* \qquad \text{eq. 1-11}$$
$$Xe^0 + Xe^* \xrightarrow{interaction} (Xe....Xe)^* \qquad \text{eq. 1-12}$$
$$(Xe....Xe)^* \xrightarrow{decay} 2Xe^0 + h\upsilon \text{ (172 nm)} \qquad \text{eq. 1-13}$$

The advantage of the xenon excimer lamp is that no additional additive (e.g. hydrogen peroxide or ozone) have to be used to generate reactive radicals. Beside the hydroxide radicals, H• and hydrated electrons (e^-_{aq}) can be formed directly from water [97].

$$H_2O + h\nu \rightarrow \bullet OH + H\bullet \qquad \phi(\bullet OH)_{\lambda=185nm} = 0{,}33 \qquad \text{eq. 1-14}$$
$$H_2O + h\nu \rightarrow \bullet OH + H^+ + e^-_{aq} \qquad \phi(e^-_{aq})_{\lambda=185nm} = 0{,}045 \qquad \text{eq. 1-15}$$

The quantum yield of the OH-radical formation and the molar absorbance of the water in the VUV range ($\varepsilon_{\lambda=172\ nm} \approx 10.8\ dm^3\ mol^{-1}\ cm^{-1}$ [98]) provide high local concentration of the •OH and H• ([•OH]> 10^{-4} mol dm^{-3} [99]) in a very thin layer [100] of the irradiated solution (l ≈ 0.04 cm). The formed primary radicals can recombine or react with organic substances in the solution.

1.4. Degradation of the target compounds by Advanced Oxidation Processes (AOPs)

As previously presented the classical water treatment processes are not efficient enough to eliminate the investigated compounds from the waste water. Many research groups investigate the possibilities of using Advanced Oxidation Processes [43, 101-106] to supplement the classical treatments.

The photolysis of the selected pharmaceuticals has been investigated by several research groups [25]. Petrović *et al.* investigated Waste Water Treatment Plants for the elimination of the most common anti-inflammatory drugs (ibuprofen, diclofenac, ketoprofen, naproxen, bezafibrate). They observed elimination efficiencies ranging between 35% and 90%,

depending on the compound [2]. Ternes also proposed Advanced Oxidation Processes for the removal of pharmaceutical compounds. Water samples were treated with ozone/UV process with 10-15 mg dm^{-3} ozone and up to 18 minutes of reaction time. These experimental conditions led to a complete degradation of the investigated compounds [107].

1.4.1. Ibuprofen

The UV and UV/H_2O_2 photolysis of ibuprofen and other three pharmaceutically active compounds (PhACs: diphenhydramine, phenazone and phenytoin) have already been investigated. The quantum yield of the UV photolysis and the second order rate of the UV/H_2O_2 photolysis of ibuprofen were determined. The obtained values are $\phi = 0.1923$ mol e^{-1} and $k_{OH/PhAC} = 6.67\times10^9$ mol^{-1} dm^3 s^{-1} respectively [108]. In the same study generation of the intermediates was monitored during the photodegradation of the compounds in the UV/H_2O_2 process. For all the selected compounds, most of the intermediates were hydroxylation products, mainly including benzoic acid, 1,4-benzenedicarboxylic acid, *m*-hydroxybenzoic acid, *para*-hydroxybenzoic acid and some aliphatic acids. The results also verified that OH-radicals were the main reactive species in the reaction.

Huber *et al.* investigated the degradation of ibuprofen by different AOP techniques (O_3, UV/H_2O_2 and O_3/H_2O_2). The rate constants for ozonation and UV/H_2O_2 processes were 9.6 mol^{-1} dm^3 s^{-1} and 7.4×10^9 mol^{-1} dm^3 s^{-1} respectively. For the O_3/H_2O_2 there was not data. However, they showed that in case of classical ozonation the elimination efficiency was between 41-77% depending on the investigated type of water, while the elimination rates with O_3/H_2O_2 process were between 80-90% for the same water [109].

1.4.2. Ketoprofen

Kim and Tanaka demonstrated that the degradation of ketoprofen was 90% in ten minutes of irradiation both at 254 nm (UV intensity: 0.384 mW/cm^2) and 254/185 nm (UV intensity: 0.388 mW/cm^2) in pure water [104]. Kim *et al.* investigated the degradation of ketoprofen by UV and UV/H_2O_2, the removal for these processes were 90 and 100% respectively using 1.6 and 1.9 minute of irradiation with 38 and 45 mJ cm^{-2} UV dose, respectively [103].

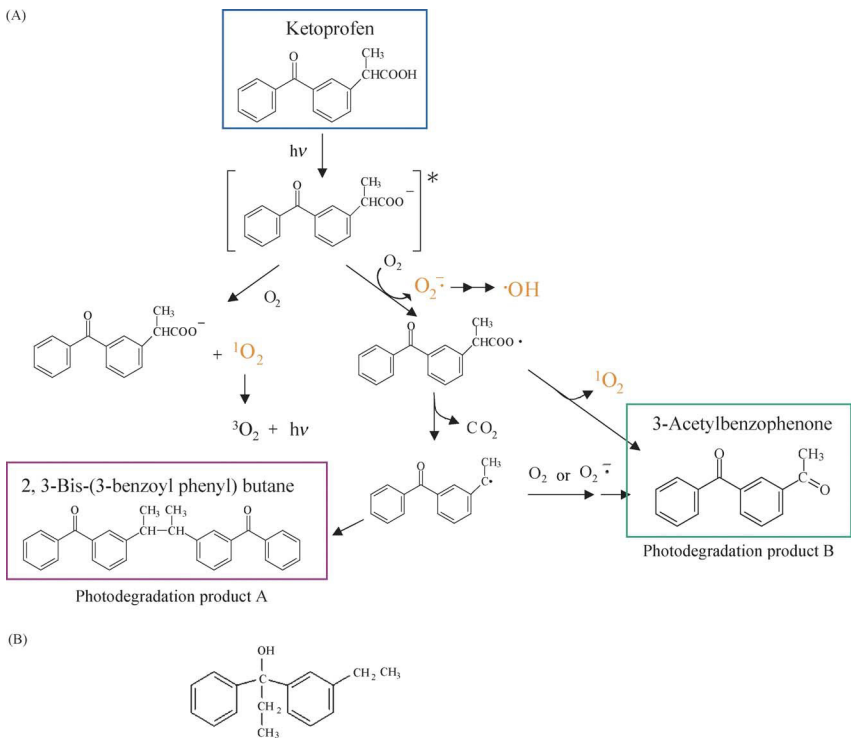


Figure 1-5 Estimated photodegradation pathway of ketoprofen (A); estimated chemical structure of photodegradation product C (B) [110]

The photodegradation of ketoprofen by Advanced Oxidation Processes (AOPs) was investigated also by Ayako Nakajima *et al*. Irradiation were carried out by Fluorescence and UV lamps, but a significant change and effective degradation were reached only by the UV lamp irradiating at 254 nm. The degradation was very fast, it lasted for 60 seconds and three by-products were generated, from which two were identified with H^1-NMR spectroscopy as 2,3-bis-(3-benzophenyl) butane and 3-acetylbenzophenone. The third by-product could not be isolated, but it can be either a lower molecular weight degradation by-product or the recombination product of the two identified products (**Figure 1-5**) [110].

1.4.3. Naproxen

The UV (254 nm; UV intensity: 0.384 mW/cm^2) and UV/VUV (254/185 nm; UV intensity: 0.388 mW/cm^2) photolysis of naproxen was also investigated by Kim and Tanaka [104]. They observed that the removal of naproxen in ten minutes was around 30 and 50%, respectively. From the AOP techniques Kim *et al.*[103] investigated the UV and UV/H_2O_2 for the degradation of naproxen in the case of the irradiation by 254 nm light the removal efficiency was 20%, meanwhile by UV/H_2O_2 it was 100%. The phototransformation of naproxen was investigated also by Boscá *et al.* and Jimenez *et al.* [111, 112]. They found that

the photodegradation of naproxen led to the formation of three major products as shown in **Figure 1-6** [111, 112].

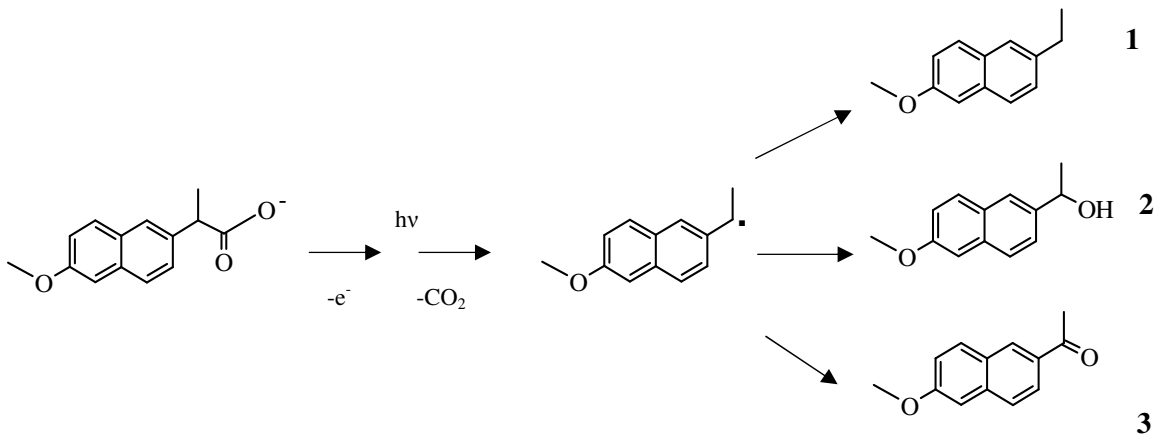


Figure 1-6 Reaction of the phototransformation of naproxen [111, 112]

The first step of this reaction is the conversion of the carboxylate group ($RC(=O)O^-$) to carboxyl radical (RC(=O)O•) by photoionization followed by decarboxylation ($-CO_2$). The radical thus formed will be hydrogenated to give the product **1** (1-ethyl-6-methoxynaphthalene) or react with molecular oxygen leading to the formation of alcohol **2** (6-methoxy-2-1-ol-naphylethan) or of ketone **3** (2-acetyl-6-methoxynaphthalene). In aerobic conditions, the major products are **2** and **3** while in anaerobic media **1** and **2** have higher concentrations.

2. Objectives

In recent years the interest about the occurrence of pharmaceuticals in the aquatic environment has been growing. After their use, the non-metabolized products are transferred into sewage treatments plants (STPs). Studies show that most of the classical wastewater treatment processes are not efficient enough for the elimination of these pharmaceuticals because of their low biodegradability, therefore, these compounds are present in STP effluents which are released in surface waters. There are several studies about the elimination mechanisms of these compounds. Beside the traditional techniques, oxidation processes may bring a solution for the complete elimination of these emerging pollutants.

The goal of this work was the investigation of the degradation of three Non Steroidal Anti-Inflammatory Drugs (NSAIDs): ibuprofen, ketoprofen and naproxen. UV photolysis, UV/VUV photolysis and VUV photolysis were applied as elimination processes. The efficiency of these processes was also compared. The same experimental setup and low-pressure mercury vapour light sources with identical geometrical and electrical parameters were used in the case of UV and UV/VUV photolysis. In case of the VUV photolysis Xe-excimer lamp was used with the same output as the previous lamps, therefore, the comparison of the methods was accurate.

Further objectives were the determination of the kinetical parameters of these photodegradations, as well as the identification of the formed photoproducts. To get information about the mechanism of the degradation of these compounds different types of radical scavengers were used and the influence of dissolved molecular oxygen was investigated.

The photosensitising characteristics of benzophenone type compounds, such as ketoprofen, are well known on living organisms (e.g. skin diseases). It has not been investigated jet wether this effect influences in some way the degradation of non-biological systems (pharmaceutical compounds). In this work our aim was to examine the antagonistic or synergistic effect of the investigated compounds on the photodegradation of each other.

3. Materials and Methods

3.1. Materials

Ibuprofen ((S)-2-(p-isobutylphenyl) propionic acid) was purchased from Fluka (puriss > 99,0 %; CAS: 51146-56-6), ketoprofen ((S, R)-2-(p-isobutylphenyl) propionic acid) from Sigma Aldrich (purum ≥98 %, CAS: 22071-15-4) and naproxen ((S)-2-(6-methoxy-2-napthyl)-propionic acid) from Fluka (purum 98%; CAS: 22204-53-1). Sodium phosphate, monohydrate and disodium phosphate, heptahydrate were purchased from Sigma Aldrich.

For the HPLC measurements, acetic acid, methanol and acetonitrile (Scharlau) were used for the preparation of the eluent. Purified water was obtained from MILLIPORE Synergy185 (resistivity: 18 MΩ cm^{-1}).

As hydroxyl radical scavenger methanol (HPLC grade) was applied from Scharlau, for scavenging other oxygen centred radicals sodium azide (Aldrich) was used.

For the ESR spectroscopic measurements as radical scavenger 5,5'-dimethyl-1-pyrrolin-N-oxyde (DMPO) from Aldrich was used.

3.2. Photochemical reactors and light sources

3.2.1. UV and UV/VUV photolysis of the selected compounds

Low-pressure mercury vapour lamps can be used as light sources in water treatment technologies for the disinfection of drinking water [53]. The emission spectrum of the low-pressure mercury lamps is very narrow in the UV range at the wavelength of 254 nm and VUV range at 185 nm (**Figure 3-1**). Special high purity quartz (Suprasil quartz) sleeve must be used to ensure that the 185 nm radiation passes through the wall of the lamp.

During the UV photolysis of ibuprofen, ketoprofen and naproxen two types of reactors and lamps were used.

For the experiments performed in Hungary low pressure mercury vapour lamps from LightTech were used. A low pressure mercury vapour lamp was used for the UV photolysis experiments (GCL307T5/CELL, further called UV lamp) with a normal quartz sleeve transmitting the UV light over 200 nm. For UV/VUV experiments a second low pressure

mercury lamp was used (GCL307T5VH/CELL, further called UV/VUV lamp) with a high purity quartz sleeve.

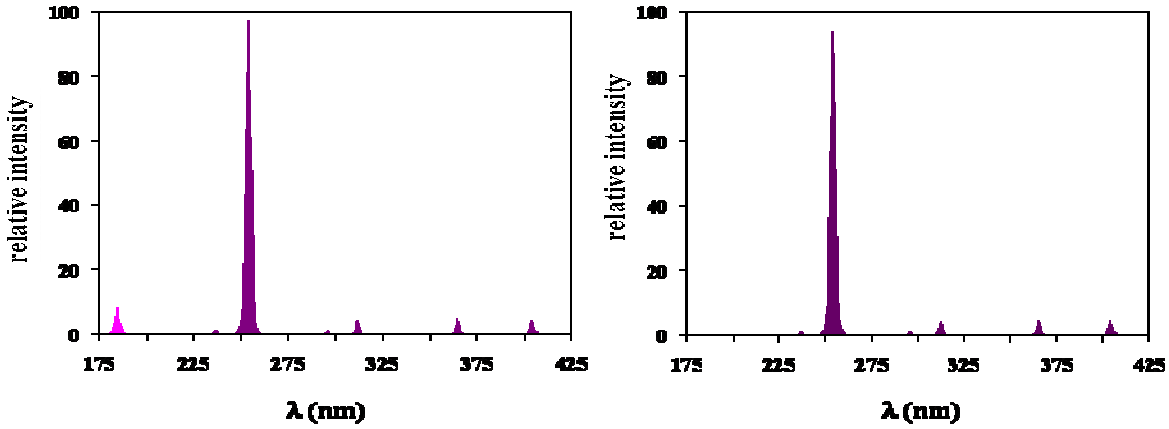


Figure 3-1 Emission spectra of the applied UV/VUV and UV lamps

The geometrical and electrical parameters of these lamps were identical. Their inner diameter was 20.5 mm, their length was 307 mm and their electrical input power was 15 W. To determine the UV light intensity (I_0) emitted by these light sources, iron-oxalate actinometry was used [113]. The basis of the method is that Fe^{3+} ions, in form of $K_3[Fe(C_2O_4)_3]$ complex are photochemically transformed into Fe^{2+} ions. The Fe^{2+} ions form an intense red complex with the 1,10-phenantroline. The concentration of the formed Fe(II) ion can be calculated by the absorption of the phenantroline complex. The light intensity determined by this actinometric process is 3.45 (± 0.09) × 10^{-5} einstein s^{-1}. The light emitted at 185 nm was evaluated by taking into account that 6% of the 254 nm light intensity was emitted at 185 nm (manufacturer data).

The experiments carried out in a system where the irradiated mixture was recirculated (**Figure 3-2**). The low pressure mercury lamp (3) was centred in the water-cooled, double-walled tubular glass reactor (4) (length 340 mm, inner diameter 30 mm) and 220 cm^3 aqueous solution was circulated (375 cm^3 min^{-1}) continuously around the lamp, which was immersed directly in the solution. The irradiated solution (pH = 7.4, regulated by phosphate buffer) was thermostated at 25 °C. During the experiments oxygen or nitrogen gas was bubbled (855 cm^3 min^{-1}) through the solution in the thermostated reservoir (6) and the solution was continuously stirred with a magnetic stirrer bar (7). Prior to each measurement, the gas was bubbled through the investigated solution at least for 10 minutes and the kinetic measurements were started by switching on the lamp.

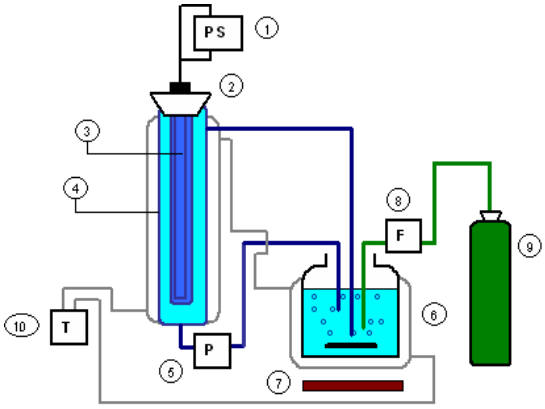


Figure 3-2 The applied apparatus for the Hungarian research work
(1) power supply; (2) Teflon packing ring; (3) UV or UV/VUV lamp; (4) reactor; (5) pump; (6) reservoir; (7) magnetic stirrer; (8) flow meter; (9) oxygen or nitrogen cylinder; (10) thermostat

The experiments in the French laboratory were carried out in a cylindrical (water-cooled, double-walled glass) batch reactor, using the same pH and temperature parameters as above. The inner diameter of the reactor was 610 mm (5000 cm^3 volume). In these cases the lamp (3) was switched on 30 minutes before the beginning of the measurements and it was immersed into the solution manually. Parallel with the heating up of the lamp, oxygen or nitrogen was bubbled through the solution.

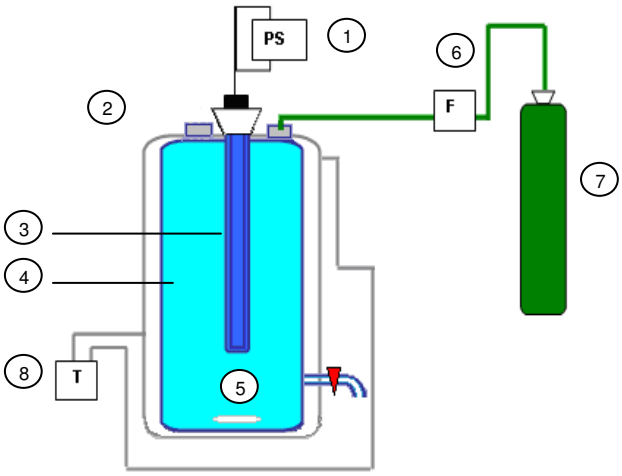
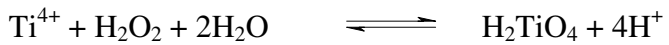


Figure 3-3 The applied apparatus for the French research work
(1) power supply; (2) Teflon packing ring; (3) UV lamp; (4) reactor; (5) magnetic stirrer; (6) flow meter; (7) oxygen or nitrogen cylinder; (8) thermostat

The experiments in the batch reactor were carried out with a low-pressure mercury vapour lamp Heraeus NN 40/20. The photon flux of this lamp ($I_0 = 8.3\times10^{-6}$ einstein s^{-1}) was determined by hydrogen peroxide actinometry as described by Nicole *et al*. Hydrogen peroxide was been used as the actinometer in the dilute solution. In this case the absorbance

of the solution was less than 0.02. The quantum yield of hydrogen peroxide photolysis at 253.7 nm is known and is equal to 1 [114].

Hydrogen peroxide was measured by colorimetric method using titanium(IV) ions according to the following reaction:



$$Ti^{4+} + H_2O_2 + 2H_2O \rightleftharpoons H_2TiO_4 + 4H^+ \qquad \text{eq. 3-1}$$

The method was carried out as follows:

- 2 cm^3 of a solution of $TiCl_4$ prepared in 2N H_2SO_4,
- 2 cm^3 of a solution of sulfuric acid (36 N)
- dilute solution of H_2O_2 at different irradiation times up to 25 cm^3 was added.

The optical density was measured at 410 nm in cells with 1 cm or 5 cm optical pathway after stabilization of the colour (30 minutes). From the molar absorption coefficient of the complex (ε = 695 $dm^3\ mol^{-1}\ cm^{-1}$) determined by calibration, the concentration of H_2O_2 in the samples was calculated using the following equation:

$$c_{H_2O_2} = \frac{A \times V_T}{\varepsilon \times \ell \times V_S} \qquad \text{eq. 3-2}$$

In this case A is the absorbance of the sample after subtracting the blank value, V_T is the total volume (cm^3),V_S is the volume of the investigated sample (cm^3), ℓ is the optical pathlength (mm) and ε is the molar absorption coefficient ($dm^3\ mol^{-1}\ cm^{-1}$) [115].

3.2.2. The VUV photolysis of the selected compounds by Xe-excimer lamp

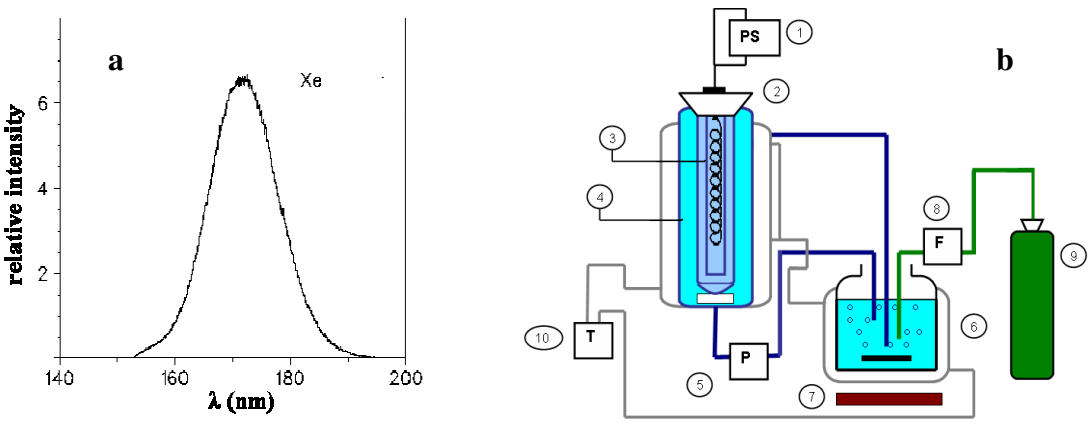


Figure 3-4 The emission spectra (a) and the apparatus applied for the Xe-excimer photolysis (VUV) (b)
(1) power supply; (2) Teflon packing ring; (3) VUV Xe-excimer lamp; (4) reactor; (5) pump; (6) reservoir; (7) magnetic stirrer; (8) flow meter; (9) oxygen or nitrogen cylinder; (10) thermostat

The xenon excimer lamp (15 W, Osram) was placed inside the reactor (**Figure 3-4**). The entire apparatus can be described as xenon excimer flow-through photoreactor. With this apparatus, all solutions of ibuprofen, ketoprofen and naproxen were irradiated with 172 nm

VUV light. The temperature of the reactor was regulated at 25 °C, a flow rate of 300 cm^3 min^{-1} was used and the solutions were continuously stirred inside the reservoir.

3.3. Analytical methods

Among the commonly used analytical methods (spectrophotometry, potentiometry) the analysis of samples was performed on HPLC-MS and GC-MS. All the presented results are the average of at least three experiments, where the error was within 1%.

3.3.1. High Performance Liquid Chromatography

To determine the kinetic parameters of the degradation of the investigated compounds, samples were analyzed by HPLC. Analyses were carried out on two systems. The first system was an Agilent 1100 HPLC with UV and MS detection using C18 (LichroCHART 125-4.5 µm) column. 1% acetic acid aqueous solution and acetonitrile was used in 1:1 ratio for elution, with a 0.8 cm^3 min^{-1} flow rate. Detection wavelengths were 220, 260 and 230 nm for ibuprofen, ketoprofen and naproxen, respectively. For all measurements, the following MS parameters were applied: drying gas (nitrogen, 300°C, 12 dm^3/min); nebulizer pressure 2.4 bar, capillary voltage 3000V. All the measurements were performed both in positive and negative mode.

The second system was a Waters chromatograph with an autosampler (Waters 717 plus), equipped with high pressure binary HPLC pump (Waters 1525), a dual λ absorption detector (Waters 2487) and a multi λ fluorescence detector (Waters 2475). A C18 Inertsil ODS-3V column (5 µm, 4.6×250 mm) was used.

Quantification wavelengths for UV detectors were the same as in the first case. In case of ibuprofen the fluorescence detection was carried out by excitation at 260 nm and emission at 290 nm. In the case of naproxen the wavelength of excitation was 280 nm, and the wavelength of emission was 320 nm. The degradation of ketoprofen was not followed by fluorescence detection because of its non-fluorescence property.

For the analysis of the aliphatic by-products of the investigated compounds a Merck-Hitachi HPLC (L-7100 pump and L-4250 UV-Vis detector, Hitachi D-7000 System Manager) was used. The separation was carried out at 206 nm on a GROM-RESIN ZH column.

3.3.2. Gas Chromatography

In case of ibuprofen, the degradation products could be identified by GC-MS after liquid-liquid extraction using a Hewlett Packard 5890 Series II Plus Gas Chromatograph coupled with a 5972 Series Mass Selection Detector. The samples were prepared by liquid-liquid extraction with dichloromethane. 200 cm^3 of sample was intensively agitated for 3 minutes in a decanting funnel 2 times with 10 cm^3 of dichloromethane. After the separation of the two phases, the organic phase was collected in a flask. The collected sample was evaporated to 1 cm^3 under nitrogen stream. The analyses were carried out in splitless mode. Helium was used as carrier gas. The oven temperature started at 40°C for 30 min, then it was risen up to 350°C with the rate of 15°C/min, the final temperature was maintained for 10 min. The mass detector worked in scan mode between 50 and 500 molecular weight unit.

3.3.3. Total Organic Carbon (TOC) determination

The Total Organic Carbon content (TOC) gives information about the mineralization efficiency (carbon dioxide and water formation) of the organic pollutants. The measurements were carried out using Euroglas TOC 1200-type device, by following the amount of carbon dioxide released during the burning of the sample solutions at 1000°C in a high-purity oxygen-argon gas mixture. The calibrations were done using potassium hydrogen phthalate standard solutions in a 5-50 ppm concentration range. The carbon content of the Milli Q water used for the preparation of the solutions was subtracted from the values of samples.

3.3.4. Electron spin resonance (ESR) spectroscopy

The electron spin resonance (ESR) spectroscopy is suitable only for the examination of the materials containing unpaired electrons (e.g. free radicals). Since the electron can only absorb radiation with defined energy, the transitions of ESR spectroscopy have resonant characteristics.

The ESR spectra were measured on a Bruker EleXsys 500CW X band device using 2 mW output and 1 G modulation. Ketoprofen solution with 1×10^{-4} mol dm^{-3} concentration was measured after UV/VUV photolysis. As radical scavenger 5,5'-dimethyl-1-pyrrolidine-N-oxyde (DMPO) was applied which traps non-specifically the oxygen- and carbon centred radicals.

4. Results and Discussion

4.1. Determination of the photophysical properties of the investigated compounds

4.1.1. Characterisation of the UV spectrum of the investigated compounds

The UV absorbance of ibuprofen, ketoprofen and naproxen was measured to determine their molar absorbances. Ketoprofen has an intensive absorbance at 260 nm, ibuprofen at 222 nm and a weak one around 260 nm, while naproxen has an intensive absorbance at 230 nm and two weak absorption peaks at 270 and 330 nm (**Figure 4-1**). The molar absorption coefficients were determined using the Beer-Lambert law at the maximum absorption wavelength of each compound and at 254 nm (the radiation wavelength of the UV lamp). In the case of ibuprofen the molar absorption coefficients are ε_{254nm} = 415 $dm^3mol^{-1}cm^{-1}$ and ε_{222nm} = 9175 $dm^3mol^{-1}cm^{-1}$, the values for ketoprofen are ε_{254nm} = 14104 $dm^3mol^{-1}cm^{-1}$ and ε_{260nm} = 15309 $dm^3mol^{-1}cm^{-1}$, and the coefficients in the case of naproxen are $\varepsilon_{254\ nm}$ = 1076 $dm^3mol^{-1}cm^{-1}$, $\varepsilon_{270\ nm}$ = 1310 $dm^3mol^{-1}cm^{-1}$ and $\varepsilon_{310\ nm}$ = 416 $dm^3mol^{-1}cm^{-1}$.

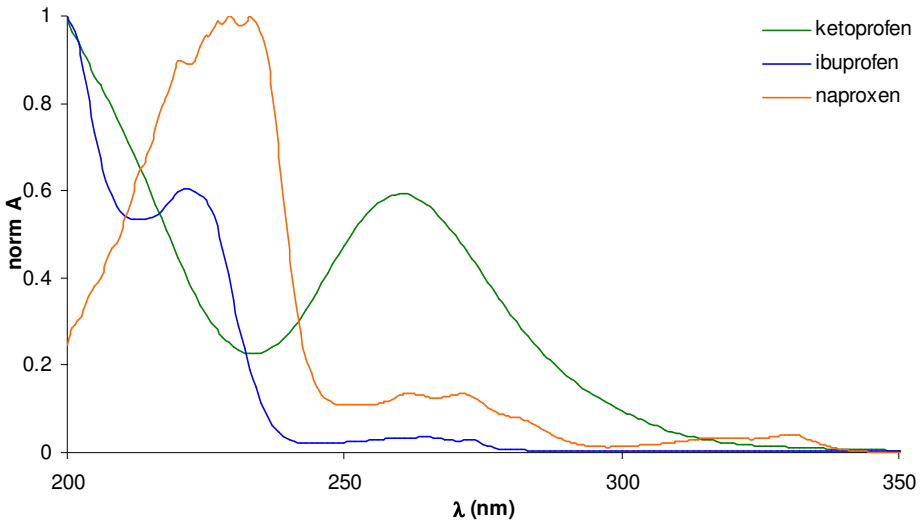


Figure 4-1 The UV spectra of the investigated compounds ($c_{IBU,\ KET} = 1\times10^{-4}$ mol dm^{-3}, $c_{NAP} = 6\times10^{-5}$ mol dm^{-3})

4.1.2. Determination of the fluorescence quantum yield of the target compounds

The fluorescence quantum yield was determined for naproxen and ibuprofen. Firstly the spectra of the investigated compound and that of a reference compound were recorded at identical excitation wavelengths. As reference compound phenol was used ($\phi_{f,phenol}$ = 0,07 [116, 117]).

The fluorescence quantum yield was calculated using the following equation:

$$I_{f,X} = \phi_{f,X} \times I_{a,X} \times k \qquad \text{eq. 4-1}$$

$I_{f,x}$ is the intensity measured at the wavelength where the maximum fluorescence is observed, $\phi_{f,X}$ is the fluorescence quantum yield of the X compound, $I_{a,X}$ is the light intensity absorbed by the X compound at the excitation wavelength, $I_{a,X} = I_0 \times (1-10^{-Ax})$; A is the absorption of the X solution.

For naproxen $\phi_{f,naproxen}$ = 0.77 was obtained. This value shows that fluorescent emission is the main process of the deactivation of the excited naproxen. In the case of ibuprofen the $\phi_{f,ibuprofen}$ =0.056 value was obtained.

4.2. Ultraviolet, ultraviolet/vacuum-ultraviolet and vacuum-ultraviolet photolysis of ibuprofen and ketoprofen, separately

4.2.1. Decomposition of ibuprofen and ketoprofen by UV (254 nm) light

In the first step, to optimise the experimental conditions, the photolysis of ibuprofen was followed spectrophotometrically. Samples were taken in every 5 minutes. Because of the fast degradation of ketoprofen, in the first minute samples were taken in every 10 seconds. **Figure 4-2** and **Figure 4-3** show the change of the UV spectra during the degradation of the two compounds. During the first period of decomposition, the increase of absorbance at certain wavelength for both compounds suggests the formation of at least one by-product. These intermediates start to decompose after 20 minutes and 40 seconds, respectively. During a one hour photolysis the major aromatic photoproducts of ketoprofen were totally degraded.

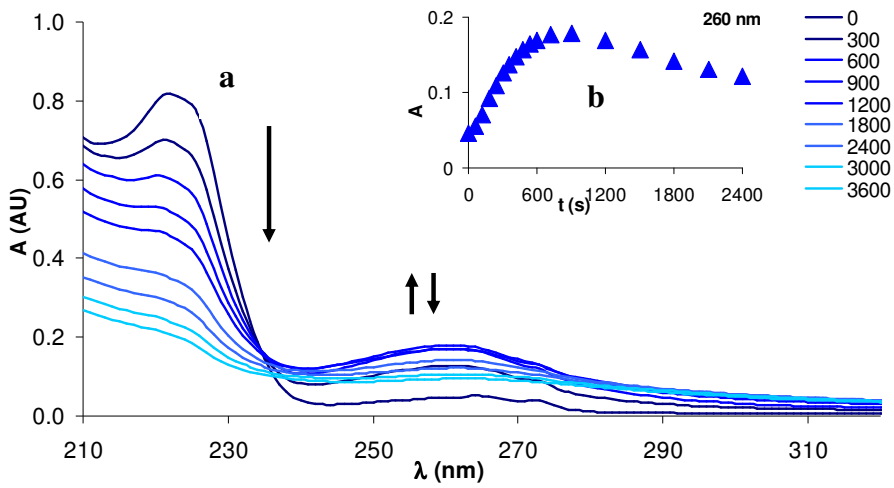


Figure 4-2 Evolution of the UV spectrum of ibuprofen (a) and of the absorbance at 260 nm (b) in function of the UV irradiation time in oxygen saturated solutions ($c_0 = 1\times10^{-4}$ mol dm^{-3}, l = 10 mm, t = 0-3600 s)

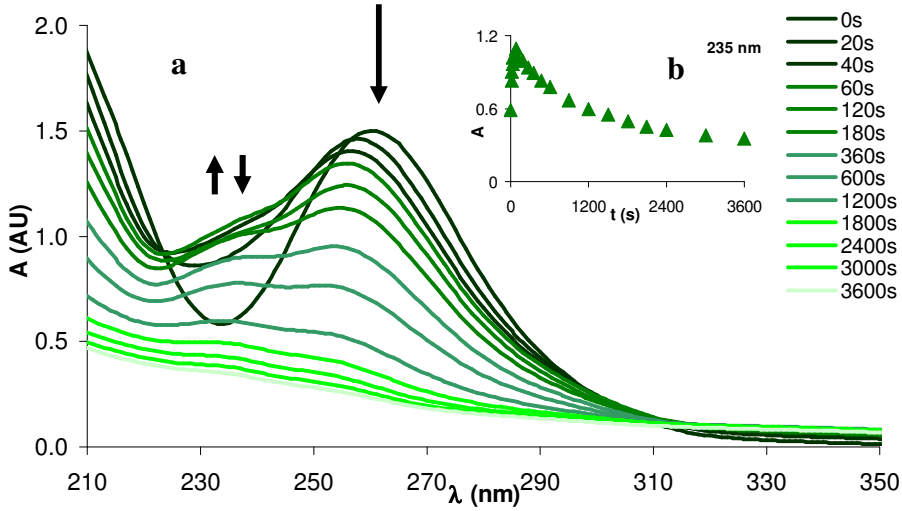


Figure 4-3 Evolution of the UV spectrum of ketoprofen (a) and of the absorbance at 235 nm (b) in function of the UV irradiation time in oxygen saturated solutions ($c_0 = 1\times10^{-4}$ mol dm^{-3}, l = 10 mm, t = 0-3600 s)

Based on the spectrophotometric results, the decrease of the absorbance of ibuprofen at 220 nm and of ketoprofen at 260 nm cannot be described with a simple exponential curve, suggesting the formation of more than one photoproduct.

To be able to determine the kinetic parameters of the photodecomposition of these pharmaceuticals the target molecules and the formed by-products were separated, and their degradation was followed by HPLC. Using 254 nm light in the presence of dissolved oxygen, ibuprofen was completely degraded within 1 hour (**Figure 4-4 a**), while the disappearance of ketoprofen was faster. It was completely degraded in about 90 seconds (**Figure 4-4 b**). No significant concentration dependence can be seen on the degradation curves. A particular phenomenon was observed during the degradation of ibuprofen: a slight induction period appeared in the presence of dissolved molecular oxygen within the first 250-300 seconds.

This could be explained by the slower formation of a species which accelerate the degradation of ibuprofen. The formation of the degradation product which would elute together with the target molecule, may also contribute to an overestimation of the ibuprofen peak area but reasonable changes in the elution parameters and the GC-MS results did not support this possibility. With the decrease of the initial concentration this period diminished, suggesting that species formed directly from ibuprofen contribute to the degradation reaction in the initial period. In the oxygen free solutions (**Figure 4-5**) this phenomena could not be observed. Because this phenomenon was only observed in the presence of dissolved molecular oxygen, it strongly supported the involvement of oxygen centred radicals in the degradation of ibuprofen. During the degradation of ketoprofen no induction period could be observed, independent of the presence or absence of dissolved molecular oxygen.

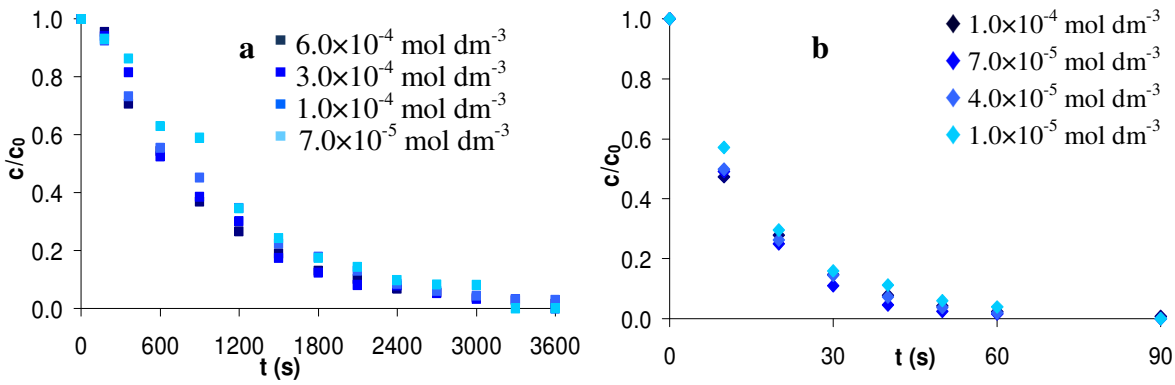


Figure 4-4 UV photolysis of ibuprofen (a) and ketoprofen (b) in presence of dissolved molecular oxygen

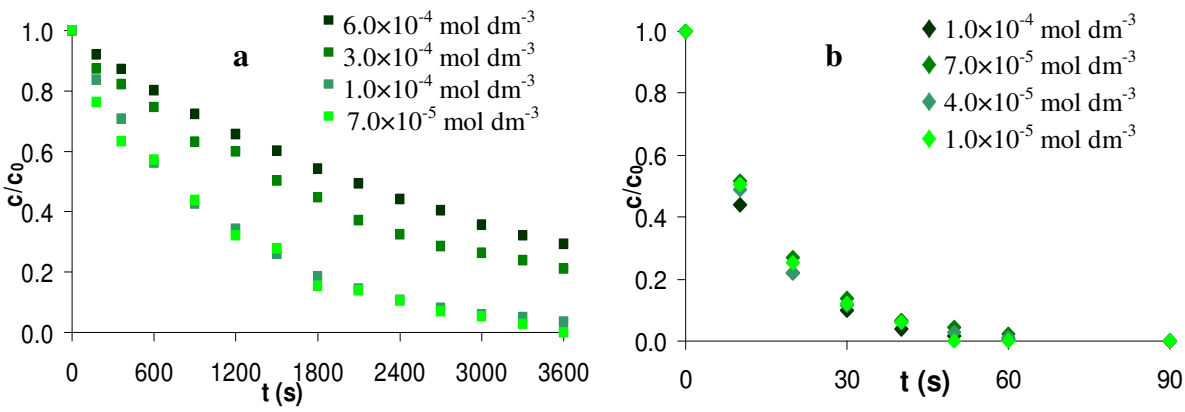


Figure 4-5 UV photolysis of ibuprofen (a) and ketoprofen (b) in absence of dissolved molecular oxygen

Based on the presented results it can be stated that the initial concentration dependence of the degradation is very strong, the kinetic parameters show a pseudo first order behaviour. This behaviour is not valid only during the photolysis of ibuprofen in oxygen free solutions. It

was very surprising; that the relative degradation rates are higher at higher initial concentrations (**Table 4-2** and **4-3**). The relative rate of decomposition of ketoprofen is practically independent from the presence of dissolved oxygen, while ibuprofen degraded slower in absence of oxygen. This difference is well presented by the half lifetimes of the compounds in **Table 4-1** as well as by the decomposition rates (presented later in **Table 4-2** and in **Table 4-3**).

Table 4-1 Half lifetimes (in seconds) during UV degradation in the presence of N_2 and O_2

	c_0 (mol dm^{-3})	O_2	N_2
IBU	7.0×10^{-5}	700	760
	1.0×10^{-4}	600	740
	3.0×10^{-4}	600	1620
	6.0×10^{-4}	700	2100
KET	1.0×10^{-5}	10	10
	4.0×10^{-5}	10	10
	7.0×10^{-5}	10	11
	1.0×10^{-4}	8	7.5

4.2.1.1. Reaction rate of decomposition and quantum yield (ϕ) of UV photolysis

Charasteristic parameters of photolytic processes are the reaction order of the decomposition and the quantum yield. It must be stated that the order of degradation for complex reactions can be considered only as nominative for certain conclusions.

By plotting $\ln(c_0/c)$ versus the degradation time a straight line is observed, suggesting a pseudo first order degradation kinetic for both compounds. The slope of this graph gives the formal rate constant k (s^{-1}). From these values the initial degradation reaction rates (r_0) can be calculated as $r_0 = k\times c_0$, where c_0 (mol dm^{-3}) is the initial concentration of the target molecule.

The influence of the dissolved molecular oxygen and the initial concentration of the target molecules on the UV degradation rate of the two pharmaceuticals can be seen in **Figure 4-6**. The calculated data are given in **Table 4-2** for ibuprofen and in **Table 4-3** for ketoprofen.

The influence of dissolved molecular oxygen on the degradation of ibuprofen depends on the initial concentration of the target molecule. At lower concentrations (7×10^{-5} and 1×10^{-4} mol dm^{-3}) the effect of molecular oxygen on the degradation can be neglected. However, at

higher concentrations (3×10^{-4} and 6×10^{-4} mol dm^{-3}) the degradation of ibuprofen is less efficient in oxygen free solutions. Dissolved molecular oxygen can be take role in the formation of oxygen centred radicals [100], which are able to accelerate the photodecomposition, and/or contribute to the formation of reactive by-products. In the presence of oxygen the degradation starts with the already mentioned induction period, in the case of ibuprofen. The kinetic parameters were calculated from data after this period.

In the case of ketoprofen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}) a slight difference can be observed between the reaction rates in the presence and absence of the dissolved molecular oxygen, but generally the formal first order rate constants are independent from the initial concentration and from the presence of the dissolved molecular oxygen.

The rate constants calculated for both molecules confirm first order kinetics for oxygen free solutions. However, in the presence of dissolved molecular oxygen, the rate constants depend on the initial concentration, suggesting the complex nature of the degradation processes under these experimental conditions.

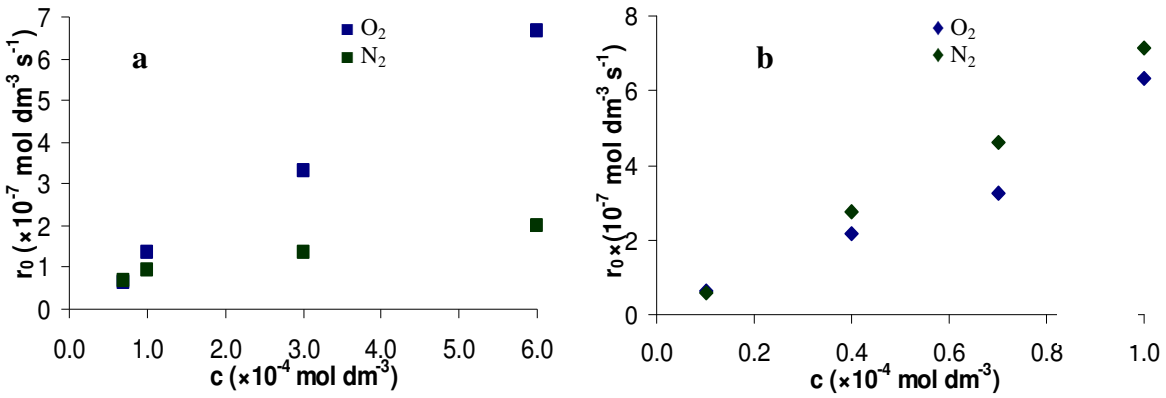


Figure 4-6 Initial rate of the degradation of ibuprofen (a) and ketoprofen (b) in function of they concentration during UV photolysis

The quantum yields were calculated by the following equation [100]:

$$\ln\frac{[C]}{[C]_o} = -2.303\varepsilon\ell\phi I_o t \qquad \text{eq. 4-2}$$

The calculated quantum yields are shown in **Table 4-2** and **4-3**. The values determined in this work are less than one, suggesting that beside the degradation other deactivation processes without degradation also take place in the systems.

The calculated quantum yields also serve an explanation for the much faster degradation of ketoprofen. Beside the higher absorption of the 254 nm light, it uses the absorbed light for

degradation twice as efficient as ibuprofen, which means less deactivation processes without degradation during the UV photolysis of ketoprofen.

Table 4-2 Kinetic parameters of the UV degradation of ibuprofen

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3}s^{-1})	ϕ
O_2	7.0×10^{-5}	9.2×10^{-4}	6.5×10^{-8}	0.11
	1.0×10^{-4}	1.4×10^{-3}	1.4×10^{-7}	0.16
	3.0×10^{-4}	1.1×10^{-3}	3.3×10^{-7}	0.13
	6.0×10^{-4}	1.1×10^{-3}	6.7×10^{-7}	0.13
N_2	7.0×10^{-5}	9.9×10^{-4}	6.9×10^{-8}	0.12
	1.0×10^{-4}	9.2×10^{-4}	9.2×10^{-8}	0.11
	3.0×10^{-4}	4.5×10^{-4}	1.3×10^{-7}	0.05
	6.0×10^{-4}	3.3×10^{-4}	2.0×10^{-7}	0.04

Table 4-3 Kinetic parameters of the UV degradation of ketoprofen

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3}s^{-1})	ϕ
O_2	1.0×10^{-4}	6.31×10^{-2}	6.31×10^{-6}	0.225
	7.0×10^{-5}	4.65×10^{-2}	3.26×10^{-6}	0.166
	4.0×10^{-5}	5.39×10^{-2}	2.16×10^{-6}	0.192
	1.0×10^{-5}	5.16×10^{-2}	5.16×10^{-7}	0.184
N_2	1.0×10^{-4}	7.16×10^{-2}	7.16×10^{-6}	0.256
	7.0×10^{-5}	6.61×10^{-2}	4.63×10^{-6}	0.236
	4.0×10^{-5}	6.90×10^{-2}	2.76×10^{-6}	0.246
	1.0×10^{-5}	5.84×10^{-2}	5.84×10^{-7}	0.208

4.2.2. Decomposition of ibuprofen and ketoprofen by UV/VUV (254/185 nm) light

The spectrophotometric results of the UV/VUV degradation showed the same characteristics that were discussed in the case of UV photolysis, except for the fact that the complete degradation of ibuprofen was notably faster. The degradation of the target molecules and the formation and degradation of photoproducts were followed by HPLC analysis. The results of the photolysis in oxygenated solutions are shown in **Figure 4-7**.

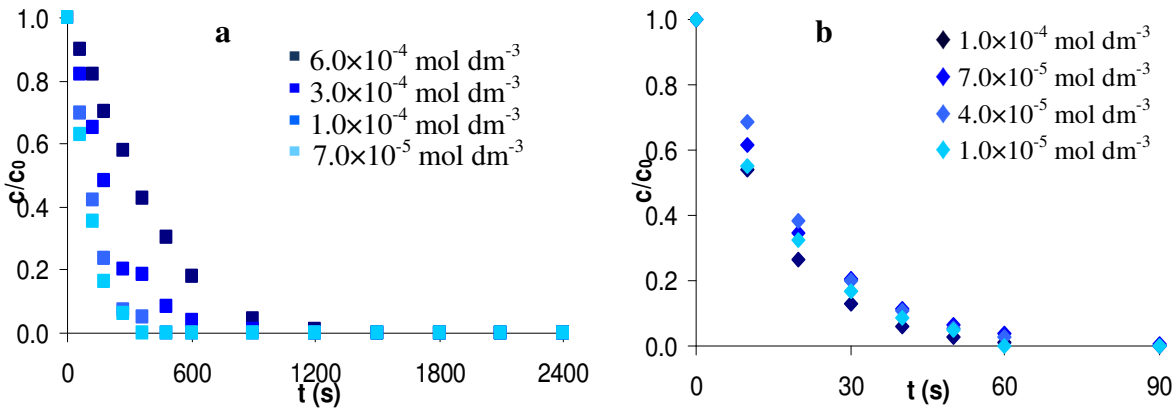


Figure 4-7 UV/VUV photolysis of ibuprofen (a) and ketoprofen (b) in presence of dissolved molecular oxygen

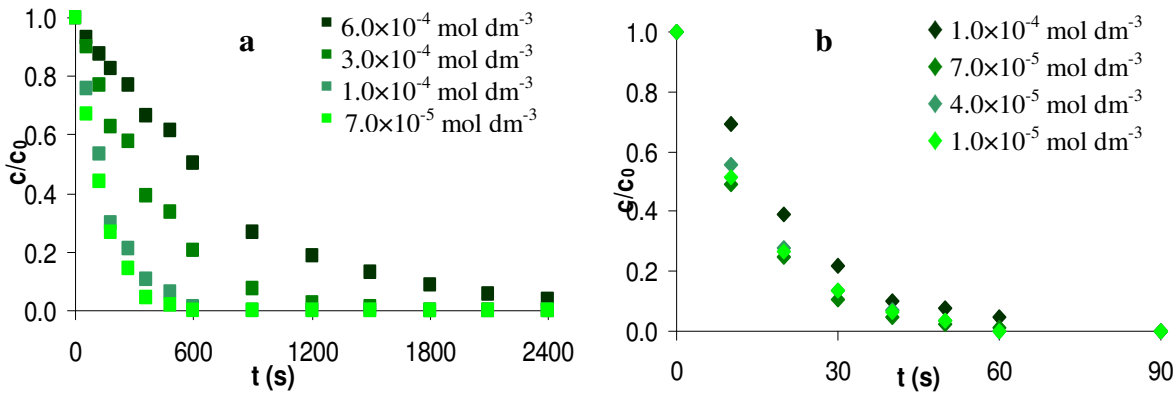


Figure 4-8 UV/VUV photolysis of ibuprofen (a) and ketoprofen (b) in oxygen free solutions

It can be seen that in the case of ketoprofen no significant acceleration could be achieved by VUV combination (**Figure 4-7 b, Figure 4-8 b**). It indicates that in the decomposition of ketoprofen, the UV photolysis is the dominant process. In case of ibuprofen the UV/VUV irradiation is more effective than the UV photolysis. Depending on the initial concentration degradation more than seven times faster could be achieved, even in oxygen free solutions (**Figure 4-7 a, Table 4-5**). This effect can be contributed to the HO-radicals generated directly from water by 185 nm irradiation, which can initiate faster degradation of the pharmaceutical compounds. The role of dissolved molecular oxygen in this case is to prevent the recombination of the hydrogen and hydroxyl radicals, producing other oxygen centred radicals, such as hydroperoxyl radicals. In the case of ibuprofen, dissolved molecular oxygen only accelerates the degradation at higher initial concentration, while for ketoprofen the effect is within the experimental error.

Table 4-4 Half life times (in seconds) during UV/VUV degradation in presence of N_2 and O_2

	c_0 (mol dm^{-3})	O_2	N_2
IBU	7.0×10^{-5}	100	110
	1.0×10^{-4}	129	130
	3.0×10^{-4}	185	315
	6.0×10^{-4}	330	600
KET	1.0×10^{-5}	11	13
	4.0×10^{-5}	12	10
	7.0×10^{-5}	11	11.5
	1.0×10^{-4}	10	10

An important difference between the two types of photolysis, is that there is no induction period in the case of UV/VUV photolysis of ibuprofen. This can be explained by the changed degradation mechanism resulting in higher reaction rates (**Table 4-5**).

4.2.2.1. Reaction rate and quantum yield (ϕ) for UV/VUV degradation

The reaction rates of the UV/VUV degradation of ibuprofen and ketoprofen have been also determined in the presence and absence of dissolved molecular oxygen. The methodology of the determination of the pseudo first order rate coefficients (k) and the calculation of the initial degradation rate (r_0) was similar than to the UV photolysis.

Table 4-5 Initial reaction rates and rate constants of UV/VUV degradation of ibuprofen in presence and absence of oxygen [123]

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3} s^{-1})
O_2	7.0×10^{-5}	9.94×10^{-3}	6.96×10^{-7}
	1.0×10^{-4}	8.55×10^{-3}	8.55×10^{-7}
	3.0×10^{-4}	5.70×10^{-3}	17.1×10^{-7}
	6.0×10^{-4}	3.40×10^{-3}	20.4×10^{-7}
N_2	7.0×10^{-5}	8.07×10^{-3}	5.65×10^{-7}
	1.0×10^{-4}	6.58×10^{-3}	6.58×10^{-7}
	3.0×10^{-4}	2.88×10^{-3}	8.64×10^{-7}
	6.0×10^{-4}	1.38×10^{-4}	8.28×10^{-7}

Table 4-6 Initial reaction rates and rate constants of the UV/VUV degradation of ketoprofen in presence and absence of oxygen

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3}s^{-1})
O_2	1.0×10^{-4}	4.98×10^{-2}	4.98×10^{-6}
	7.0×10^{-5}	5.58×10^{-2}	3.91×10^{-6}
	4.0×10^{-5}	5.52×10^{-2}	2.21×10^{-6}
	1.0×10^{-5}	5.41×10^{-2}	5.41×10^{-7}
N_2	1.0×10^{-4}	5.19×10^{-2}	5.19×10^{-6}
	7.0×10^{-5}	7.24×10^{-2}	5.07×10^{-6}
	4.0×10^{-5}	6.56×10^{-2}	2.62×10^{-6}
	1.0×10^{-5}	6.64×10^{-2}	6.64×10^{-7}

The dependence of initial reaction rates on the initial concentration of the target compounds and the presence or absence of the dissolved molecular oxygen can be seen in **Figure 4-9**.

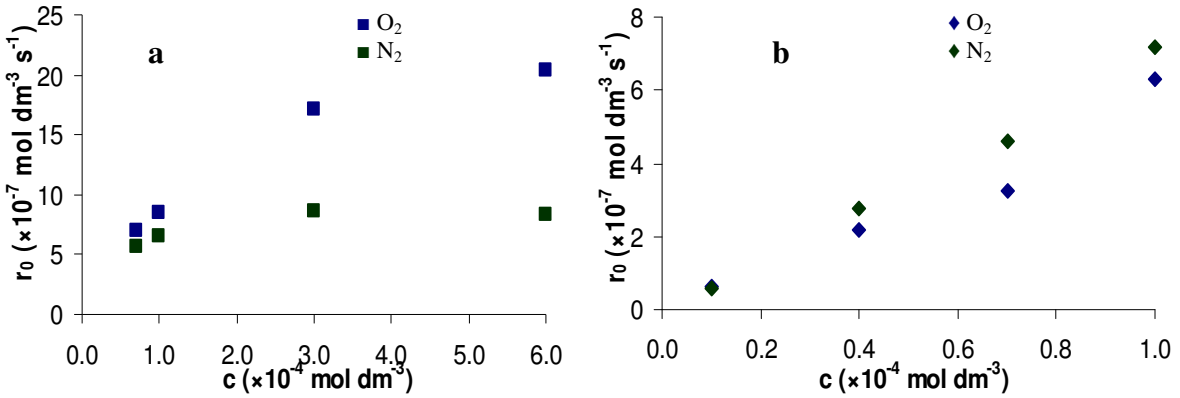


Figure 4-9 Initial reaction rates of ibuprofen (a) and ketoprofen (b) degradation as a function of initial concentration in UV/VUV photolysis

The comparison of the shape of these curves in case of ibuprofen and ketoprofen is interesting. The different shapes support the already suggested difference in the degradation mechanism of the two compounds.

The results of photodegradation of ibuprofen and ketoprofen at a selected initial concentration (1.0×10^{-4} mol dm^{-3}) have been compared in UV and VUV photolysis, both in presence and absence of dissolved molecular oxygen (**Figure 4-10**). Its effect is not significant at this concentration. It can be clearly seen that the presence of the VUV light significantly accelerates the degradation of ibuprofen, while in case of ketoprofen the degradation has the same efficiency with both methods.

UV degradation of ibuprofen in oxygenated solution is complete within 60 minutes, while the total degradation of ketoprofen is reached in 90 seconds. With UV/VUV light the ibuprofen

degradation is highly accelerated, the same degree of the degradation has been reached in 15 minutes whereas there is no significant change for the degradation of ketoprofen.

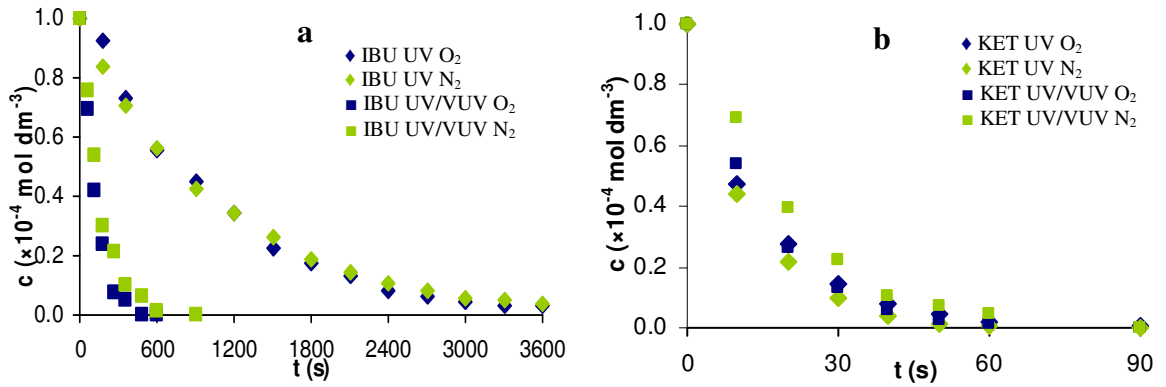
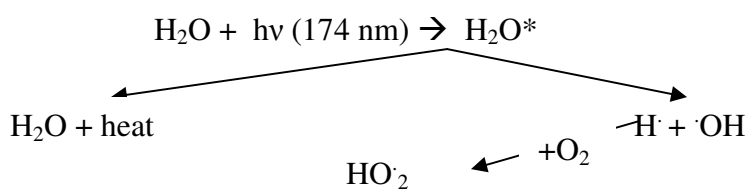


Figure 4-10 UV and UV/VUV degradation of ibuprofen (a) and ketoprofen (b) in presence and absence of dissolved molecular oxygen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3})

4.2.3. VUV (Xenon excimer, 172 nm) photolysis of ibuprofen and ketoprofen

The degradation of ibuprofen and ketoprofen using xenon excimer lamp (chapter 3.2.2.) have been carried out.

This kind of radical generation based on the reactions



According to the scheme, the dissolved oxygen has an important role in the VUV photolysis, generally. To investigate the influence of dissolved molecular oxygen concentration on the degradation three different kind of gases, oxygen, nitrogen and air (20.8 % oxygen content) were used.

The concentration of ibuprofen and ketoprofen solutions was 1.0×10^{-4} mol dm^{-3} and they have been irradiated with the xenon excimer lamp (VUV-172 nm) for 30 minutes in the photoreactor described in the chapter 3.2.2. The influence of the dissolved oxygen has been described in **Figure 4-11**.

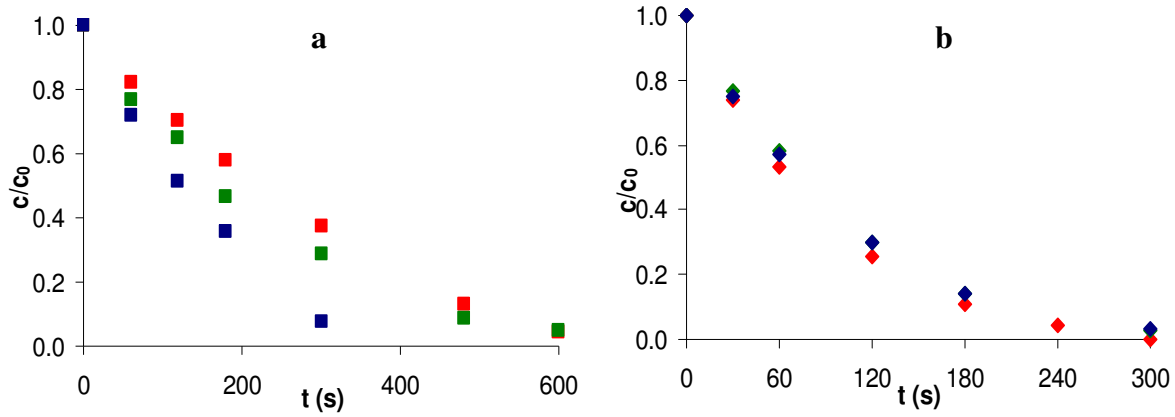


Figure 4-11 The VUV degradation of ibuprofen (a) and ketoprofen (b) ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}) at different concentration of dissolved oxygen (either oxygen, or nitrogen or air is the equilibrium gas phase)

On the degradation of ketoprofen the dissolved oxygen practically has no influence. It decomposition is slower than it was observed UV and UV/VUV decomposition.

Similar tendency was observed in the decomposition of ibuprofen, but the deviations of measurements are higher.

The target compound concentration dependence of the degradations has been also investigated at similar experimental conditions as they given before. In these measurements the irradiations have been carried out with the 1.0×10^{-5} mol dm^{-3}, 4.0×10^{-5} mol dm^{-3}, 7.0×10^{-5} mol dm^{-3}, 1.0×10^{-4} mol dm^{-3} concentrations for both compounds.

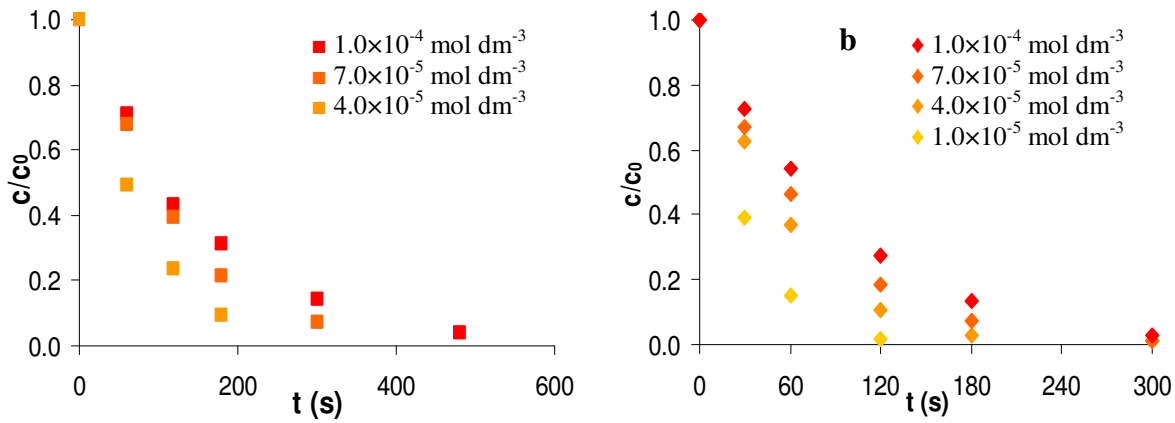


Figure 4-12 Concentration dependence of the VUV degradation of ibuprofen (a) and ketoprofen (b) in dissolved air (20.8 % oxygen content)

The statements are;

- the decomposition is strongly depend of the initial concentration of target compounds
- the degradation rate slightly higher in case of ibuprofen, contrary the precious results,
- the relative rate at higher concentration is lower; therefore the decomposition can not be characterized with a formal first order kinetic behaviour.

These observations indicate qualitatively the direct reaction of excited water (in the solvent cage) with the target molecules. The competitive reaction, the OH-radical formation has a minor role in the decomposition of ketoprofen. In the decomposition of ibuprofen the contribution of OH-radicals to the decomposition slightly increases.

Due to the previous experiments, we can establish that ibuprofen with 1.0×10^{-4} mol dm^{-3} concentration was completely eliminated in 10 minutes. Therefore, the ibuprofen solutions were irradiated for the laid down time with the xenon excimer lamp. It has to be stated that the 1.0×10^{-5} mol dm^{-3} concentration ibuprofen solution was under the limit of detection of the applied apparatus. In this case ibuprofen was completely degraded in the first minute of the irradiation. In the previous figure the measurement of the 4.0×10^{-5} mol dm^{-3}, 7.0×10^{-5} mol dm^{-3} and 1.0×10^{-4} mol dm^{-3} concentration solutions is presented. The higher is the concentration of ibuprofen, the slower is the degradation rate.

In the case of ketoprofen all the applied concentrations were above the limit of detection. In this case initial concentration dependence can be observed. In the case of the highest concentration the degradation rate is the slowest. Even at the highest investigated concentration (1.0×10^{-4} mol dm^{-3}) ketoprofen was completely eliminated in 300 seconds. For both compounds dissolved air was used to bubble through the irradiated solutions.

4.3. Ultraviolet, ultraviolet/vacuum-ultraviolet and vacuum-ultraviolet photolysis of the mixture of ibuprofen and ketoprofen

During photosensitization the sun- or artificial light induced abnormal reactions are mediated by chemicals in biological systems. This phenomenon occurs more frequently due to the long list of new chemicals entering our environment (drugs, cosmetics, industrial chemicals) and also to the social appreciation of sun-tan. Phototoxicity can appear in any patient provided that their skin is exposed to enough doses of light and the photosensitizer is present at the appropriate concentration. Cell degeneration or even cell death may occur in the epidermis (topically-applied photosensitizers) and in the dermis (systemic photosensitizers) as well [72, 119].

A number of reports appeared in the medical literature on photocontact dermatitis sensitized by ketoprofen [120-124]. Ketoprofen shows a light-induced activity higher than other propionic acid derivatives and is considered phototoxic in vitro [125-129]. The typical clinical manifestations are severe, erythema and excoriations [130]. Most of these effects have been associated with photoallergy [124].

Ketoprofen photodegradation involves a triplet state; the photogenerated excited drug species undergo a photodecarboxylation reaction, with high quantum yield, via the key intermediacy of the benzylic radical, a short-lived species [64]. To our recent knowledge the photosensitizing effect of ketoprofen on another compound during photolysis has not been investigated yet.

4.3.1. Photodecomposition by UV photolysis (254 nm)

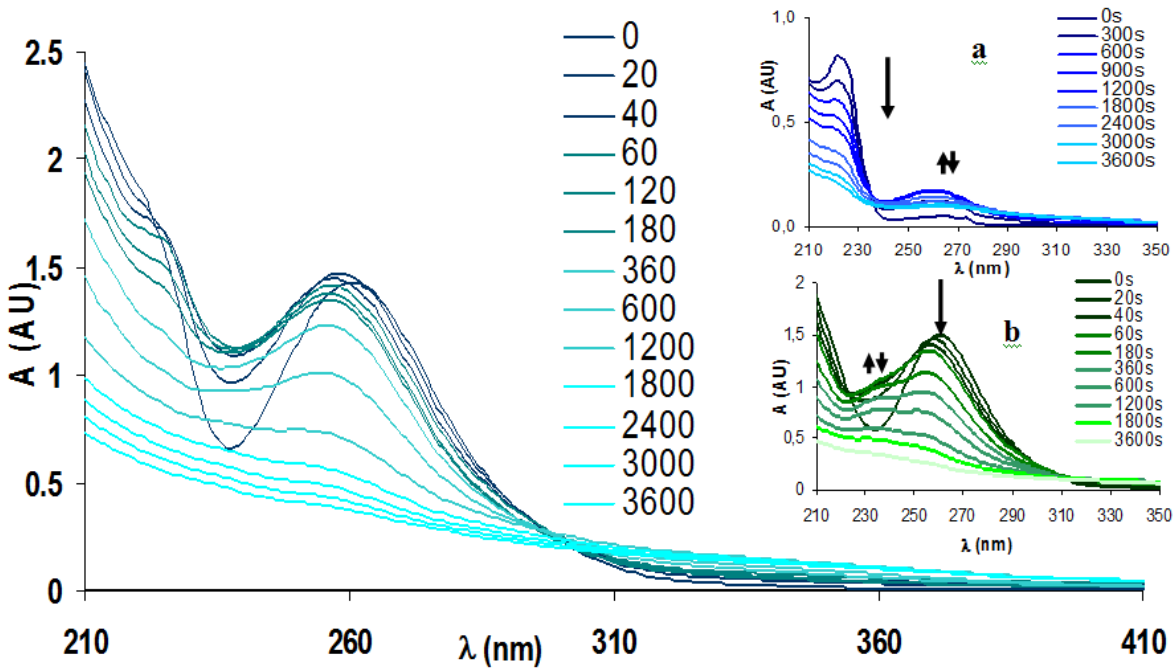


Figure 4-13 UV spectrum of the mixture solution in function of the irradiation time ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}, UV photolysis, oxygen saturated); UV spectra of ibuprofen (a) and ketoprofen (b) when irradiated separately

The photodegradation of an equimolar mixture (1.0×10^{-4} mol dm^{-3}) of ibuprofen and ketoprofen were investigated in the first step. **Figure 4-13** shows the change of the UV spectrum as a function of the irradiation time. The spectrum of the mixture corresponds to the addition of individual spectra. The inflexion point moves to the higher energy range with the time of photolysis. The real curiosity is observed by the HPLC-UV analysis of the photolysis of the mixture.

The effect of dissolved molecular oxygen was also investigated. The following figures show the degradation curves of ibuprofen (**Figure 4-14 a, Figure 4-15 a**) and ketoprofen (**Figure 4-14 b, Figure 4-15 b**) either alone in the solution or in mixture, in the presence and absence of oxygen.

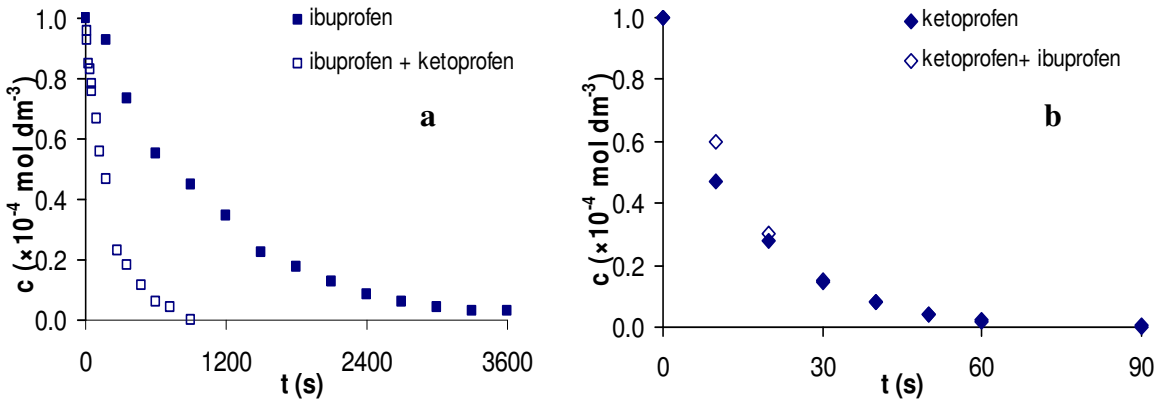


Figure 4-14 UV degradation of ibuprofen (a) and ketoprofen (b) in the mixture solution (□, ◊) and separately (■, ♦) in oxygenated solutions

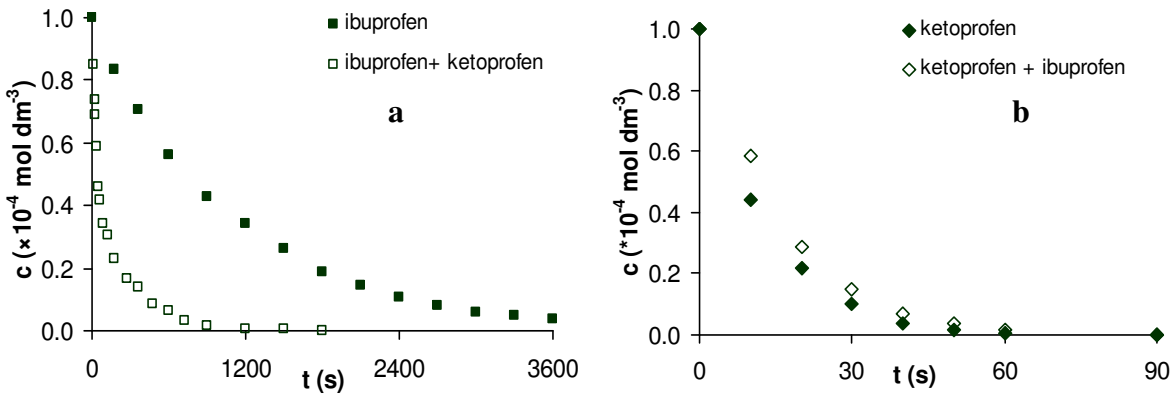


Figure 4-15 UV degradation of ibuprofen (a) and ketoprofen (b) in the mixture (□, ◊) solution and separately (■, ♦) in oxygen free solutions

The degradation of ibuprofen is faster in the presence of ketoprofen. The half lifetime of the degradation decreases from 600 seconds to 120 seconds. The presence of ibuprofen has no significant influence on the degradation rate of ketoprofen. This effect can be observed in oxygen free solutions as well: the half lifetime of ibuprofen decreases from 740 s to 50 s. The results of ibuprofen are collected in **Table 4-7**. This effect can be explained by the well known photosensitizing properties of benzophenone type compounds and more particularly of ketoprofen. Excited ketoprofen can transfer a part of the energy to ibuprofen, accelerating its degradation. There can be a direct energy transfer and probably not by interaction of excited

oxygen. The major route of photosensitizer deactivation is the energy transfer giving back the ground state. On the other hand ibuprofen has higher rate of degradation even when ketoprofen is totally degraded. This can be due to the photosensitizing properties of ketoprofen by-products.

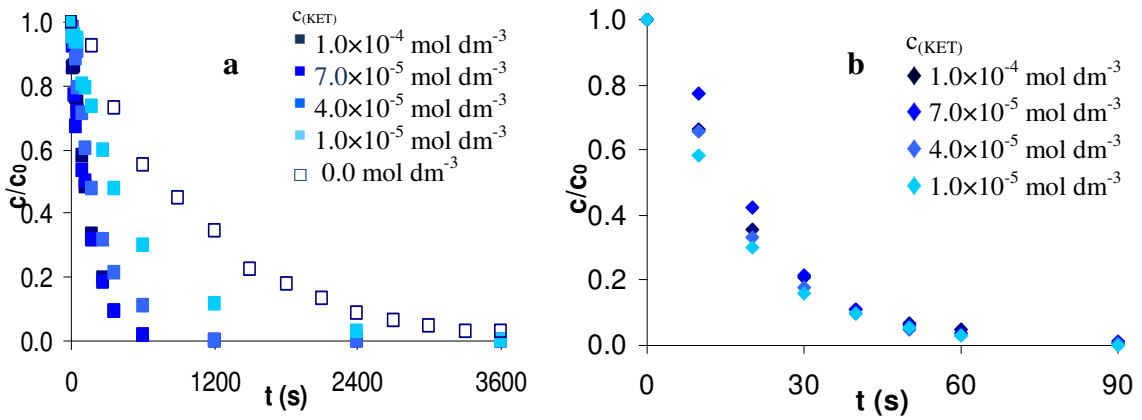


Figure 4-16 UV degradation of (a) ibuprofen (□, ■,) and (b) ketoprofen (♦) in oxygen saturated solutions at fixed concentration of ibuprofen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}) in presence of ketoprofen of different concentrations (1×10^{-4} - 1×10^{-5} mol dm^{-3})

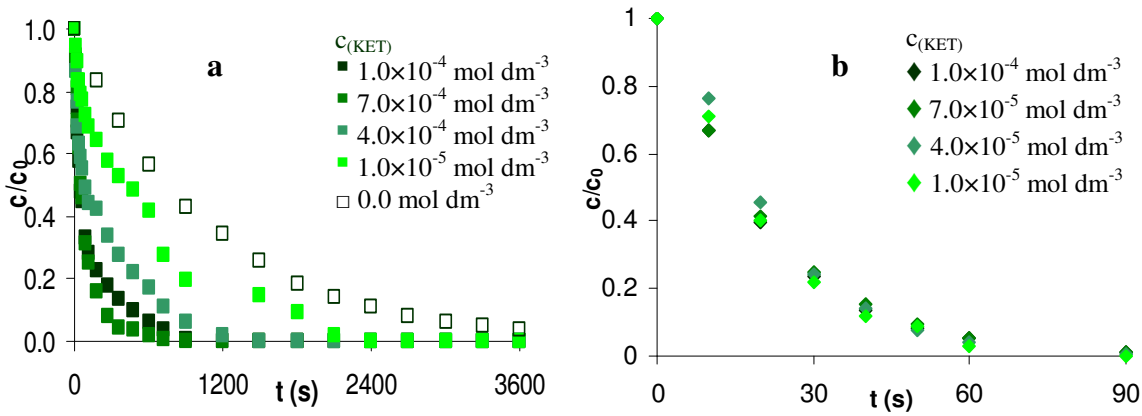


Figure 4-17 UV degradation of (a) ibuprofen (□, ■,) and (b) ketoprofen (♦) in oxygen free solutions at fixed concentration of ibuprofen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}) in presence of ketoprofen of different concentrations (1×10^{-4} - 1×10^{-5} mol dm^{-3})

The influence of the ketoprofen concentration on the degradation of ibuprofen has been investigated (c_0(KET) = 1.0×10^{-4} mol dm^{-3}, 7.0×10^{-5} mol dm^{-3}, 4.0×10^{-5} mol dm^{-3} and 1.0×10^{-5} mol dm^{-3}) with a fixed concentration of ibuprofen (1.0×10^{-4} mol dm^{-3}). The effect of dissolved oxygen was also investigated. The results are shown on the **Figure 4-16** and **Figure 4-17**.

Table 4-7 Half lifetimes (s) of ibuprofen (1.0×10^{-4} mol dm^{-3}) with the addition of different ketoprofen concentrations during UV degradation in oxygenated and oxygen free (N_2) solutions

	KET concentration c_0 (mol dm^{-3})	O_2	N_2
IBU	1.0×10^{-4}	120	50
	7.0×10^{-5}	100	50
	4.0×10^{-5}	140	65
	1.0×10^{-5}	180	400
	0	600	740

4.3.1.1. Decomposition rate and quantum yield (ϕ) of the UV photolysis

The effect of dissolved molecular oxygen on the reaction rates of the UV degradation of the mixed system was also investigated. Degradation rate constants (k) and initial degradation rates (r_0) were determined similarly as in the case of UV photolysis of individual compounds.

Table 4-8 The kinetic parameters of the UV degradation of ibuprofen (1.0×10^{-4} mol dm^{-3}) in the absence and presence of different concentrations of ketoprofen

	KET concentration c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol $dm^{-3}s^{-1}$)	ϕ
O_2	1.0×10^{-4}	4.70×10^{-3}	4.70×10^{-7}	0.570
	7.0×10^{-5}	6.56×10^{-3}	6.56×10^{-7}	0.795
	4.0×10^{-5}	4.16×10^{-3}	4.16×10^{-7}	0.504
	1.0×10^{-5}	1.56×10^{-3}	1.56×10^{-7}	0.201
	0	1.36×10^{-3}	1.36×10^{-7}	0.165
N_2	1.0×10^{-4}	5.01×10^{-3}	5.01×10^{-7}	0.607
	7.0×10^{-5}	7.62×10^{-3}	7.62×10^{-7}	0.923
	4.0×10^{-5}	3.10×10^{-3}	3.10×10^{-7}	0.375
	1.0×10^{-5}	1.34×10^{-3}	1.34×10^{-7}	0.162
	0	9.23×10^{-4}	9.23×10^{-8}	0.112

It can be stated that the effect of ketoprofen on the UV degradation of ibuprofen is more significant in oxygen free solutions than in oxygen saturated solutions. The presence of oxygen has no significant effect on the degradation of ketoprofen alone.

The kinetic parameters of the fixed initial concentration of ibuprofen (1.0×10^{-4} mol dm^{-3}) in the presence of different concentrations of ketoprofen are shown in **Table 4-8** and parameters concerning the degradation of ketoprofen in **Table 4-9**.

Table 4-9 The kinetic parameters of the UV degradation of ketoprofen in the presence of ibuprofen (1.0×10^{-4} mol dm^{-3})

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3}s^{-1})	ϕ
O_2	1.0×10^{-4}	5.33×10^{-2}	5.33×10^{-6}	0.190
	7.0×10^{-5}	5.42×10^{-2}	3.79×10^{-6}	0.193
	4.0×10^{-5}	5.83×10^{-2}	2.33×10^{-6}	0.203
	1.0×10^{-5}	5.94×10^{-2}	5.94×10^{-7}	0.211
N_2	1.0×10^{-4}	4.68×10^{-2}	4.68×10^{-6}	0.167
	7.0×10^{-5}	4.87×10^{-2}	3.41×10^{-6}	0.173
	4.0×10^{-5}	5.43×10^{-2}	2.17×10^{-6}	0.194
	1.0×10^{-5}	5.29×10^{-2}	5.29×10^{-7}	0.189

4.3.2. Photodecomposition by UV/VUV (254 nm+185 nm) photolysis

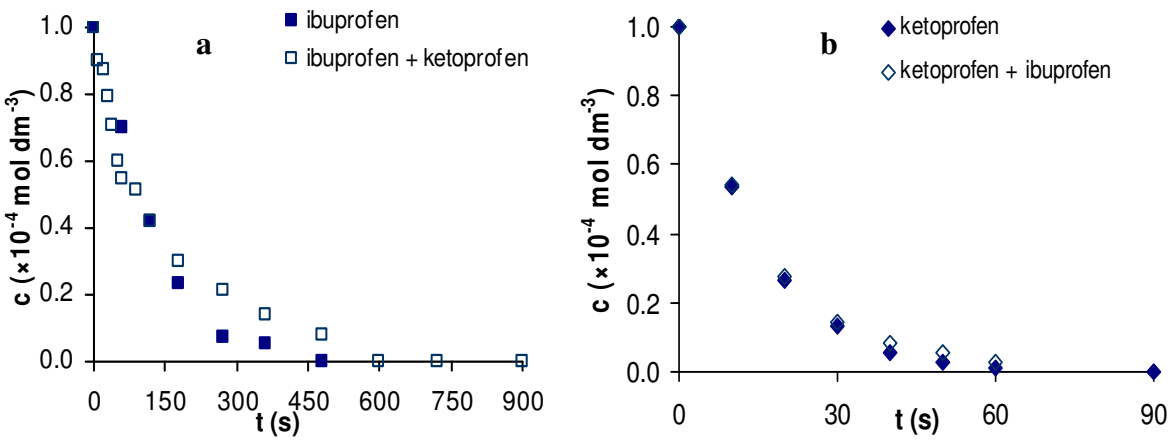


Figure 4-18 UV/VUV degradation of ibuprofen (a) and ketoprofen (b) in the mixture solutions and as single compound in oxygenated solutions

The UV/VUV photolysis of the mixture containing the two compounds was also investigated. Similarly to UV photolysis, ibuprofen had no considerable effect on the decomposition of ketoprofen (**Figure 4-18 b).** But in opposite to UV photolysis, ketoprofen practically had no effect on the photolysis of ibuprofen (**Figure 4-18 a**) in the presence of dissolved oxygen. On the other hand, in oxygen free solutions (**Figure 4-19)** the decomposition rate of both compounds was higher in their mixture, than when they were measured alone. The experimental results can be interpreted by the reaction of OH-radicals generated by the VUV irradiation. The much higher decomposition rate of ibuprofen is caused by radical reactions, and the accelerating effect of ketoprofen is insignificant. In the decomposition of ketoprofen, the contribution of radical reactions is significant, but the

dominant decomposition way is UV photolysis. In oxygen free solutions, the peroxy type reaction can not form, therefore the contribution of the radical decomposition way is moderate and the accelerating effect of ketoprofen on the decomposition of ibuprofen is important. In oxygen free solutions, the degradation of ketoprofen is faster in the presence of ibuprofen, caused likely by the radicals formed from ibuprofen.

It is worth to mention that both compounds degrade faster in the mixture solution than alone in nitrogen saturated solution.

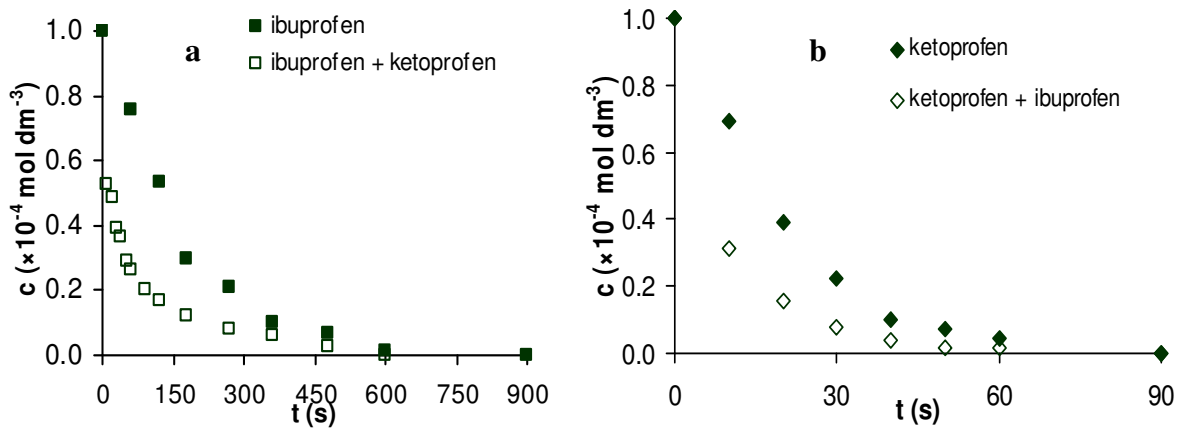


Figure 4-19 Comparison of the UV/VUV degradation of ibuprofen (a) and ketoprofen (b) in the mixture solutions and as single compound in oxygen free solutions

This reasoning is confirmed by the measurements performed with different molar ratio of the compounds in similar conditions. The results are shown in **Figure 4-20** and **Figure 4-21**.

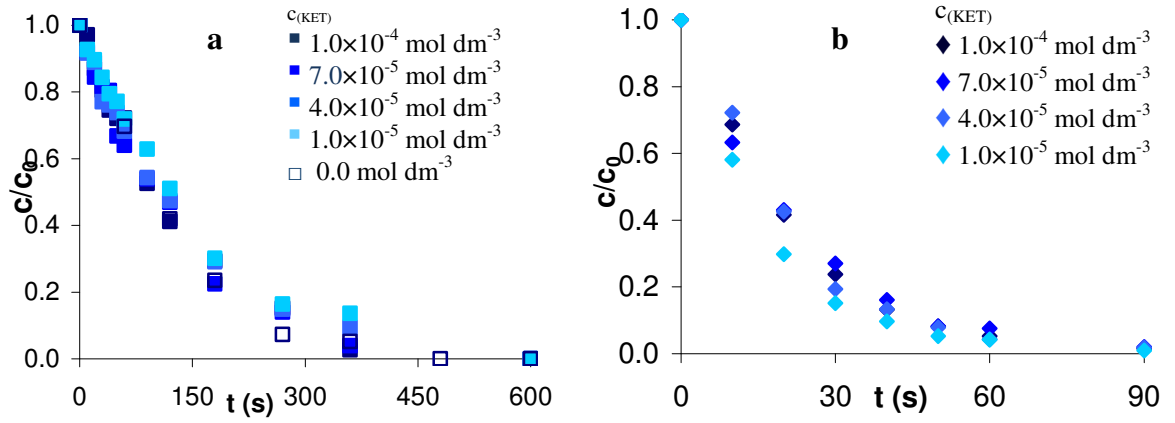


Figure 4-20 The UV/VUV degradation of ibuprofen (a) and ketoprofen (b) in oxygen saturated mixture solutions with different ketoprofen concentrations and constant ibuprofen concentration (1.0×10^{-4} mol dm^{-3})

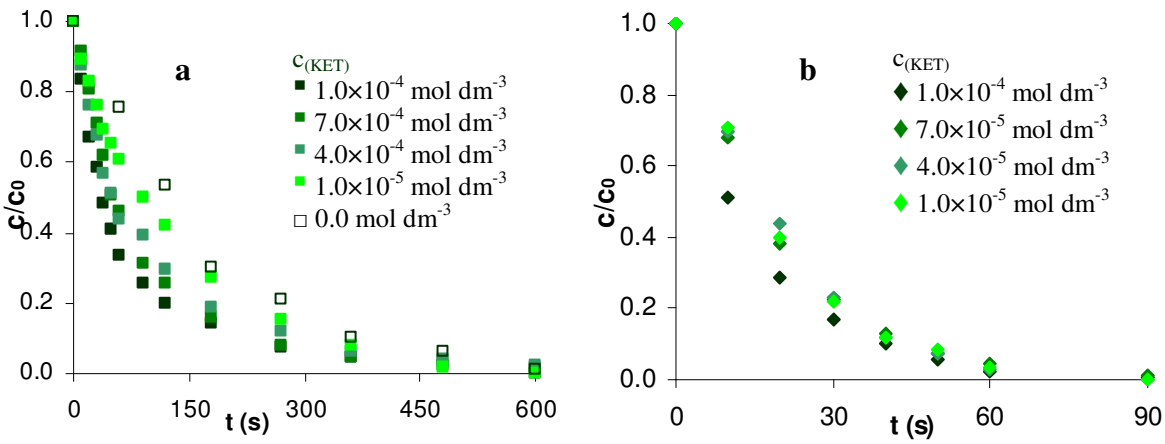


Figure 4-21 The UV/VUV degradation of ibuprofen (a) and ketoprofen (b) in oxygen free mixture solutions with different ketoprofen concentrations and constant ibuprofen concentration (1.0×10^{-4} mol dm^{-3})

The half lifetimes of the UV/VUV degradation of ibuprofen and ketoprofen in the mixture solutions are given in **Table 4-10** and **Table 4-11**. The data summarized in these tables confirm the previous statements.

Table 4-10 The half lifetimes (s) of ibuprofen (1.0×10^{-4} mol dm^{-3}) in presence of different ketoprofen concentrations during the UV/VUV degradation in presence of N_2 and O_2

	KET c_0 (mol dm^{-3})	**O_2**	**N_2**
IBU	1.0×10^{-4}	100	45
	7.0×10^{-5}	130	45
	4.0×10^{-5}	100	50
	1.0×10^{-5}	100	90

Table 4-11 The half lifetimes (s) of ketoprofen in the presence of ibuprofen (1.0×10^{-4} mol dm^{-3}) during the UV/VUV degradation in presence of N_2 and O_2

	c_0 (mol dm^{-3})	**O_2**	**N_2**
KET	1.0×10^{-4}	15	10
	7.0×10^{-5}	15	15
	4.0×10^{-5}	< 10	15
	1.0×10^{-5}	15	15

The kinetical parameters collected in the **Table 4-12** and **Table 4-13** are in accordance with the interpretation given above.

Table 4-12 The kinetic parameters of the UV/VUV degradation of ibuprofen (1.0×10^{-4} mol dm^{-3}) in the presence of ketoprofen of different concentrations

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol$dm^{-3}s^{-1}$)
O_2	1.0×10^{-4}	6.70×10^{-3}	6.70×10^{-7}
	7.0×10^{-5}	5.90×10^{-3}	4.13×10^{-7}
	4.0×10^{-5}	6.77×10^{-3}	2.71×10^{-7}
	1.0×10^{-5}	7.49×10^{-3}	7.49×10^{-8}
N_2	1.0×10^{-4}	1.56×10^{-2}	1.56×10^{-6}
	7.0×10^{-5}	1.15×10^{-2}	8.05×10^{-6}
	4.0×10^{-5}	7.52×10^{-3}	3.01×10^{-7}
	1.0×10^{-5}	7.84×10^{-3}	7.84×10^{-8}

The following table contains the data of the degradation of the solutions with different ketoprofen concentrations in the presence of ibuprofen.

Table 4-13 The kinetic parameters of the UV/VUV degradation of ketoprofen in the presence of ibuprofen (1.0×10^{-4} mol dm^{-3})

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol $dm^{-3}s^{-1}$)
O_2	1.0×10^{-4}	7.22×10^{-2}	7.22×10^{-6}
	7.0×10^{-5}	6.52×10^{-2}	4.56×10^{-6}
	4.0×10^{-5}	6.45×10^{-2}	2.58×10^{-6}
	1.0×10^{-5}	6.49×10^{-2}	6.49×10^{-7}
N_2	1.0×10^{-4}	6.11×10^{-2}	6.11×10^{-6}
	7.0×10^{-5}	5.22×10^{-2}	3.65×10^{-6}
	4.0×10^{-5}	5.49×10^{-2}	2.20×10^{-6}
	1.0×10^{-5}	5.32×10^{-2}	5.32×10^{-7}

4.3.3. VUV degradation of the mixture solution of ibuprofen and ketoprofen

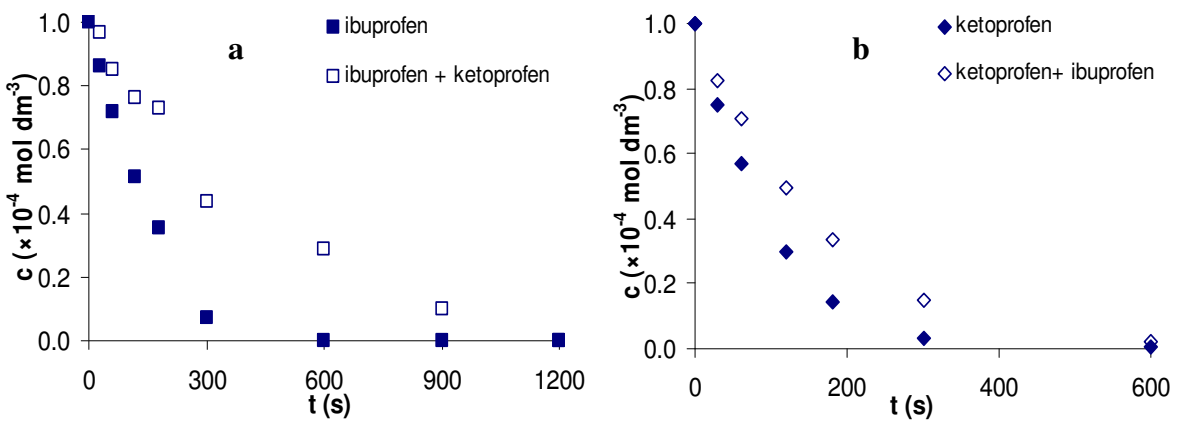


Figure 4-22 Comparison of the VUV degradation of ibuprofen (a) and ketoprofen (b) in their mixture and separately in oxygen saturated solutions

Ibuprofen and ketoprofen in their mixture was decomposed in oxygenated and oxygen free solutions. The results are given on the **Figure 4-22 and Figure 4-23**.

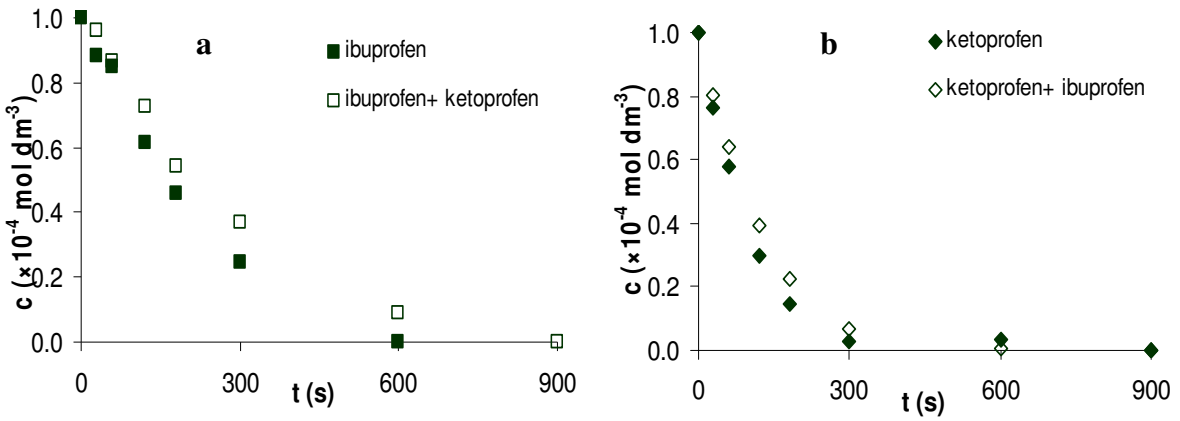


Figure 4-23 Comparison of the VUV degradation of ibuprofen (a) and ketoprofen (b) in their mixture and separately in oxygen free solutions

The degradation of the compound separately was faster than in the mixture in consequence with their competition for the very reactive species. In oxygenated solution this effect was expressed. The competitive reactions were confirmed by the series of experiments carried out with addition of different amounts of the partner compound, which are depicted in **Figure 4-24.**

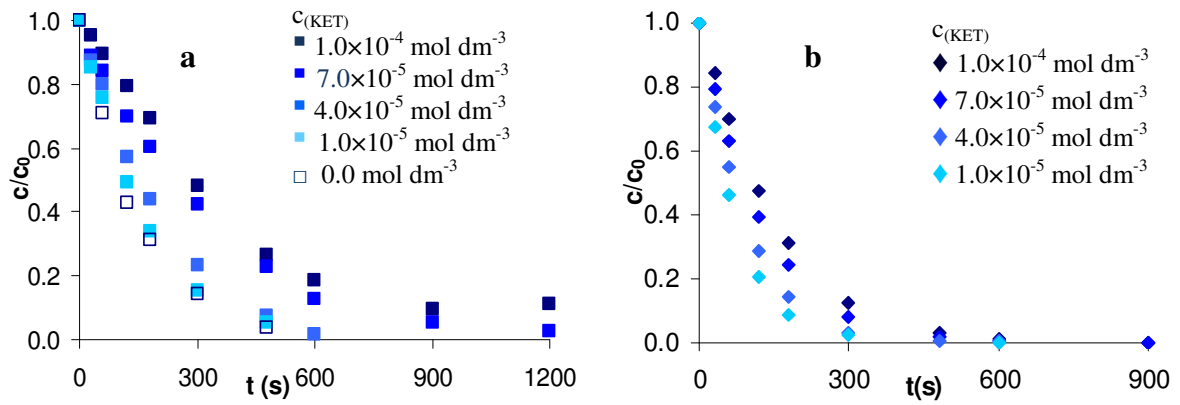


Figure 4-24 The VUV degradation of ibuprofen (a) and ketoprofen (b) (1.0×10^{-4} mol dm^{-3}) in oxygen saturated mixture solutions with addition of ketoprofen of different concentrations

4.4. Ultraviolet, ultraviolet/vacuum-ultraviolet and vacuum-ultraviolet photolysis of naproxen

4.4.1. Decomposition of naproxen by UV (254 nm) light

Figure 4-25 shows the UV spectrum of naproxen in aqueous solution. Naproxen has a main absorption band centred at 230 nm, the second band centred around 270 nm, and a third band of lower intensity around 320 nm.

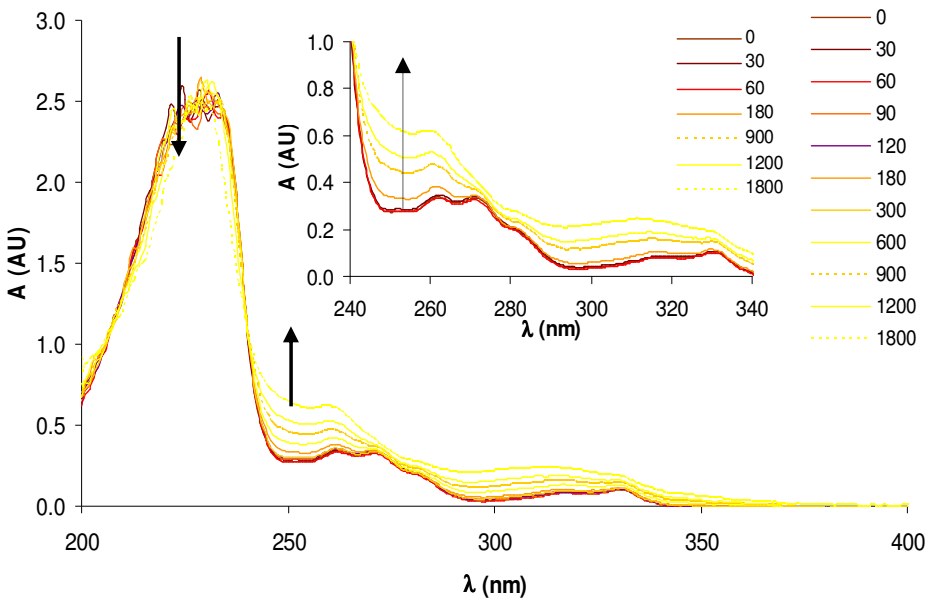


Figure 4-25 UV spectrum of naproxen as a function of the irradiation time ($c_{NAP} = 6.0\times10^{-5}$ mol dm^{-3}, UV photolysis)

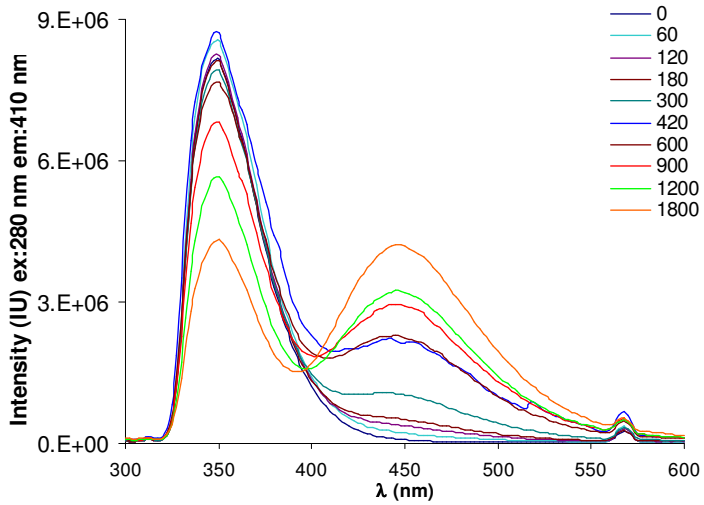


Figure 4-26 Evolution of the fluorescence spectra of naproxen as a function of the irradiation time ($c_{NAP} = 6.0\times10^{-5}$ mol dm^{-3}, UV photolysis)

As previously mentioned, naproxen has a fluorescence band with a maximum at 350 nm. During the irradiation the fluorescence spectrum is strongly modified as depicted in **Figure 4-26**. The main band is originally centred at 350 nm. By the decomposition of the target compound another fluorescence band appears at 460 nm.

The kinetics of the degradation of naproxen was investigated by HPLC. The results are shown in **Figure 4-27**.

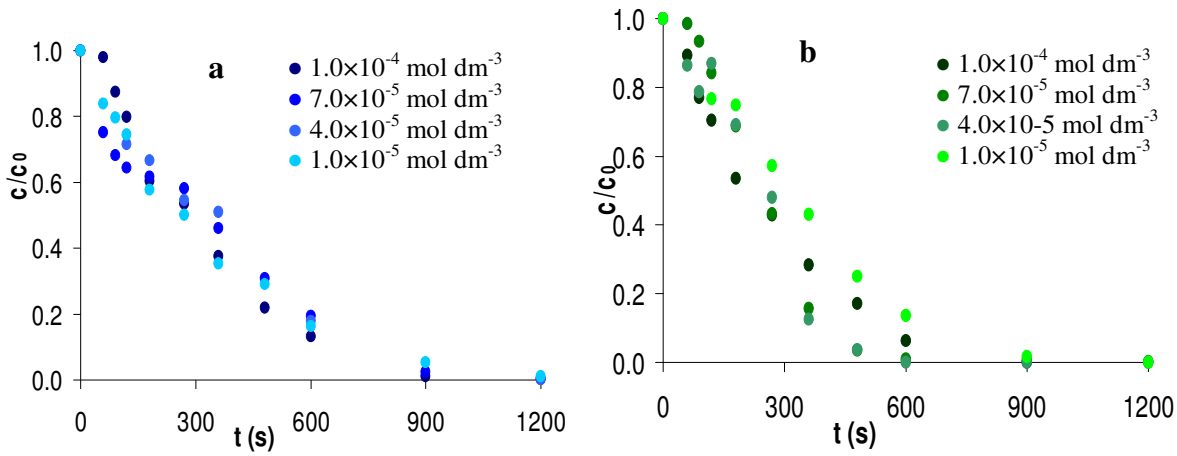


Figure 4-27 The UV decomposition of naproxen in presence of oxygen (a) and in oxygen free solutions (b)

In the presence of dissolved oxygen the degradation of naproxen is proportional to its initial concentration, but the relative decomposition rate is independent from it. In the absence of oxygen, dependence appears in the relative decomposition rates. At higher initial concentrations the rate of decomposition is higher. In the case of a concentration of 1.0×10^{-5} mol dm^{-3} the effect of dissolved oxygen is not significant. The complete degradation of naproxen is reached in 1200 seconds. In the presence of oxygen a very short induction period can be observed.

Table 4-14 The half lifetimes (s) during UV degradation in presence of N_2 and O_2

	c_0 (mol dm^{-3})	O_2	N_2
NAP	1.0×10^{-5}	270	200
	4.0×10^{-5}	360	260
	7.0×10^{-5}	300	240
	1.0×10^{-4}	320	250

4.4.1.1. Reaction rate and quantum yield of UV degradation

The degradation rates of naproxen were calculated as for ibuprofen and ketoprofen (*Chapter 4.2.1.1.*). The data are collected in **Table 4-15**. The quantum yields of the degradations were also calculated [74].

The formal first order rate constants seem to be independent of the initial concentration and from the presence of dissolved oxygen. In the presence of dissolved oxygen the degradation starts with the induction period. The kinetic parameters were calculated from data obtained after this period. The rate constants calculated this way for oxygen free solutions showed first order kinetics. The influence of dissolved molecular oxygen and the initial concentration of the target molecules on the initial degradation rates are shown in **Figure 4-28** and **Figure 4-29**.

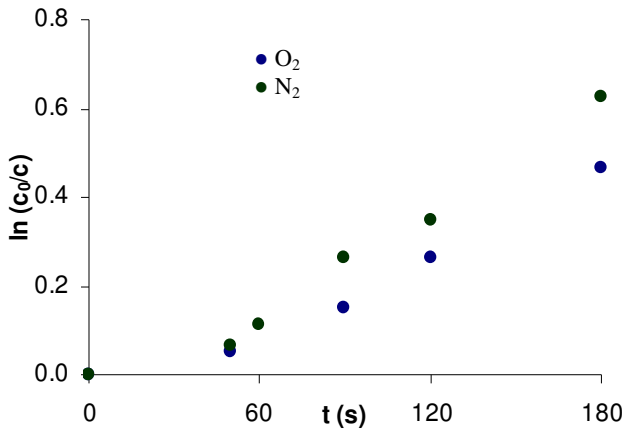


Figure 4-28 The kinetics of the UV degradation of naproxen in oxygen saturated and in oxygen free solutions ($c_0 = 1.0\times10^{-4}$ mol dm^{-3})

Table 4-15 The kinetic parameters of the UV degradation of naproxen

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3} s^{-1})	ϕ
O_2	1.0×10^{-5}	2.83×10^{-3}	2.82×10^{-8}	0.083
	4.0×10^{-5}	2.54×10^{-3}	1.01×10^{-7}	0.075
	7.0×10^{-5}	2.55×10^{-3}	1.78×10^{-7}	0.075
	1.0×10^{-4}	2.92×10^{-3}	2.92×10^{-7}	0.086
N_2	1.0×10^{-5}	2.88×10^{-3}	2.88×10^{-8}	0.085
	4.0×10^{-5}	2.51×10^{-3}	1.00×10^{-7}	0.074
	7.0×10^{-5}	5.74×10^{-3}	2.30×10^{-7}	0.169
	1.0×10^{-4}	3.97×10^{-3}	3.97×10^{-7}	0.117

The emitted photon flux I_0 of the UV light source was determined by the same method that was used for ibuprofen and ketoprofen. The quantum yield values determined in this

work are less than a unit, suggesting that beside the degradation other deactivation processes without degradation take place also in the systems.

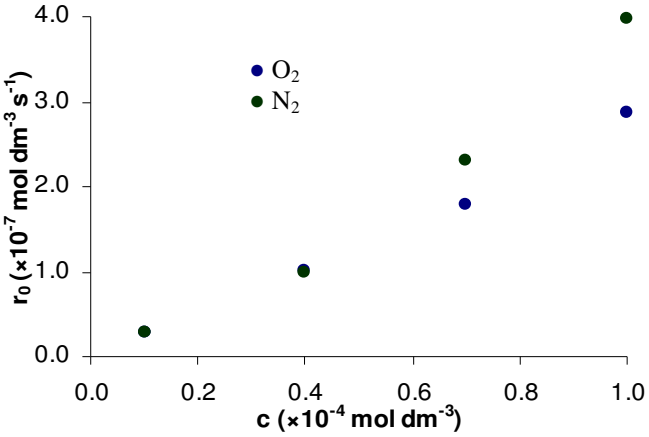


Figure 4-29 The concentration dependence of the initial reaction rates of the UV degradation of naproxen and the effect of the dissolved molecular oxygen

4.4.2. Decomposition of naproxen by UV/VUV (254/185 nm) irradiation

The UV/VUV degradation of naproxen was also investigated. The degradation combining UV (254 nm) and VUV (185 nm) light was carried out in the reactor described previously.

The spectrophotometric analysis of the UV/VUV degradation showed that the complete degradation of naproxen is faster but the product distribution is similar as it was presented for the UV photolysis. The degradation of the target molecule and formation and degradation of the by-products were followed by chromatographic separation.

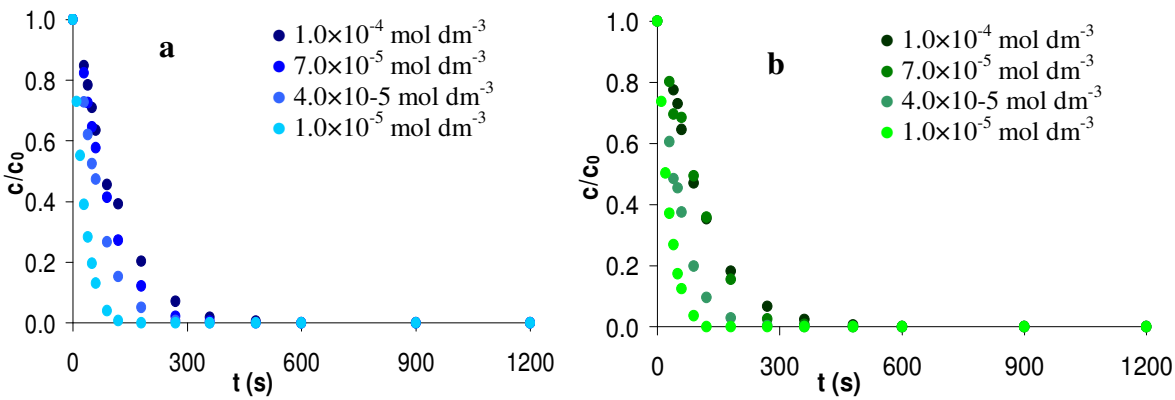


Figure 4-30 UV/VUV photodegradation of naproxen in presence of oxygen (a) and nitrogen (b)

The results of the photolysis in solutions saturated with oxygen are shown in **Figure 4-30 a**. In the case of the UV/VUV photolysis it can be stated that the relative rate of degradation increases with decreasing concentration, but the actual rates increase.

Depending on the initial concentration, the degradation can be up to ten times faster in comparison with UV degradation, even in oxygen free solutions (**Figure 4-30 b**). This effect can be explained by the reaction of OH-radicals generated directly from water by 185 nm irradiation. The role of dissolved molecular oxygen in this case is to prevent the recombination of the hydrogen and hydroxyl radicals, producing other oxygen centred radicals, such as hydroperoxyl radicals.

Table 4-16 The half lifetimes (s) during UV/VUV degradation in presence of N_2 and O_2

	c_0 (mol dm^{-3})	O_2	N_2
NAP	1.0×10^{-5}	15	15
	4.0×10^{-5}	55	40
	7.0×10^{-5}	55	55
	1.0×10^{-4}	90	70

4.4.2.1. Reaction rate of naproxen decomposition in UV/VUV degradation

The degradation rates of naproxen were calculated and are given in **Table 4-17**. The calculations show that the formal first order rate constants of the degradation are slightly dependent of the initial concentration of the target molecule, suggesting the complex nature of the degradation processes under these experimental conditions. Dissolved molecular oxygen has no influence on this parameter. (**Figure 4-31**). The constants calculated in this way for the oxygen free solutions confirm the first order kinetics. The influence of dissolved molecular oxygen and the initial concentration of naproxen on the initial degradation rates are shown in **Figure 4-31** and **Table 4-17**.

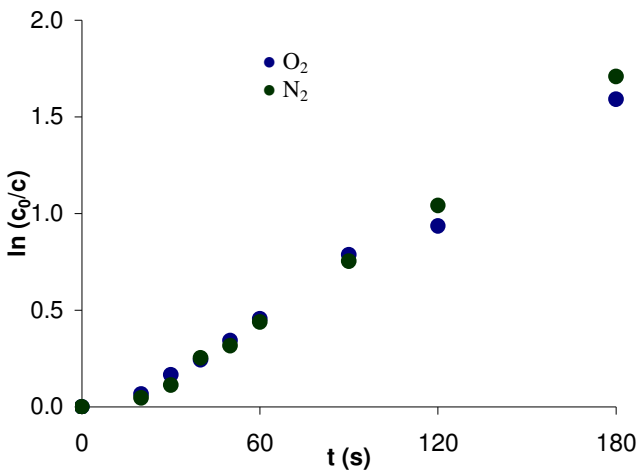


Figure 4-31 The kinetics of the UV/VUV degradation of naproxen in oxygen saturated and in oxygen free solutions ($c_0 = 1.0\times10^{-4}$ mol dm^{-3})

Table 4-17 Kinetical parameters of the UV/VUV degradation of naproxen

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3} s^{-1})
O_2	1.0×10^{-5}	3.42×10^{-2}	3.42×10^{-7}
	4.0×10^{-5}	1.72×10^{-2}	6.88×10^{-7}
	7.0×10^{-5}	1.34×10^{-2}	9.38×10^{-7}
	1.0×10^{-4}	1.06×10^{-2}	1.06×10^{-6}
N_2	1.0×10^{-5}	3.54×10^{-2}	3.54×10^{-7}
	4.0×10^{-5}	1.97×10^{-2}	7.88×10^{-7}
	7.0×10^{-5}	1.26×10^{-2}	8.82×10^{-7}
	1.0×10^{-4}	1.11×10^{-2}	1.11×10^{-6}

4.4.3. VUV photolysis of naproxen

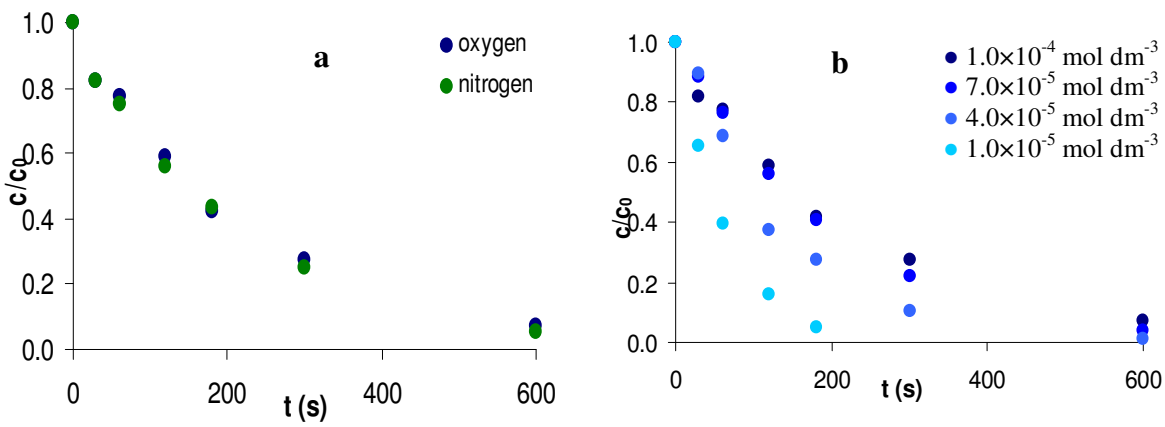


Figure 4-32 VUV degradation of naproxen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}) in the presence and in the absence of dissolved oxygen (a) and concentration dependence of the degradation (b) in oxygen saturated solutions

The VUV photolysis of naproxen was carried out in the same experimental conditions as in the case of ibuprofen and ketoprofen. The **Figure 4-32** represents the degradation of naproxen in the presence and in the absence of oxygen **(a)** and of four oxygenated solutions of different naproxen concentrations (1.0×10^{-5} mol dm^{-3}, 4.0×10^{-5} mol dm^{-3}, 7.0×10^{-5} mol dm^{-3} and 1.0×10^{-4} mol dm^{-3}) **(b)**.

This decomposition behaviour is very similar to ketoprofen one. Dissolved oxygen has no noticeable effect on the decomposition. The decrease in the relative concentration (compared to its initial value) is highly dependent on the naproxen concentration suggesting the direct radical formation from the target compound.

4.4.4. VUV degradation of the mixture solution of naproxen and ketoprofen

The effect of ketoprofen on naproxen degradation (and by changing of position, the effect of naproxen on ketoprofen degradation) was also investigated. The experiments show similar results with the observations in the relation of ibuprofen/ketoprofen (**Figure 4-33**). Both compounds decompose with a higher rate alone, than in their mixture.

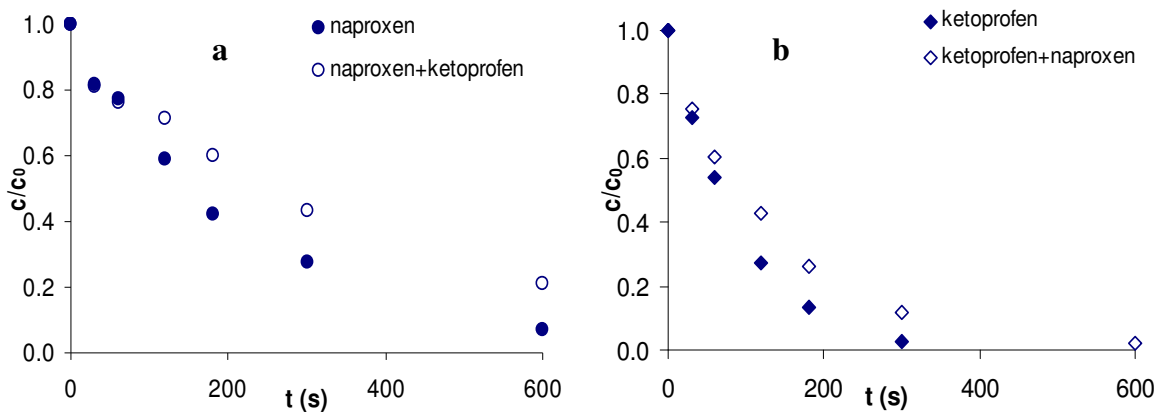


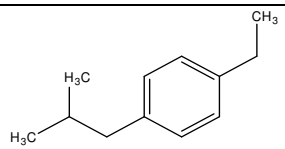
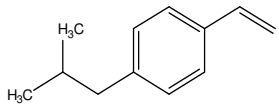
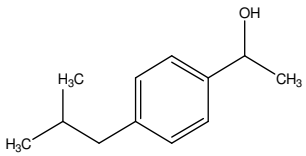
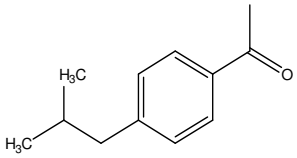
Figure 4-33 VUV degradation of naproxen (a) and ketoprofen (b) in their mixture solutions and alone

4.5. Photoproducts identification

4.5.1. By-products in the decomposition of ibuprofen and ketoprofen

The by-products of ketoprofen were determined by HPLC-MS, and GC-MS was used for the degradation products of ibuprofen. The results are summarized in **Table 4-18** and **4-19**. The retention times presented in the tables are from the GC-MS and HPLC-MS measurements, respectively. The main process of the by-product formation is decarboxylation [29, 131, 132].

Table 4-18 The indentified UV photoproducts of ibuprofen (analysed by GC-MS)

Name	t_{ret} (min)	m/z	Structure
1-ethyl-4-(2-methylpropyl)-benzene	9.65	162	
1-ethenyl-4-(2-methylprophyl)-benzene	9.95	160	
1-(1-hydroxyethyl)-4-isobuthyl-benzene	10.89	178	
4'-(2-Methylpropyl) acetophenone*	11.08	176	

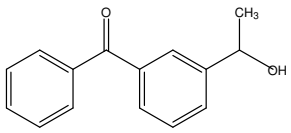
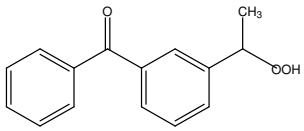
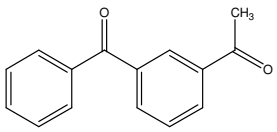
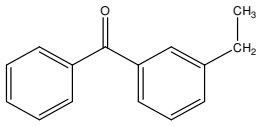
In the photolysis of ibuprofen, the main photoproducts are (1-ethyl-4-(2-methylpropyl)-benzene, 1-ethenyl-4-(2-methylpropyl)-benzene, 1-(1-hydroxyethyl)-4-isobutyl-benzene and 4'-(2-methylpropyl) acetophenone). The 4'-(2-methylpropyl) acetophenone was determined as a by-product of photo-Fenton processes [29, 131, 132] marked with *, for the three other products no photolytical literature was found. All of them were completely decomposed during one hour irradiation by UV/VUV photolysis, but using UV photolysis one unidentified photoproduct (t_{ret} = 10.27 min) was not degraded during this time. The evolution of the by-products of ibuprofen was followed by HPLC-UV and three main compounds were detected.

The obtained results are presented in **Figure 4-34 a** and **Figure 4-35 a**, these retention times were measured by HPLC-UV.

The by-products of ketoprofen (3-acetylbenzophenone, 3- ethylbenzophenone, 3-hydroxyethyl benzophenone and 3-hydroperoxyethyl benzophenone) in the presence of dissolved molecular oxygen were completely degraded in 15 minutes by UV/VUV photolysis. In the absence of oxygen this period was longer (one hour). Using UV photolysis, in the presence of dissolved oxygen, one hour was needed for the total degradation of the intermediates. The by-products of ketoprofen marked with * were found in the photolytical literature [133, 134] and 3-hydroxyethyl benzophenone and 3-acetylbenzophenone were not mentioned in the literature.

In the absence of dissolved oxygen, using UV photolysis 3-hydroperoxyethyl benzophenone did not form in the decomposition of ketoprofen.

Table 4-19 The indentified UV photoproducts of ketoprofen (analysed by HPLC-MS)

Name	t_{ret} (min)	m/z	Structure
3-hydroxyethyl benzophenone	4.6	226	
3-hydroperoxyethyl benzophenone*	5.6	242	
3-acetylbenzophenone	6.6	224	
3- ethylbenzophenone*	18.0	210	

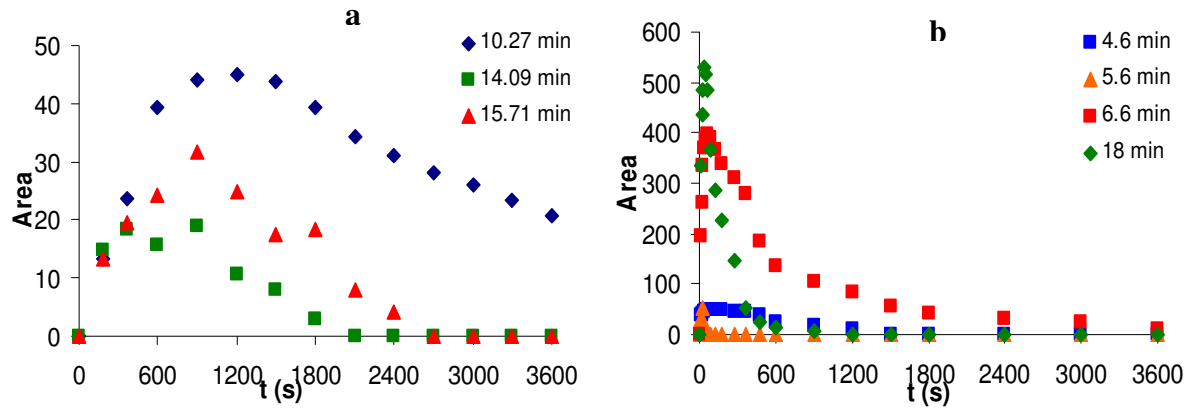


Figure 4-34 The transformation of the by-products during UV photolysis of ibuprofen (a) and ketoprofen (b) (c_0 = 1.0×10^{-4} mol dm^{-3}) in the presence of dissolved oxygen

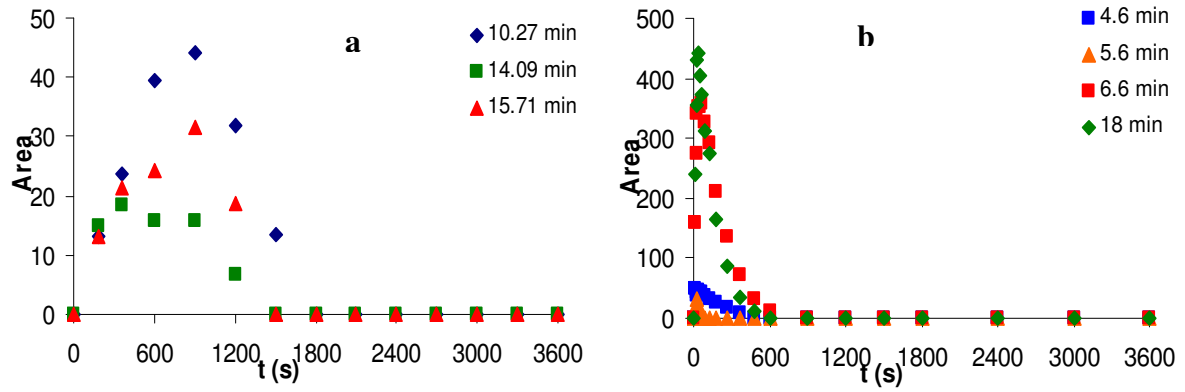


Figure 4-35 The evolution of the by-products of the UV/VUV photolysis of ibuprofen (a) and ketoprofen (b) (c_0 = 1.0×10^{-4} mol dm^{-3}) in the presence of dissolved molecular oxygen

The indentified by-products were measured. In the case of 7.0×10^{-4} mol dm^{-3} initial concentration only the by-product with the retention time of 10.27 minutes was formed and degraded within a time of one hour. In oxygen free solutions there was no qualitative difference in relation to oxygenated solutions but a slight difference was observed in the quantity of the formed products. During the UV/VUV photolysis (**Figure 4-35**) the intermediates degraded significantly faster for both compounds. In the case of ibuprofen all main by-products were eliminated within 30 minutes. The complete degradation of ketoprofen by-products needed 15 minutes. In oxygen free solutions degradation of the by-products was slightly slower than in oxygenated solutions. By the diminution of the ketoprofen concentration firstly the 3-hydroperoxyethyl benzophenone disappeared and then the 3-ethylbenzophenone.

The analysis of the by-products suggested the formation of some aliphatic acids. The determined aliphatic carboxylic acids during the UV photolysis of ibuprofen (c_0 = 1.0×10^{-4} mol dm^{-3}) were oxalic, maleic, malic, acetic, fumaric and formic acids. During the UV/VUV photolysis tartaric acid appeared, too. From these mentioned aliphatic acids maleic, oxalic and formic acids could be determined in considerable concentrations. After an hour of photolysis the concentration of these acids were still increasing.

In the case of ketoprofen during the UV degradation the same acids with small molecular mass could be determined. In the case of UV/VUV photolysis the malic acid disappeared. The concentration of oxalic acid was still increasing after 5 hours of UV photolysis.

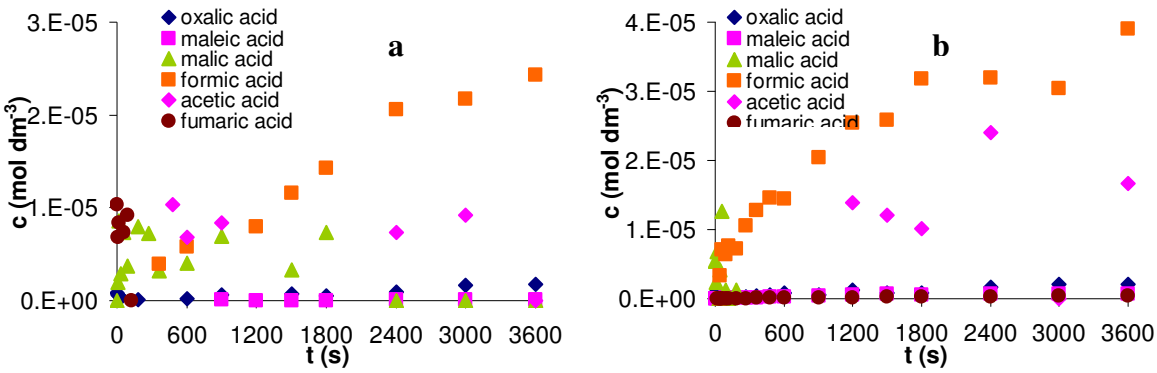


Figure 4-36 Evolution of the aliphatic by-products of ibuprofen (a) and ketoprofen (b) formed during UV photolysis in oxygenated solutions

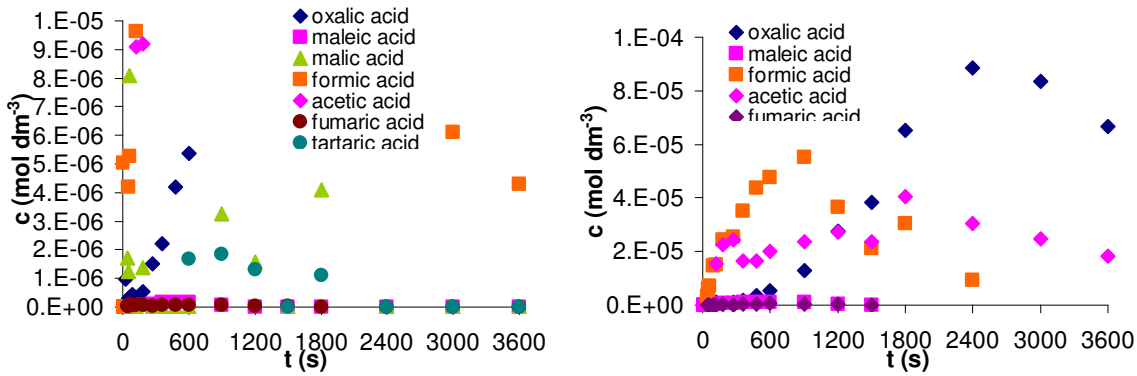


Figure 4-37 Evolution of the aliphatic by-products of ibuprofen (a) and ketoprofen (b) formed during UV/VUV photolysis in oxygen free solutions

In **Figure 4-36** the results of oxygen saturated solutions are presented. In oxygen free solutions compared to oxygen saturated solutions, there was no difference in the case of ibuprofen during the UV photolysis. In the case of the UV/VUV measurements of oxygenated

solutions of ibuprofen the maleic, fumaric and tartaric acids disappeared. The formation of aliphatic acids in oxygen free solutions during the degradation of ketoprofen was also investigated. In the case of UV photolysis the same products formed as in oxygenated solutions (**Figure 4-37**). The difference can be observed in the case of UV/VUV photolysis of ketoprofen solutions in the absence of oxygen is that in this case the formation of acetic acid cannot be observed, instead malic acid appears.

4.5.2. By-products of naproxen decomposition

The identification of naproxen photoproducts was carried out on HPLC-UV-MS. During the UV photolysis four main by-products were detected, out of the four three were identified. These products are mentioned in the literature [111, 112]. Their evolution and their data are given in the **Table 4-20** and in **Figure 4-38**.

Table 4-20 The determined UV photoproducts of naproxen by HPLC-MS

Name	t_{ret} (min)	m/z	Structure
1-(2-methoxy naphthalene-6-yl)ethane-1,2 diol	9.7	218	
2-methoxy-6-vinylnaphthalene	9.95	185.4	
1-(2- methoxy naphthalene-6-yl)ethanone	11.08	201.3	

The main step of the formation of the by-products is decarboxylation [111, 112]. The main photoproducts were completely degraded in twenty minutes using UV/VUV photolysis. Under UV photolysis only one by-product was not degraded in one hour; more than 95 % of the three other main photoproducts were decomposed.

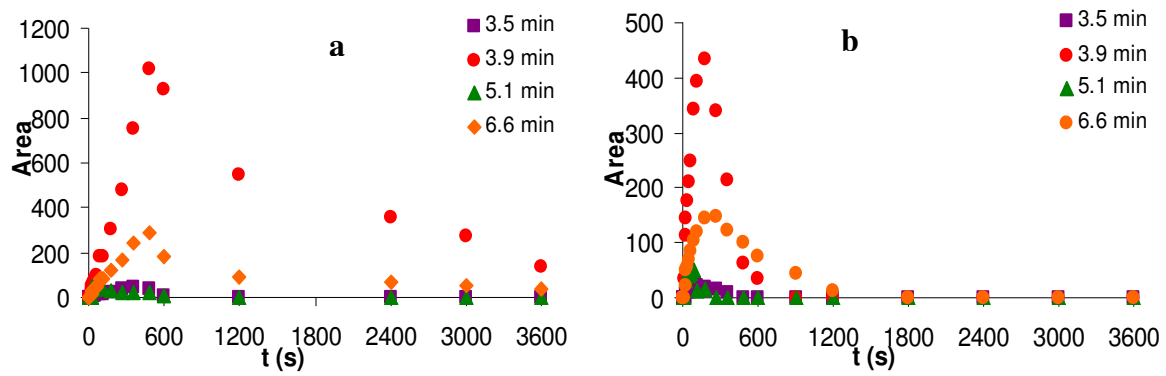


Figure 4-38 Evaluation of the main by-products formed during UV (a) and UV/VUV (b) photolysis of naproxen

Due to the TOC content (as seen in *Chapter 4.5.2*) when the complete degradation of naproxen was finished, a significant amount of organic carbon remained in the samples. The structure of naproxen already suggested the formation of some aliphatic acids. The measured aliphatic acids from the UV and UV/VUV photolysis of naproxen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}) in the presence and in the absence of dissolved molecular oxygen were acetic, propionic, oxalic, malic and succinic acids, as it can be seen in **Figure 4-39**.

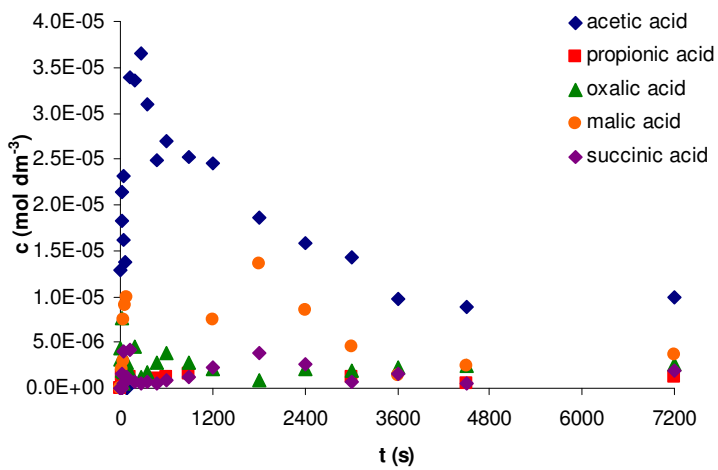


Figure 4-39 Evolution of the aliphatic by-products formed during UV/VUV photolysis of naproxen

4.6. Distinction of photolytic and radical reaction pathways

4.6.1. The effect of methanol on the decomposition of ketoprofen

During these measurements, methanol as specific OH-radical scavenger was used [135, 136]. Methanol reacts with the hydroxyl radicals by the following reaction:

$$CH_3OH + \bullet OH \rightarrow \bullet CH_2OH + H_2O \qquad k = (0.78\text{-}1.0)\times10^{9}\ dm^{3}\ mol^{-1}\ s^{-1} \quad [137]$$

The experimental conditions were the same as it was previously showed (with exception of methanol addition). The initial concentrations of the target compounds were the same as previously (1.0×10^{-5} mol dm^{-3}, 4.0×10^{-5} mol dm^{-3}, 7.0×10^{-5} mol dm^{-3} and 1.0×10^{-4} mol dm^{-3}) and the added methanol concentration was 0.1 mol dm^{-3}.

The results are shown on the **Figure 4-40** and **Figure 4-41.**

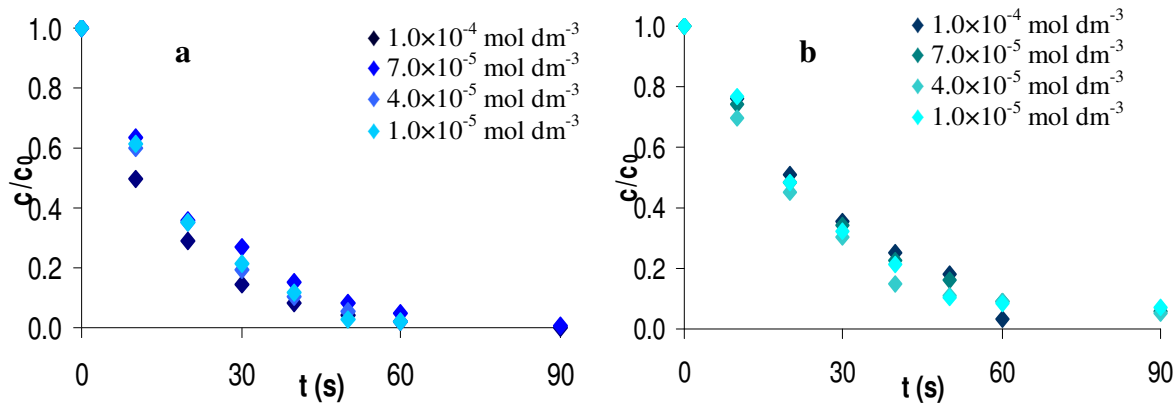


Figure 4-40 The UV degradation of ketoprofen in absence (a) and in presence (b) of methanol in oxygenated solutions

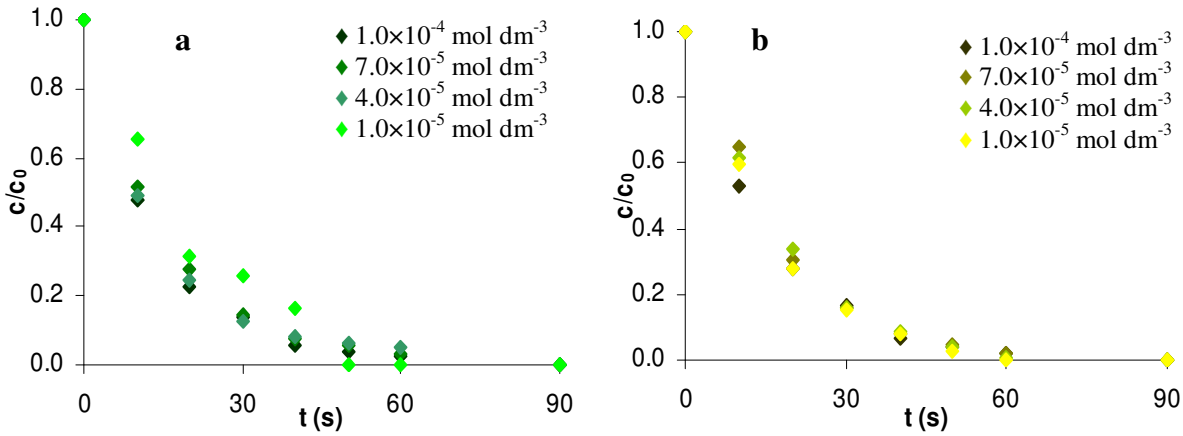


Figure 4-41 The UV degradation of ketoprofen in absence (a) and in presence (b) of methanol in oxygen free solutions

The radical scavenging by methanol is a good possibility to separate the photolytic and OH-radical reaction pathways of decompositions investigated. Supposing a perfect inhibition by methanol, in case of its addition the photolytic reaction is dominant in the decomposition.

The overall rate and rate constants were determined by the same way as it was given in *chapter 4.2.1.1*. The measurements were performed both in the presence and absence of methanol. The results are given in **Figure 4-42.**

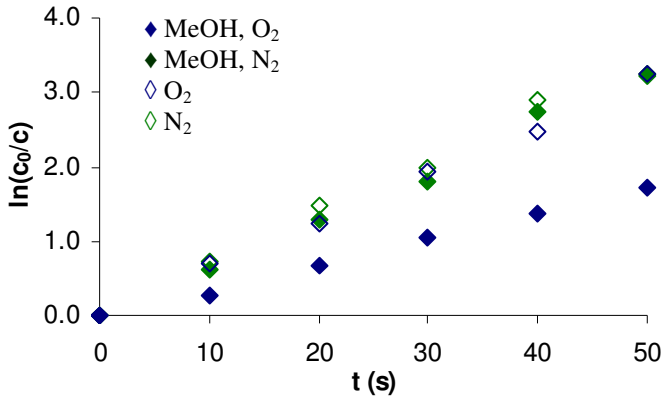


Figure 4-42 The kinetics of the UV degradation of ketoprofen in presence and in absence of methanol in oxygen saturated and in oxygen free solutions ($c_0 = 1.0\times10^{-4}$ mol dm^{-3})

According to the presentation, the transformation is a pseudo first order reaction. The calculated rate coefficients are given in the **Table 4-21.** The calculated initial rates are also given in this table. These data are depicted in **Figure 4-43**, too. The results show, that methanol practically has no inhibition effect in oxygen free solutions, but its effect is significant in oxygenated solutions. The decomposition rate of the methanol inhibited solutions is lower in oxygenated solutions, than in oxygen free solutions. One of the possible interpretations for this observation is the relaxation ability of oxygen molecule in the solution. In consequence of this process a smaller part of ketoprofen decomposes.

Table 4-21 Kinetical parameters of the UV degradation of ketoprofen

		c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3} s^{-1})	ϕ
O_2	UV	1.0×10^{-4}	6.31×10^{-2}	6.31×10^{-6}	0.225
		7.0×10^{-5}	4.65×10^{-2}	3.26×10^{-6}	0.166
		4.0×10^{-5}	5.39×10^{-2}	2.16×10^{-6}	0.192
		1.0×10^{-5}	5.16×10^{-2}	5.16×10^{-7}	0.184
	UV+MeOH	1.0×10^{-4}	3.42×10^{-2}	3.42×10^{-6}	0.122
		7.0×10^{-5}	3.64×10^{-2}	2.55×10^{-6}	0.130
		4.0×10^{-5}	3.96×10^{-2}	1.58×10^{-6}	0.141
		1.0×10^{-5}	3.77×10^{-2}	3.77×10^{-7}	0.135
N_2	UV	1.0×10^{-4}	7.16×10^{-2}	7.16×10^{-6}	0.255
		7.0×10^{-5}	6.61×10^{-2}	4.63×10^{-6}	0.236
		4.0×10^{-5}	6.90×10^{-2}	2.76×10^{-6}	0.246
		1.0×10^{-5}	5.84×10^{-2}	5.84×10^{-7}	0.208
	UV+MeOH	1.0×10^{-4}	6.15×10^{-2}	6.15×10^{-6}	0.220
		7.0×10^{-5}	6.15×10^{-2}	4.31×10^{-6}	0.220
		4.0×10^{-5}	6.11×10^{-2}	2.44×10^{-6}	0.218
		1.0×10^{-5}	6.23×10^{-2}	6.23×10^{-7}	0.222

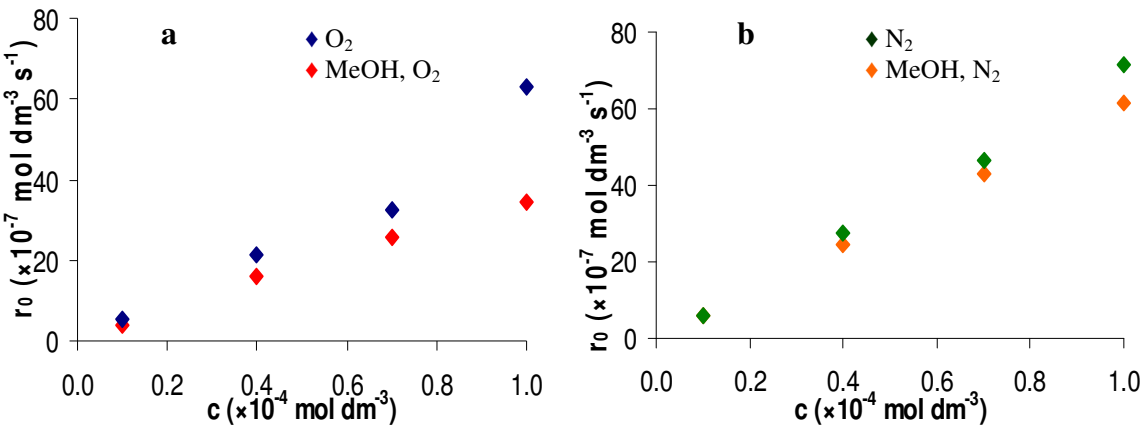


Figure 4-43 The concentration dependence of the initial reaction rates of the UV degradation of ketoprofen in presence (a) and in absence (b) of oxygen and the effect of methanol addition

The influence of methanol on the UV/VUV photolysis of ketoprofen was also investigated using the same experimental conditions as showed previously. The results of these experiments are shown in **Figure 4-44** and **Figure 4-45.**

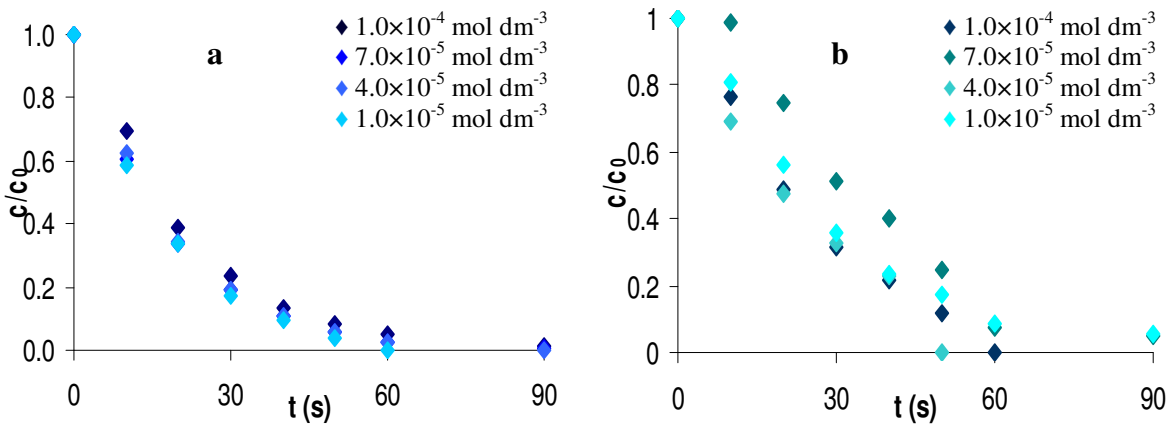


Figure 4-44 Comparison of the UV/VUV degradation of ketoprofen in absence (a) and in presence (b) of methanol in oxygenated solutions

In accordance with the previous results methanol has an effect on decomposition of ketoprofen. In oxygen free solution, this influence is moderate, and in oxygenated solution it is notable. By the previous results it can be established that the hydroxyl radicals have role in the degradation of ketoprofen although this effect is not primary.

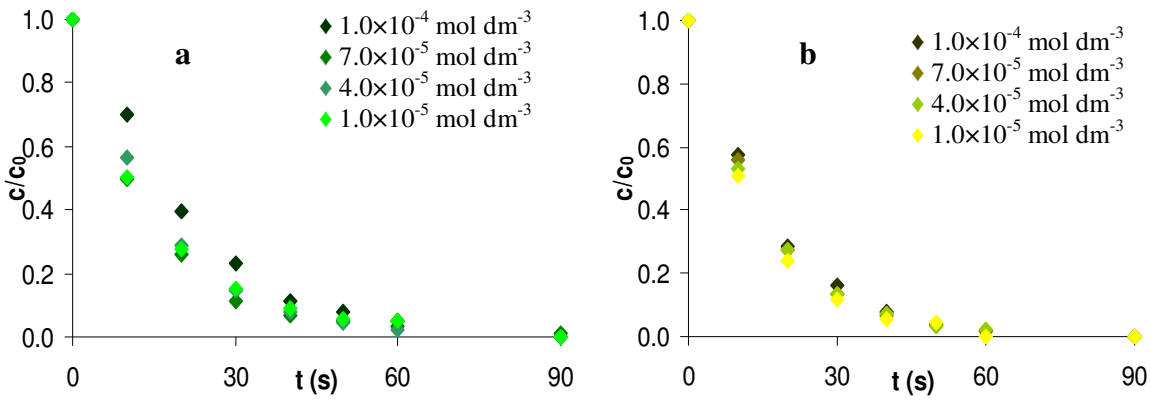


Figure 4-45 Comparison of the UV/VUV degradation of ketoprofen in absence (a) and in presence (b) of methanol in oxygen free solutions

The kinetical parameters of the UV/VUV photolysis were also determined for these results. They are collected in **Table 4-22** and depicted in **Figure 4-46.** It is worthy to mention, that the values of calculated decomposition rate coefficients are practically the same (within the standard deviation of measurements) in methanol inhibited reactions both in oxygenated and oxygen free solutions.

Table 4-22 Kinetical parameters of the UV/VUV degradation of ketoprofen

		c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3} s^{-1})
O_2	UV/VUV	1.0×10^{-4}	4.98×10^{-2}	4.98×10^{-6}
		7.0×10^{-5}	5.58×10^{-2}	3.91×10^{-6}
		4.0×10^{-5}	5.52×10^{-2}	2.21×10^{-6}
		1.0×10^{-5}	5.41×10^{-2}	5.41×10^{-7}
	UV/VUV+MeOH	1.0×10^{-4}	3.70×10^{-2}	3.70×10^{-6}
		7.0×10^{-5}	2.42×10^{-2}	1.69×10^{-6}
		4.0×10^{-5}	3.74×10^{-2}	1.50×10^{-6}
		1.0×10^{-5}	3.44×10^{-2}	3.44×10^{-7}
N_2	UV/VUV	1.0×10^{-4}	5.19×10^{-2}	5.19×10^{-6}
		7.0×10^{-5}	7.24×10^{-2}	5.07×10^{-6}
		4.0×10^{-5}	6.56×10^{-2}	2.62×10^{-6}
		1.0×10^{-5}	6.64×10^{-2}	6.64×10^{-7}
	UV/VUV+MeOH	1.0×10^{-4}	6.33×10^{-2}	6.33×10^{-6}
		7.0×10^{-5}	6.66×10^{-2}	4.66×10^{-6}
		4.0×10^{-5}	6.62×10^{-2}	2.65×10^{-6}
		1.0×10^{-5}	7.20×10^{-2}	7.20×10^{-7}

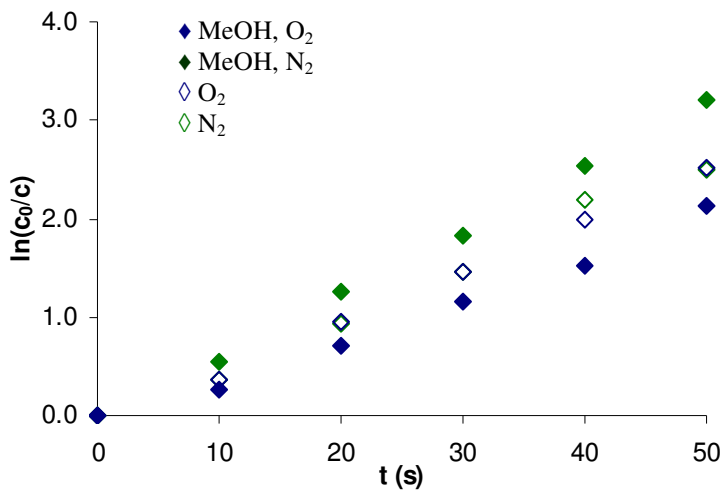


Figure 4-46 The kinetics of the UV/VUV degradation of ketoprofen in presence and in absence of methanol in oxygen saturated and in oxygen free solutions ($c_0 = 1.0\times10^{-4}$ mol dm^{-3})

4.6.2. The effect of sodium azide on the photolytic decomposition

To decide, if there is the formation of other oxygen centred radicals next to the hydroxyl radicals, the UV and UV/VUV degradation of ketoprofen was investigated at 1.0×10^{-4} mol dm^{-3} initial concentration in the presence of sodium azide. The sodium azide is a very strong and not selective radical scavenger, it reacts with most of the radicals which contain oxygen. Due to this fact it reacts not only with the hydroxyl but with the hydroperoxyl radicals and superoxide radical ions. It captures the singlet oxygen, but to prove the role of the singlet oxygen is not enough to be convinced of the inhibiting effect of degradation in the presence of Na-azide (0.1 mol dm^{-3}), it needs to prove its presence by other independent techniques.

The results of the measurements are shown in the **Figure 4-47** and **4-48**.

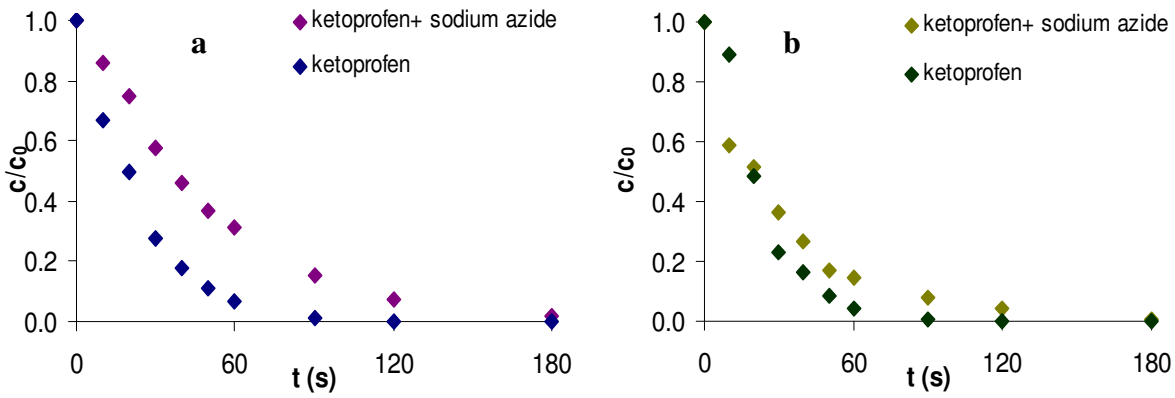


Figure 4-47 UV degradation of ketoprofen in absence and in presence of sodium azide in oxygenated (a) and oxygen free (b) solutions

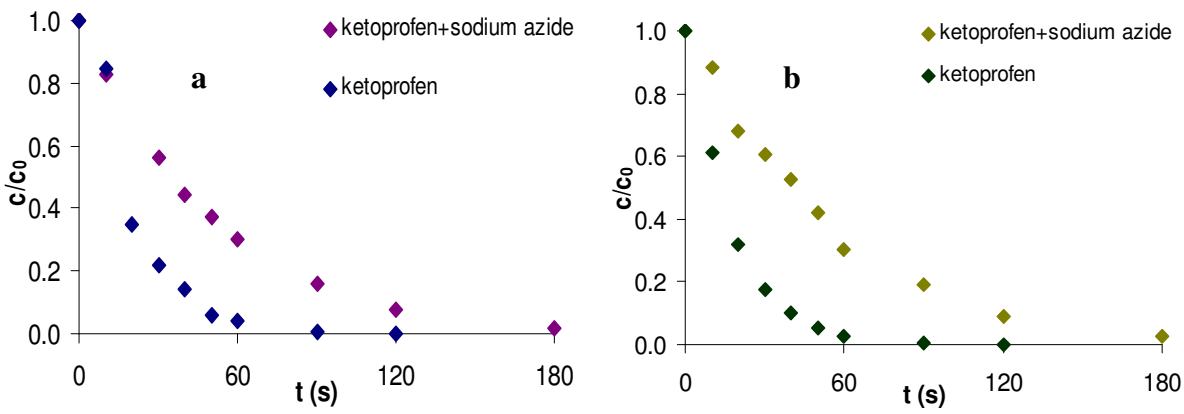


Figure 4-48 UV/VUV degradation of ketoprofen in absence and in presence of sodium azide in oxygenated (a) and oxygen free (b) solutions

According to the results, the sodium azide has larger inhibiting effect than only the methanol, a specific hydroxyl radical scavenger. These results are in accordance with the results obtained by methanol inhibition experiences. The azide-ion has no inhibition effect in oxygen free solution photolyzed by UV irradiation. The effect increases by change of oxygen concentration in the solution. Expressed inhibition effect was measured in UV/VUV photolysis of ketoprofen. This effect is nearly the same both in oxygenated and oxygen free solution.

4.6.3. Detection of other radicals generated during the degradation of ketoprofen

By the help of ESR spectroscopy in the presence of the proper scavenger not only the oxygen centred, but other radicals can be detected. In the interest of this statement experiments were carried out in the presence of 5,5'-dimethyl-1-pyrrolin-N-oxyde (DMPO), which is trapping oxygen-, carbon centred and other radicals non specifically.

These measurements were carried out in cooperation with Dr. László Korecz at the Hungarian Academy of Science, Research Center of Chemistry, Department of Molecular Spectroscopy, Laboratory of Electron Spin Resonance.

For the measurements oxygen free 1.0×10^{-4} mol dm^{-3} ketoprofen solution was used in the presence of DMPO. The spectra were taken at 1 and at 5 minutes of photolysis. The following figure shows the ESR spectra of the one minute photolysis:

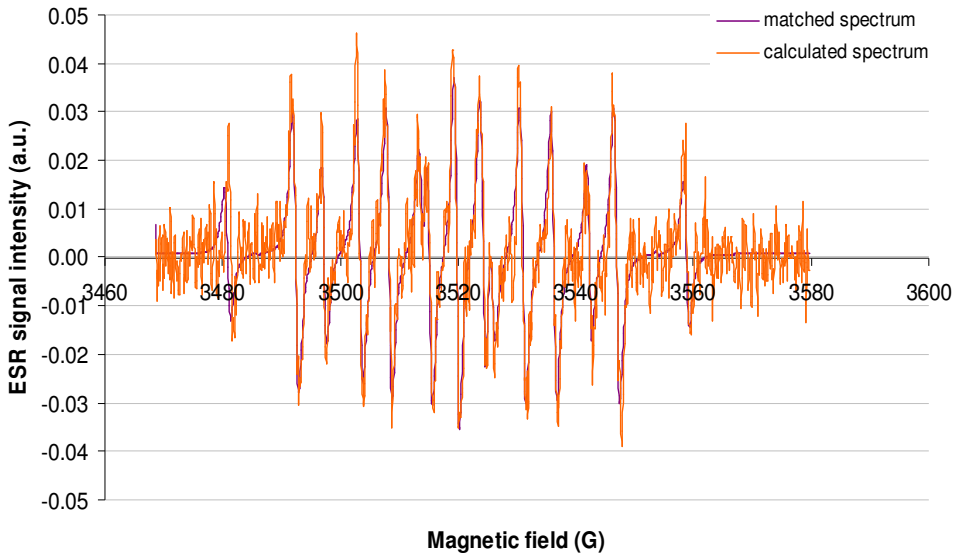


Figure 4-49 ESR spectra (matched and calculated) of the one minute UV/VUV photolysis of ketoprofen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3})

The matching of the ESR spectra was carried out by the software developed by professor Antal Rockenbauer [138].

On the **Figure 4-49** the superposition of the two spectra can be seen. The two radicals determined are a trapped hydrogen atom (g = 2.0053; a_N = 16.47 G; $a_{H(2)}$ = 22.52 G) and a trapped COO_2 radical (g = 2.0054; a_N = 15.91 G; $a_{H(2)}$ = 22.79 G). The proportion of the two spectra was 0.27 which increased to 0.93 for the measurements at five minutes.

This refer to that the concentration of the carboxyl radical is decreasing during the photolysis. On the other hand the generation of the carboxyl radical is not surprising as we proved by our previous HPLC-MS measurements that the formation of a by-product of ketoprofen starts with its decarboxylation.

Due to the previous results it is proven that not only oxygen centred radicals can be generated during the photolytic decomposition of ketoprofen.

4.6.4. The effect of methanol on the UV degradation of ibuprofen

The effect of the methanol as radical scavenger on the photodegradation of ibuprofen was also investigated.

In the case of ibuprofen the same experimental conditions were applied, the initial concentration of ibuprofen was 1.0×10^{-4} mol dm^{-3}. During the UV photolysis, the methanol has no effect on the decomposition of ibuprofen, as the data given in **Figure 4-50** show.

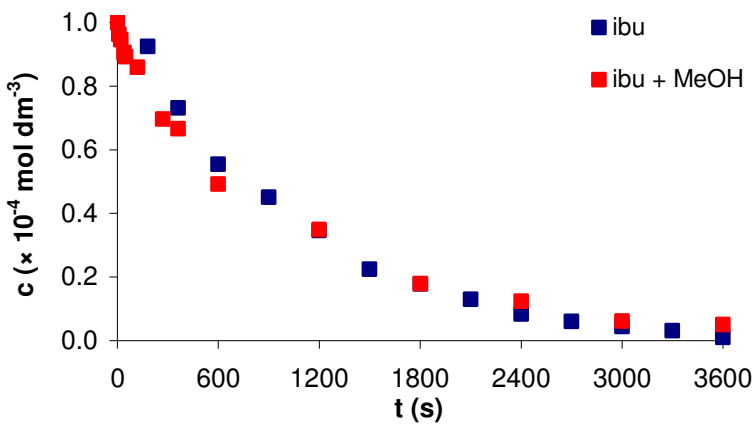


Figure 4-50 Effect of the methanol on the UV degradation of ibuprofen in oxygenated solutions

The calculated rates and rate coefficients in the presence and absence of methanol are practically the same values (**Table 4-23**) and the kinetical equation seems to be formally first order.

Table 4-23 Kinetical parameters of the UV degradation of ibuprofen in presence and absence of methanol

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3} s^{-1})	ϕ
UV	1.0×10^{-4}	1.0×10^{-3}	1.0×10^{-7}	0.12
UV+MeOH	1.0×10^{-4}	8.9×10^{-4}	8.9×10^{-8}	0.11

The influence of methanol on UV/VUV photolysis of ibuprofen is significant. This result is in accordance with the previous statements, namely the ibuprofen reacts partly with the OH-radicals generated by VUV irradiation of water. The results of this investigation are shown in **Figure 4-51.**

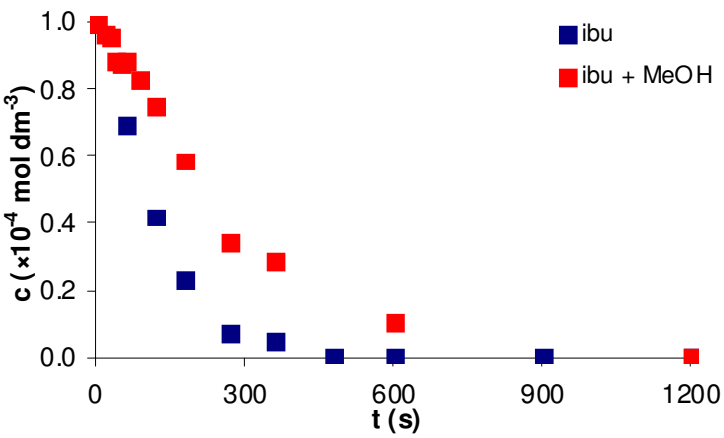


Figure 4-51 UV/VUV degradation of ibuprofen in absence and in presence of methanol in oxygenated solutions ($c_0 = 1.0\times10^{-4}$ mol dm^{-3})

4.6.4.1. The rate constants of the UV/VUV degradation of ibuprofen

The kinetical parameters of the methanol inhibited UV/VUV photolysis were determined similarly as presented previously.

Table 4-24 Kinetical parameters of the UV/VUV degradation of ketoprofen

	c_0 (mol dm^{-3})	k (s^{-1})	r_0 (mol dm^{-3} s^{-1})
UV	1.0×10^{-4}	8.5×10^{-3}	8.5×10^{-7}
UV+MeOH	1.0×10^{-4}	3.6×10^{-3}	3.6×10^{-7}

The data, given in the **Table 4-24** show an important inhibition, the decomposition rate is the half value as determined without the addition of methanol. It follows that the half of ibuprofen decomposes by UV/VUV radiation on radical way. It is in accordance with the findings, that the decomposition of ibuprofen by way of UV/VUV is about two times higher, than by UV irradiation.

4.6.5. Investigation of the effect of methanol on the UV and UV/VUV degradation of ibuprofen in the presence of ketoprofen

The photolytical degradation of ibuprofen was investigated by addition of methanol in the presence of ketoprofen ($c_0 = 1\times10^{-5}$ mol dm^{-3}). The obtained result is presented in **Figure 4-52**.

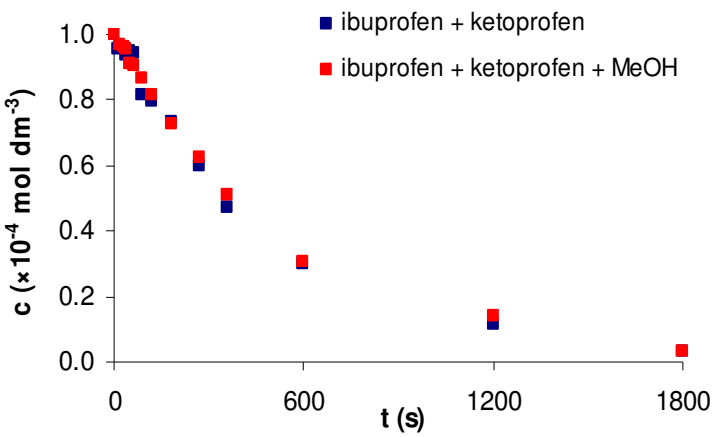


Figure 4-52 UV degradation of ibuprofen mixed with ketoprofen in the presence and absence of methanol

During the UV photolysis methanol has no apperciable effect on ibuprofen decomposition in the presence of ketoprofen. The accelerating effect of ketoprofen is very

important , as it was found in experiments presented previousely (see for example in **Figure 4-52**)

The measurements using UV/VUV irradiation result a good accordance with our preciding statements, namely the methanol decreases the decomposition rate of ibuprofen by radical scavenging, as it was excepted (**Figure 4-53**).

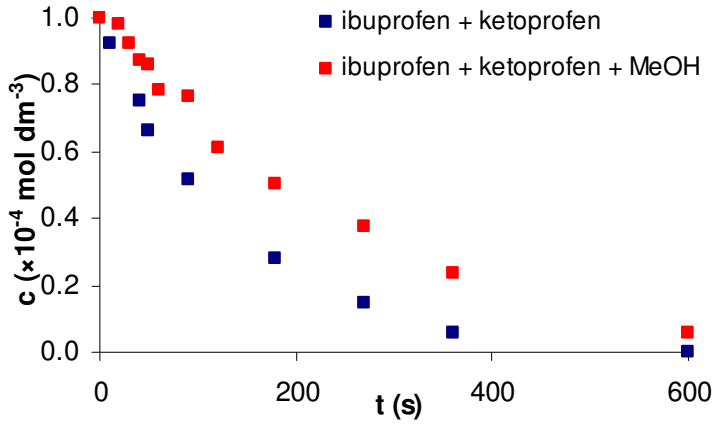


Figure 4-53 UV/VUV degradation of ibuprofen mixed with ketoprofen in the presence and absence of methanol

4.7. Mineralisation of the target compounds during UV, UV/VUV and VUV photolysis

4.7.1. Mineralization of ibuprofen and ketoprofen

To get information about the mineralization, Total Organic Carbon (TOC) was determined. Solutions with an initial concentration of 1.0×10^{-4} mol dm^{-3} of the target compounds in the presence of dissolved molecular oxygen were used. The results are presented in **Figure 4-54** for ibuprofen and **Figure 4-55** for ketoprofen.

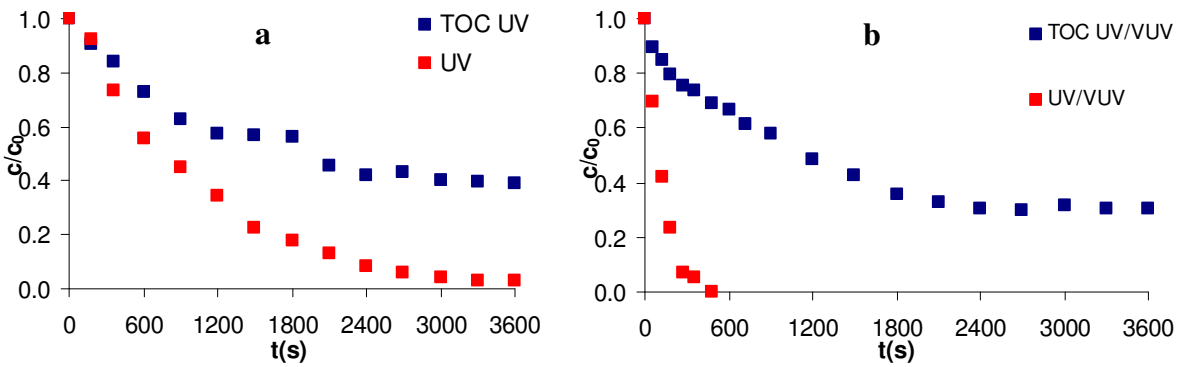


Figure 4-54 Evolution of TOC content and target molecule in the UV (a) and UV/VUV (b) photolysis of ibuprofen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}in oxygenated solutions)

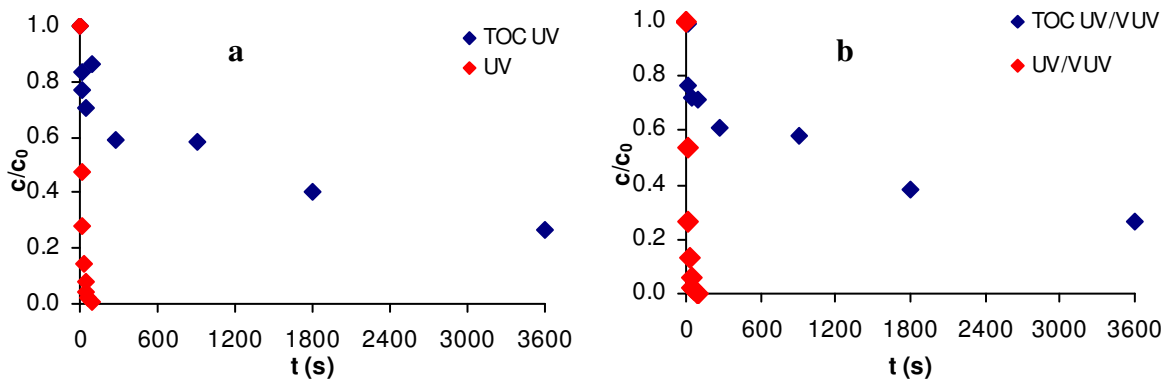


Figure 4-55 Evolution of TOC content and target compound in the UV (a) and UV/VUV (b) photolysis of ketoprofen ($c_0 = 1.0\times10^{-4}$ mol dm^{-3}, oxygenated solutions)

As the results show, both compounds are almost completely degraded during one hour of photolysis (ketoprofen degraded in one minute). The TOC measurements show, that the rate of mineralization was around 60% for both compounds and there is no significant difference between the two types of photolysis.

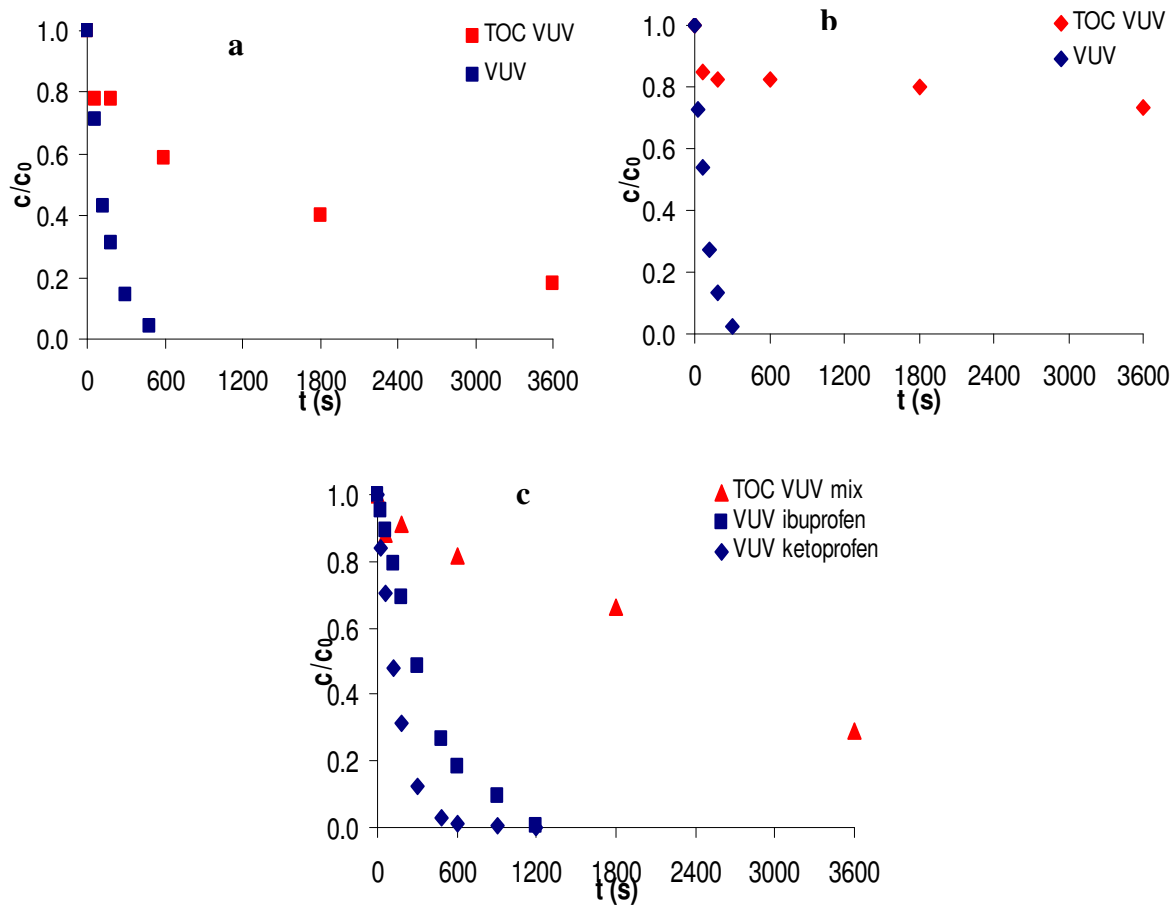


Figure 4-56 TOC of ibuprofen (a) (1.0×10^{-4} mol dm^{-3}), ketoprofen (b) (1.0×10^{-4} mol dm^{-3}) and ibuprofen mixed with ketoprofen (c) (1.0×10^{-4} mol dm^{-3}- 1.0×10^{-4} mol dm^{-3}) irradiated by xenon excimer lamp

In the case of the VUV degradation of ibuprofen (1.0×10^{-4} mol dm^{-3}), ketoprofen (1.0×10^{-4} mol dm^{-3}) and mixed solution the degree of mineralisation also was determined. The results are gathered in **Figure 4-56**.

After 60 minutes of irradiation, ibuprofen, ketoprofen and the mixed solutions contain 20 %, more than 70 % and 30 % organic carbon, respectively.

4.7.2. Mineralization of naproxen

Total Organic Carbon (TOC) was measured for initial concentration of 1.0×10^{-4} mol dm^{-3} of naproxen in oxygenated solutions. The results are presented in **Figure 4-57**.

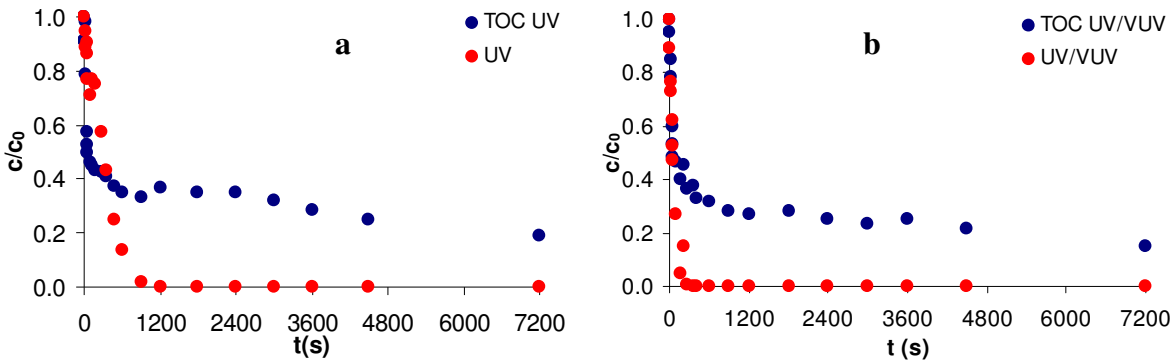


Figure 4-57 Evaluation of the TOC content during the UV (a) and UV/VUV (b) photolysis in comparison with the degradation of naproxen

Naproxen is totally degraded after twenty minutes of photolysis. From the results of the TOC measurements, the degree of mineralization was around 70% for the UV and UV/VUV photolysis during one hour and 80 and 90%, respectively during two hours of irradiation.

5. Summary

According to literature, more and more active pharmaceuticals are released into the environment even by biologically treated sewage water. This thesis is based on experimental work dealing with three non steroidal anti-inflammatory drugs and their photolysis with ultraviolet (UV), ultraviolet combined with vacuum ultraviolet (UV/VUV) and vacuum ultraviolet (VUV, emits photons of higher energy than the previous) light.

These methods of photolysis were chosen because they are modern and will hopefully be used as the final step of treating sewage water in the future (disinfection). On the other hand it is useful to know ways of removing pharmaceuticals from sewage water. These three methods were chosen mainly because the first two can be conducted with cost-effective, low pressure mercury vapor lamp, furthermore as we raise the energy of irradiation, the formation of radicals, known for their reactivity, come into the forefront.

Some of the conditions of these reactions have been systematically investigated, including the initial concentration of the target molecule and the influence of dissolved molecular oxygen on the reaction.

During this work light sources with identical geometric and electric properties were used for the UV and UV/VUV photolysis, and reactors with similar geometric parameters were used.

In the case of VUV photolysis the electrical properties of the light source (Xe-excimer lamp) were identical to the light source of the two other methods, so the comparison of these methods is accurate.

Based on the results it can be stated that:

1. During UV photolysis

A. the degradation rate of the investigated substances is in direct relevance to their light absorbing characteristics (molar absorbance). This degradation can be described with first order kinetics.

B. The presence of dissolved molecular oxygen in the solution has no significant influence on the degradation rate with the exception of ibuprofen where there is a deviation from first

order kinetics in oxygen free solutions. As we head towards smaller concentrations the relative degradation rate decreases.

C. Methanol, as OH-radical scavenger and the azide-ion as a broad spectrum radical scavenger has no notable inhibiting effect on the degradation of either of the investigated compounds, therefore photolytic degradation is the primary way of degradation.

2. During UV/VUV photolysis

A. where 185 nm light was also used beside the 254 nm light, insignificant increase of the degradation rate was measured in case of ketoprofen, while for ibuprofen and naproxen this increase became quite significant. The relative degradation rate rises at higher initial concentrations. This can be explained by the increased ratio of radicals that contribute to the reaction.

B. Dissolved oxygen had a minor effect on the degradation rate of ketoprofen, while in case of ibuprofen and naproxen this effect is significant.

C. In accordance with the previous statement, methanol as an OH-radical scavenger has a slight influence on the degradation of ketoprofen while it is significant inhibitor for the degradation of ibuprofen and naproxen. For Na-azide this effect is more explicit, especially in solutions where dissolved oxygen is present. This means that other than OH-radical take part in the degradation process, like peroxyde- and hydroperoxyde radical ions.

3. During VUV photolysis using Xe-excimer lamp

A. photons with much larger energy are absorbed by water, generating radicals which react with the target molecules. This is indicated by the fact that the degradation rate is independent of the initial concentration; at smaller concentrations the degradation rate is slow. This shows that the rate at which the radicals are generated by VUV irradiation determines the rate of the degradation process.

B. The presence of dissolved oxygen influenced the reaction rate less than expected. Based on the “cage-effect” which was experienced during the examination of other substances, we can state that the excited water molecule leaves this cage not because of dissolved oxygen, but due to the target molecule, generating more radicals.

C. Radical scavengers inhibit the process during VUV photolysis in slightly different way. These slight alternations can be explained by the fact that these molecules compete for the radicals differently. Na-azide as a universal radical scavenger inhibits these degradation processes more than methanol.

4. Ketoprofen is known to be ***photosensitizer*** when in interaction with a biological system. It was investigated wether this effect is also true for non-biological systems, by combining ibuprofen and ketoprofen in the same photolytic reaction, using all three methods previously mentioned.

A. In the case of UV photolysis ketoprofen accelerated the degradation of ibuprofen both in oxygenated and oxygen free solutions. The other way around this was not true; the degradation of ketoprofen was not influenced by ibuprofen.

B. Under UV/VUV photolysis this effect of ketoprofen was also noted, although not to the scale measured in UV. The photosensitizing effect of ketoprofen was somewhat smaller in oxygenated solutions than in oxygen free solutions.

C. In the case of VUV photolysis, based on the previous experiments, this effect of ketoprofen was not expected. On the contrary, according to general reaction kinetic expectations both compounds inhibited each others degradation.

D. The usage of radical scavengers reinforced our prior statement, when used in UV photolysis they have no inhibiting effect. In UV/VUV photolysis we can experience some inhibition in the degradation of ibuprofen, this inhibition is somewhat smaller, and then when ibuprofen was photolyzed alone. Ketoprofen had no notable influence on the degradation of ibuprofen when the reactions were inhibited by radical scavengers during VUV photolysis.

5. By-products formed during UV and UV/VUV photolysis were determined and their evolution in time in oxygenated and oxygen free solutions was followed. The most important by-products in case of ibuprofen are (1-ethyl-4-(2-methylpropyl)-benzene, 1-ethenyl-4-(2-methylpropyl)-benzene, 1-(1-hydroxyethyl)-4-isobutyl-benzene, 4'-(2-methylpropyl) acetophenone). Based on these findings we can say that the degradation starts with decarboxylation. During the degradation of ketoprofen we determined four intermediates, 3-acetylbenzophenone, 3- ethylbenzophenone, 3-hydroxyethyl benzophenone, and 3-hydroperoxyethyl benzophenone. In the case of naproxen we followed the evolution of four intermediers, and determined the structure of three of them. These intermediers were 1-(2-methoxy naphthalene-6-yl) ethane-1,2 diol, 2-methoxy-6-vinylnaphthalene, 1-(2-methoxy naphthalene-6-yl)ethanone.

It was also found that the degradation of these intermediers results in the formation of aliphatic oxygen type compounds, mainly carboxylic acids.

6. The ***mineralisation process*** of the target compounds was followed by measuring the total organic carbon (TOC) content. The measurements showed that the degree of mineralisation is small during the complete degradation of the substances. The mineralisation is the smallest during UV photolysis, and in the case of ketoprofen, for all the three methods.

From the three methods investigated, with the applied experimental conditions, the mineralisation of the target molecules was most efficient in the case of UV/VUV photolysis.

6. Résumé

De nos jours, l'intérêt de l'étude des composés pharmaceutiques dans le milieu aqueux est grandissant comme le montre le nombre d'articles paraissant dans les revues scientifiques à comité de lecture. Ma thèse de doctorat a eu pour objet l'étude de la photolyse de trois composés non-stéroïdiens anti-inflammatoires, l'ibuprofène, le ketoprofène et le naproxène, par rayonnement ultra-violet (UV), rayonnement ultraviolet combiné avec rayonnement ultraviolet dans le vide (UV/VUV), ainsi que par rayonnement ultraviolet dans le vide (VUV, qui émet des photons de plus grande énergie que la technique précédente). Ces méthodes de photolyse sont de plus en plus fréquentes dans les filières de traitement des eaux usées, utilisées comme étape finale de désinfection. D'autre part l'élimination des actifs pharmaceutiques doit être améliorée et mieux maîtrisée. Ces trois méthodes de photolyse ont été choisies car les deux premières ont un coût très faible, et nécessitent une lampe basse pression à vapeur de mercure. En outre, l'augmentation de l'énergie d'irradiation génère des radicaux libres, fortement réactifs.

Les effets de la concentration initiale des composés ainsi que l'influence de l'oxygène moléculaire dissous dans l'eau ont été étudiés.

Au cours de mon travail, des sources de lumière possédant les mêmes paramètres géométriques et électriques (lampe à mercure à basse pression) ainsi qu'un réacteur possédant les même paramètres géométriques ont été utilisées pour la photolyse UV et UV/VUV.

Au cours de photolyse VUV, la source de lumière appliquée (lampe Xe-excimer) possédait la même puissance d'entrée électrique que les sources de lumière utilisées en photolyse UV et UV/VUV, ce qui permet une comparaison assez fiable.

En vertu des résultats obtenus, les conclusions suivantes peuvent être tirées.

1. Au cours de la photolyse UV

A. le taux de décomposition des composés étudiés est essentiellement en relation avec leur capacité d'absorption lumineuse (absorbance molaire). La cinétique de décomposition des composés peut être décrite comme une cinétique de premier ordre.

B. La présence d'oxygène dissous n'a pas d'effet significatif sur le taux de décomposition, à l'exception de l'ibuprofène, sa décomposition dans une solution exempte d'oxygène diffère d'une cinétique de premier ordre. La vitesse de dégradation des composés est réduite à des concentrations plus faibles (par rapport à la concentration initiale).

C. Le méthanol, utilisé comme piège à radicaux OH° et ions azoture (avec un spectre large de piégeur de radicaux libres) n'a pas d'effet inhibiteur sur la décomposition des composés étudiés. Ainsi, la décomposition est principalement due à la dégradation photolytique UV et non à la formation de radicaux.

2. Au cours de la photolyse UV/VUV

A. En utilisant un rayonnement à 185 nm à la place d'un rayonnement à 254 nm, une augmentation non significative de la vitesse de décomposition du ketoprofène a été mesurée, contrairement au naproxène et à l'ibuprofène pour lesquels l'augmentation de la décomposition est devenue de plus en plus importante. Le taux de dégradation (rapport des concentrations en composé cible sur les valeurs initiales) augmente pour des concentrations initiales plus importantes. Ceci peut s'expliquer par la formation plus importante de radicaux contribuant à la dégradation.

B. L'oxygène dissous a un effet très faible sur la dégradation du ketoprofène, tandis que l'effet dans le cas du naproxène et de l'ibuprofène est bien plus grand.

C. En accord avec les précédentes remarques, le méthanol utilisé comme piège à radicaux OH° a une légère influence sur la dégradation du ketoprofène, tandis que pour les deux autres composés son effet inhibiteur est important. L'effet de l'azoture de sodium est plus prononcé, en particulier en présence d'oxygène dissous. Ceci indique que d'autres radicaux oxygénés (par exemple les radicaux peroxy- ou hydroperoxyde) jouent également un rôle dans la décomposition des composés étudiés.

3. Au cours de la photolyse VUV (lampe Xe-eximer)

A. Les photons, d'énergie beaucoup plus élevée (λ= 172 nm), sont absorbés par l'eau pour produire des radicaux libres qui réagissent avec les composés étudiés. Ceci est indiqué par le fait que le taux de dégradation est indépendant de la concentration initiale en composé. La vitesse de décomposition diminue avec la diminution de la concentration initiale, la réaction étant pratiquement indépendante de la concentration initiale. Ceci indique que l'étape limitant est la vitesse de la génération des radicaux par réaction avec le rayonnement VUV.

B. Contrairement à ce qui était attendu, la présence d'oxygène dissous dans le mélange réactionnel n'augmente pas la vitesse de réaction. Au regard d'autres expériences impliquant d'autres composés et l'observation de l'effet dit « effet de cage », on peut conclure que les molécules d'eau excitées sortent de la cage non pas à cause de l'oxygène dissous, mais par l'action des composés étudiés, produisant plus de radicaux libres.

C. Chaque inhibiteur de radicaux inhibe la réaction durant la photolyse VUV d'une manière légèrement différente. Ces différences peuvent s'expliquer par le fait que les composés

étudiés réagissent différemment avec chaque type de radicaux. L'azoture de sodium, utilisé comme piège à radicaux universel inhibe toutes ces réactions radicalaires, encore plus que le méthanol.

4. Le caractère photosensibilisateur du ketoprofène est connu lorsque celui-ci est en interaction avec des organismes biologiques. Par conséquent, il a été étudié si cet effet s'appliquait également dans des conditions non-biologiques, en combinant l'ibuprofène et le ketoprofène dans la même réaction photolytique, en utilisant les trois méthodes de photolyse pré-citées.

A. Dans le cas de la photolyse UV, la dégradation de l'ibuprofène a été accélérée par la présence du ketoprofène, que ce soit en présence et en absence d'oxygène dissous. Inversement, la décomposition du ketoprofène n'a pas été affectée par la présence de l'ibuprofen.

B. Au cours de la photolyse UV / VUV, l'effet photosensibilisateur du ketoprofène dans la décomposition de l'ibuprofène a également été observé, la décomposition est toutefois inférieure à celle lors de la photolyse UV. L'effet photosensibilisateur du ketoprofène est un peu plus faible dans des solutions contenant de l'oxygène dissous que dans des solutions sans oxygène.

C. Dans le cas de la photolyse VUV, de même que lors des expériences précédentes, l'effet photosensibilisateur du ketoprofène a été observé. En revanche, en accord avec les cinétiques des réactions, chaque composé a inhibé la décomposition de l'autre.

D. Les résultats ci-dessus sont confirmés par l'ajout d'inhibiteurs de radicaux libres : ceux-ci n'ont pas d'effet inhibiteur lors de la photolyse UV. Au cours de la photolyse UV/VUV et en présence d'inhibiteurs de radicaux, la dégradation de l'ibuprofène a été plus faible. Cette baisse, est cependant beaucoup moins élevée que lors de la photolyse de l'ibuprofène seul. Le ketoprofène n'a pas d'influence significative sur la dégradation de l'ibuprofène lors de la photolyse VUV en présence d'inhibiteurs de radicaux.

5. Les ***sous-produits générés*** lors des photolyses UV et UV/ VUV ont été déterminés et leur évolution au cours du temps en présence et en absence d'oxygène dissous a été mesurée. Dans le cas de l'ibuprofène, les principaux sous-produits observés sont le (1-étyl-4-(2-méthylpropyl)-benzène, le 1-éthenyl-4-(2- méthylpropyl)- benzène, le 1-(1-hydroxyéthyl)-4-isobuthyl- benzène, et le 4'-(2- méthylpropyl) acétophénone. Ceci suggère que la dégradation commence par une décarboxylation. Durant la décomposition du ketoprofène, quatre principaux intermédiaires ont été détectés : le 3-acétylbenzophénone, le 3-éthylbenzophénone, le 3-hydroxyéthylbenzophénone, et le 3-hydropéroxyléthylbenzophénone. Dans le cas du

naproxène, quatre intermédiaires ont été suivis. La structure de trois intermédiaires a pu être déterminée : le 1-(2-méthoxy naphtaléne-6-yl)éthane-1,2 diol, le 2-méthoxy-6-vinylnaphtaléne et le 1-(2- méthoxy naphtaléne -6-y)éthanone.

Il a également été constaté que ces intermédiaires se décomposent en composés aliphatiques oxygénés (acides carboxyliques principalement).

6. Le degré de minéralisation des composés *étudiés* a été évalué par la mesure du carbone organique total (COT). Les résultats montrent que la minéralisation est très faible lors de la décomposition des composés. La minéralisation a été la plus faible au cours de la photolyse UV, et dans le cas du ketoprofène pour les 3 méthodes de photolyse.

Des trois méthodes étudiées, dans les conditions expérimentales utilisées (à consommations d'énergie équivalentes), la minéralisation des composés étudiés s'est avérée la plus avancée dans le cas de la photolyse UV/ VUV.

7. Összefoglalás

Az irodalom szerint növekvő mennyiségben kerülnek ki gyógyszerhatóanyagok a környezetbe még a biológiailag tisztított szennyvizekkel is. Doktori disszertációm alapját képező kísérleti munkában három nemszteroid típusú gyulladáscsökkentő hatóanyag- ibuprofen, ketoprofen és naproxen- ultraibolya (UV), ultraibolya és vákuum ultraibolya (UV/VUV) és az előbbinél nagyobb energiájú fotonokat sugárzó vákuum-ultraibolya (VUV) fotolízisét vizsgáltam. Ezen fotolitikus módszereket részben azért választottam, mert a modern és várhatóan a jövőben egyre inkább elterjedő szennyvízkezelési módszerek egyre inkább alkalmaznak a folyamat végső lépéseként fotolízist (ugyan fertőtlenítésként). Másfelől a vízfelhasználásban visszakerülő, gyógyszerhatóanyagokat is tartalmazó vizekből azok eltávolítási lehetőségeit is érdemes ismerni. A három módszerre azért esett a választásom, mert az első kettő a nagyon olcsó, kisnyomású higanygőz lámpával elvégezhető, továbbá a besugárzás energiájának növelésével egyre inkább előtérbe kerülnek nagymértékű reaktivitásukról ismert szabad gyökök generálása.

Szisztematikusan vizsgáltam a reakciókörülmények hatásai közül a célvegyület kiindulási koncentrációját és vízben oldott molekulárisan oldott oxigén befolyását a vizsgált vegyületek bomlására.

Munkám során UV és UV/VUV fotolízis esetében azonos geometriai és elektromos paraméterekkel rendelkező fényforrásokat (kisnyomású higanygőz lámpa) és hasonló geometriai paraméterekkel rendelkező reaktort használtam. VUV fotolízis esetén az alkalmazott fényforrás (Xe-excimer lámpa) bemenő elektromos teljesítménye megegyezett az UV, UV/VUV fényforrások teljesítményével, lehetővé téve megbízhatóbb összehasonlítást.
Eredményeim alapján az alábbi fontosabb megállapításokat tettem.

1. UV fotolízis során

A. a vizsgált anyagok bomlásának sebessége lényegében fényelnyelőképességükkel (moláris abszorbanciájukkal) arányos. A bomlásuk formálisan első rendű kinetikával írható le a célvegyület szempontjából.

B. a jelen lévő oldott oxigén számottevő hatást nem fejt ki a bomlás sebességére. Kivételt képez ez alól az ibuprofen, melynek bomlása oxigénmentes oldatban eltér az első rendű kinetikától. Kicsiny koncentrációk irányában haladva a relatív (a kiindulási koncentrációjához viszonyított) bomlássebesség csökken.

C. metanol, mint OH-gyökfogó és azid ion, mint sokkal szélesebb spektrumú gyökfogó (és gerjesztett oxigén kioltó) gyakorlatilag nem fejt ki inhibíciós hatást egyik vegyület bomlására se, azaz UV fotolízis során a fotolitikus bomlás a meghatározó.

2. UV/VUV fotolízis során

A. a 254 nm-es sugárzás mellett 185 nm-es sugárzást is szolgáltató lámpával való megvilágítás esetén jelentéktelen mértékű bomlásnövekedés mértem ketoprofen esetében, míg ez a növekedés naproxen és ibuprofen sorrendben egyre jelentősebbé vált. A relatív (a cél-vegyület kiindulási koncentrációjára vonatkoztatott) bomlássebesség a nagyobb koncentrációk irányában növekszik, ami a bomlás gyökös hányada részarányának növekedésével értelmezhető.

B. az oldott oxigén ketoprofen esetében nagyon csekély mértékben, mint naproxen és ibuprofen esetében sokkal nagyobb mértékben növelte meg a bomlás sebességét.

C. A fentiekkel összhangban a metanol, mint OH gyökfogó a ketoprofen esetében elhanyagolható mértékű, míg a másik két vegyület bomlására jelentős mértékű inhibíciós hatást fejt ki. Na-azid estében ez a hatás kifejezettebb, különösen az oldott oxigént tartalmazó oldatokban való bomlásuknál. Ez utóbbi azt jelzi, hogy OH- gyök mellett más oxigéntartalmú gyökök (pl. hidroperoxid vagy peroxi-gyökion) is közrejátszanak a bomlásban.

3. A xenon excimer lámpát alkalmazó VUV fotolízis során

A. a sokkal nagyobb energiájú fotonokat (λ=172 nm) gyakorlatilag elnyelő víz szabad gyököket termel, és ezek reagálnak a célvegyülettel, amit jelez az, hogy a vizsgált anyagok bomlási sebessége alig függ azok minőségétől. Jellemzője a bomlásoknak, hogy a célvegyület kiindulási koncentrációjára viszonyított bomlássebesség a koncentráció csökkenésével csökken, gyakorlatilag független a kiindulási koncentrációtól. Ez azt jelzi, hogy a VUV sugárzás általi gyökgenerálás sebessége a sebességlimitáló reakciólépes.

B. A reakcióelegyben oldott oxigén jelenléte a vártnál kisebb mértékben növeli a reakciósebességet. Más vegyületek vizsgálatánál tapasztalt, úgynevezett kalitkaeffektus alapján arra lehet következtetni, hogy a gerjesztett vízmolekula a kalitkából elsősorban nem az oldott oxigén által, hanem a célvegyületek közreműködésével szabadul ki és termel szabad gyököket.

C. Gyökfogók alig eltérő mértékben gátolják a célvegyületek VUV fotolízis során bekövetkező bomlását. A kicsiny eltérések értelmezhetők azzal, hogy a reakciókban a gyökfogó általi domináns gyökbefogási reakciókkal eltérő mértékben versengenek a célvegyületek. Na-azid mint univerzális gyökbefogó nagyobb mértékben gátolja a bomlásokat, mint a metanol.

4. A ***ketoprofen***ről ismert a ***fotoérzékenyítő hatás***a biológiai szervezetekben, ezért annak megállapítására, hogy vajon ez a hatás érvényes-e nem biológiai körülmények között, vizsgáltam az ibuprofen és a ketoprofen együttes fotolízisét mindhárom módszerrel.

A. UV fotolízis esetében megállapítottam, hogy a ketoprofen gyorsította az ibuprofen bomlását mind oldott oxigén jelenlétében mind távollétében. Fordított esetben ezt nem tapasztaltam, azaz az ibuprofen nem befolyásolta a ketoprofen bomlásának sebességét.

B. UV/VUV fotolízis esetében is érvényesült a ketoprofen fotoérzékenyítő hatása az ibuprofen bomlására, noha mértéke kisebb, mint UV fotolízis esetén. Oxigéntartalmú oldatokban a ketoprofen fotoérzékenyítő hatása valamivel kisebb mértékű, mint az mérhető volt oxigénmentes oldatokban.

C. VUV fotolízis esetén, az eddigiek szerint nem is volt várható és nem is volt tapasztalható a ketoprofen fotoérzékenyítő hatása. Az általános reakciókinetikai elvárásoknak megfelelően mindkét vegyület lassította egymás bomlását.

D. Gyökfogók alkalmazása megerősítette az iménti megállapításokat, UV fotolízis esetében nem fejtenek ki bomláscsökkentő hatást. UV/VUV fotolízis alkalmazásánál már tapasztalható volt az ibuprofen bomlássebességének csökkenése. Ez a csökkenés azonban lényegesen kisebb mértékű, mint az ibuprofen egyedüli fotolízisében volt tapasztalható. VUV fotolízis esetében a ketoprofennek nem volt számottevő hatása az ibuprofen gyökfogókkal inhibiált bomlására.

5. Meghatároztam az UV és UV/VUV fotolízis során keletkező ***bomlástermékek***et és vizsgáltam azok időbeni alakulását oxigénnel telített és oxigénmentes oldatokban is. A jelentősebb mennyiségben előforduló bomlástermékek ibuprofen esetén az (1-etil-4-(2-metilpropil)-benzol, a 1-etenil-4-(2-metilpropil)-benzol, a 1-(1-hidroxietil)-4-isobutil-benzol, és a 4'-(2-metilpropil) acetofenon. Ennek alapján kijelenthető, hogy a bomlás dekarboxileződéssel indul. Ketoprofen esetén kimutatott négy fő köztiterméket a 3-acetilbenzofenon, a 3- etilbenzofenon, a 3-hidroxietil benzofenon, és a 3-hidroperoxietil benzofenon voltak. Naproxen esetében négy köztitermék alakulását követtük nyomon, ezek közül háromnak a szerkezetét is sikerül meghatározni. Ezek az 1-(2-metoxi naftalén-6-il)etán-1,2 diol, a 2-metoxi-6-vinilnaftalén és a 1-(2- metoxi naftalén-6-il)etanon.

Megállapítottam továbbá, hogy az így meghatározott köztitermékek tovább bomlanak alifás oxigéntartalmú vegyületekké (zömében karbonsavakká).

6. A célvegyületek ***teljes szerves széntartalom*** (TOC) mérésével nyomon követett ***mineralizáció***ja azt mutatja, hogy a mineralizáció kismértékű az anyagok teljes elbomlása

során. A mineralizáció legkisebb mértékű az UV fotolízis során, és mindhárom módszernél ketoprofen esetén.

A három vizsgált módszer közül, az alkalmazott kísérleti körülmények között, azonos energiafelhasználás mellett, a kiindulási vegyületek teljes mineralizációja szempontjából az UV/VUV fotolízis bizonyult a leghatékonyabbnak.

8. References

[1] Official Journal of the European Communities DIRECTIVE 2008/105/EC of the EUROPEAN PARLIAMENT and of the COUNCIL, 16 December 2008.
[2] Petrović M. *et al,*. Trends in Analytical Chemistry, 22 (2003) 685.
[3] Bolong N. *et al.,* Desalination, 239 (2009) 229.
[4] Daughton C., Environmental Impact Assessment Review, 24 (2004) 711.
[5] Terzić S. *et al,*. Science of the Total Environment, 399 (2008) 66.
[6] Kasprzyk-Hordern B. *et al.,* Water Research, 42 (2008) 3498.
[7] Rabølle M. and Spliid N. H., Chemosphere, 40 (2000) 715.
[8] Stuer-Lauridsen F. *et al.,* Chemosphere, 40 (2000) 783.
[9] Jones O.A.H. *et al.,* Water Research, 36 (2002) 5013.
[10] Carlsson C. *et al.,* Science of the Total Environment, 364 (2006) 67.
[11] Hirsch R. *et al.,* Science of the Total Environment, 225 (1999) 109.
[12] Janex M.L. *et al.,* Water Quality Technology, (2002) 1625.
[13] National Pharmaceutical Institute, Data purchased for 2010.
[14] Pilotto A. *et al.,* Surgical Oncology, 19 (3) (2010) 167.
[15] Santos L.H.M.L.M. *et al.,* Journal of Hazardous Materials, 175 (2010) 45.
[16] Hernando M.D. *et al.,* Talanta, 69 (2006) 334.
[17] Bardou M. and Barkun A.N., Revue du rhumatisme, 77 (2010) 7.
[18] Berninger J.P. and Brooks B.W., Toxicology Letters, 193 (2010) 69.
[19] Bound J.P. *et al.,* Environmental Toxicology and Pharmacology, 21 (2006) 301.
[20] Cooper E.R. *et al.,* Science of the Total Environment, 398 (2008)26.
[21] Enick O.V. and Moore M.M., Environmental Impact Assessment Review, 27 (2007) 707.
[22] Zuccatto E. *et al.,* Journal of Hazardous Materials, 122 (2005) 205.
[23] Cunningham V.L. *et al.,* Regulatory Toxicology and Pharmacology, 53 (2009) 39.
[24] Kümmerer K., Journal of Environmental Management, 90 (8) (2009) 2354.
[25] Daughton C.G. and Ternes T.A., Environmental Health Perspectives Supplements, 107 (1999) 907.
[26] Tixier C. *et al.,* Environmental Science and Technology, 37 (2003) 1061.
[27] Hoeger B. *et al.,* Ecotoxicology and Environmental Safety, 71 (2008) 412.
[28] Brinke M. *et al.,* Aquatic Toxicology, 99 (2010) 126.
[29] Méndez-Arriaga F. *et al.,* Water Research, 44 (2010) 589.
[30] Halling-Sørensen B. *et al.,* Chemosphere, 36 (1998) 357.
[31] Ericson H. *et al.,* Aquatic Toxicology, 99 (2010) 223-231.
[32] Flippin *et al.,* Aquatic Toxicology, 81 (2007) 73–78.
[33] Cleuvers M., Ecotoxicology and Environmental Safety, 59 (2004) 309.
[34] Ternes T., Abstracts of Papers of the American Chemical Society, 219 30-ENVR (2000).
[35] Jones O. A. H. *et al.,* Critical Reviews in Environmental Science and Technology, 35 (2005) 401.
[36] Jones O. A. H. *et al.,* Environmental Pollution, 145 (2007) 738.
[37] Carballa M. *et al.,* Electronic Journal of Environment- Agricultural and Food Chemistry, 2 (2003) 309.
[38] Kümmerer K., Chemosphere, 45 (2001) 957.
[39] Jorgensen S.E. and Halling-Sørensen B., Chemosphere, 40 (2000) 691.
[40] Velagaleti R., Drug Information Journal, 31 (1997) 715.
[41] Zweiner C. and Frimmel F. H., Water Research, 34 (2000) 1881.
[42] Yiyun C. *et al.* European Journal of Medicinal Chemistry, 40 (2005) 1390.
[43] Heberer T., Toxicology Letters, 131 (2002) 5.
[44] Lindberg R. *et al.,* Chemosphere, 57 (2004) 1479.
[45] Buser H.-R. *et al.,* Environmental Science and Technology, 33 (1999) 2529.
[46] Carballa M. *et al.,* Water Research, 38 (2004) 2918.
[47] Trenholm R.A. *et al.,* Chemosphere, 65 (2006) 1990.
[48] Schröder B. and Stevens J., Application Note, 214, Gilson, Inc. (2003).

[49] Huber M.M., Dissertation, Eidgenössische Technische Hochschule, ETH, Zürich, No. 15768 (2004).
[50] Koutsouba V. *et al.,* Chemosphere, 51 (2003) 69.
[51] Kosjek T. *et al.,* Environment International, 31 (2005) 679.
[52] Lindqvist N. *et al.,* Water Research, 39 (2005) 2219.
[53] Stepfan M.I. and Williamson C.T., UV light based application; Advanced Oxidation Processes for Water and Wastewater Treatment, Parsons, P., IWA Publishing, London (2004).
[54] Bendz D. *et al.,* Journal of Hazardous Materials, 122 (2005) 195.
[55] Vane J.R. and Botting M. American Journal of Medicine, 104(3A) (1998) 2S-8S.
[56] Ternes T. A., Water Research, 32 (1998) 3245.
[57] Brun G. L. *et al.,* Environmental Toxicology and Chemistry, 25 (2006) 2163.
[58] Rosal R. *et al.,* Water Research, 44 (2010) 578.
[59] Skordi E. *et al.,* Xenobiotica, 34 (2004) 1075.
[60] Fernández C. *et al.,* Science of the Total Environment, 408 (2010) 543.
[61] Boyd G.R. *et al.,* Science of the Total Environment, 333 (2004) 137.
[62] Ericson A. and Källen B.A.J., Reproductive Toxicology, 15 (2001) 371.
[63] Giuffrida S. *et al.,* Journal of lnorganic Biochemistry, 63 (1996) 253.
[64] De Guidi G. *et al.,* Chemical Research in Toxicology, 18 (2005) 204.
[65] la Farré M. *et al.,* Journal of Chromatography A, 938 (2001) 187.
[66] Oppenländer T., Photochemical Purification of Water and Air, Wiley-VCH, Weinheim (2003).
[67] Dombi A. and Ilisz I., Nagyhatékonyságú oxidációs eljárások a környezeti kémiában, A kémia újabb eredményei, 86. kötet, Akadémiai Kiadó, Budapest (1999).
[68] Oppenländer T., Trends in Chemical Engineering, 8 (2003) 123.
[69] Mothilal, K. K. *et al.* J. Photochem. Photobiol. A 162 (2004) 9.
[70] Kasuga K. *et al.,* Inorganic Chemistry Communications, 6 (7) (2003) 807.
[71] Martínez L.A. *et al.,* Journal of Photochemistry and Photobiology B: Biology, 45 (1998) 103.
[72] Boscá F. and Miranda M.A. Journal of Photochemistry and Photoblology B: Biology, 43 (1998) 1.
[73] Segurola J.*et al.,* Journal of Photochemistry and Photobiology A: Chemistry, 122 (1999) 115.
[74] Braun A. *et al.,* Technologie photochimique, Presses Polytechniques Romandes, Lausannes (1986).
[75] Joschek H-I and Miller S. I., Journal of the American Chemical Society, 113 (1966) 3273.
[76] Esplugas S. *et al.,* Water Research, 36 (2002) 1034.
[77] Legrini O. *et al.,* Chemical Review, 93 (1993) 671.
[78] Garoma T. and Gurol M.D., Environmental Science and Technology, 39 (2005) 7964.
[79] Pengyi Z. *et al.,* Journal of Photochemistry and Photobiology A: Chemistry, 156, (2003) 189.
[80] Shen Y.-S. and Ku Y., Water Research, 32 (1998) 2669.
[81] Stefan M.I. *et al.,* Environmental Science and Technology, 30 (1996) 2382.
[82] Beltrán F.J. *et al.,* Industrial & Engineering Chemistry Research, 35 (1996) 883.
[83] Einschlag F.S.G. *et al.,* Environmental Science and Technology, 36 (2002) 3936.
[84] Scheck C.K., Frimmel F.H. Water Research, 29 (1995) 2346.
[85] De A.K. *et al.,* Journal of Hazardous Materials, B64 (1999) 91.
[86] Horng R.S., Chemospere, 55 (2004) 757.
[87] Zepp R.G. *et al.,* Chemosphere, 10 (1981) 109.
[88] Zepp R.G. *et al.,* Environmental Science and Technology, 19 (1985) 74.
[89] Haag W.R,and Hoigné J., Environmental Science and Technology, 20 (1986) 341.
[90] Zepp R.G *et al.,* Environmental Science and Technology, 21 (1987) 485.
[91] Frimmel F.H. *et al.,* Environmental Science and Technology, 21 (1987) 541.
[92] Tratnyek P.G. and Hoigné J., Environmental Science and Technology, 25(1991) 1596.
[93] Zepp G.R. *et al.,* Environmental Science and Technology, 21 (1987b) 443.
[94] Shao C. *et al.,* In Helz G.R. *et al.* (eds), Aquatic and surface photochemistry, Lewis Publishers, Boca Raton, FL, chapter 17 (1994).
[95] Marc J. and Bolton J.R., Journal of Photochemistry and Photobiology A: Chemisty, 128 (1999) 1.

[96] Leifer A., The kinetics of environmental aquatic photochemistry: theory and practice, ACS professional reference book, Washington (1988).
[97] Getoff N.Z. and Schenck G.O., Journal of Photochemistry and Photobiology, 8 (1968) 167.
[98] Weeks J.L. *et al.,* Radiation Research, 19 (1963) 559.
[99] Heit G. and Braun A.M., Journal of Information Recording, 22 (1996) 543.
[100] Heit G. and Braun A.M., Water Science and Technology, 35 (1997) 9.
[101] Madhavan J. *et al.,* Journal of Hazardous Materials, 178 (2010) 202.
[102] Verlicchi P. *et al.,* Journal of Hydrology, 389 (2010) 416.
[103] Kim I. *et al.,* Journal of Hazardous Materials, 166 (2009) 1134.
[104] Kim I. and Tanaka H., Environment International, 35 (2009) 793.
[105] Lopez A. *et al.,* Journal of Photochemistry and Photobiology A: Chemistry, 156 (2003) 121.
[106] Vogna D. *et al.,* Water Research, 38 (2004) 414.
[107] Ternes T. *et al.,* Environmental Science and Technology, 36 (2002) 3855.
[108] Yuan F. *et al.,* Water Research, 43(2009) 1766.
[109] Huber M.M. *et al.,* Environmental Science and Technology, 37 (2003) 1016.
[110] Nakajima A. *et al.,* Journal of Photochemistry and Photobiology A: Chemistry, 174 (2005) 89.
[111] Boscá F. *et al.,* Journal of Photochemistry and Photobiology A: Chemistry, 54 (1990) 131.
[112] Jimenez M.C. *et al.,* Journal of Photochemistry and Photobiology A: Chemistry, 104 (1997) 119.
[113] Hatchard C.G. and Parker C.A., Proceedings of the Royal Society A: Mathemathical, Physical and Engineering Sciences, 235 (1956) 518.
[114] Nicole J. *et al.,* Water Research 24, (1990) 157.
[115] Eisenberg G.M., Industrial & Engineering Chemistry Analytical Edition, 15 (5) (1943) 327.
[116] Murov S.L. *et al.,* Handbook of Photochemistry, 2nd ed., Marcel-Dekker, New York (1993).
[117] Gilbert A. and Baggott J., Essentials of Molecular Photochemistry, Blackwell Scientific Publications, Oxford (1991).
[118] Szabó R. *et al.,* Journal of Photochemistry and Photobiology A: Chemistry, in press.
[119] Barratt M. D. *et al.,* Journal of Photochemistry and Photobiology B: Biology, 58 (2000) 54.
[120] Mozzanica N. and Pigatto P.D., Contact Dermatitis, 23 (1990) 336.
[121] Cusano F. and Capozzi M., Contact Dermatits, 27 (1992) 50.
[122] Pigatto P.D. *et al.,* Contact Dermatitis, 29 (1993) 39.
[123] Nabeya R. T. *et al.,* Contact Dermatitis, 32 (1995) 52.
[124] Gebhardt M. and Wollina U., Zeitschrift für Rheumatologie, 54 (1995) 405.
[125] Lhiaubet-Vallet V. *et al.,* Toxicology in Vitro, 17 (2003) 651.
[126] He Y.Y. *et al.,* Photochemistry and Photobiology, 77 (2003) 585.
[127] Vinette A.L. *et al.,* Photochemistry and Photobiology, 77 (2003) 390.
[128] Sugiura M. *et al.,* Photodermatology, Photoimmunology & Photomedicine, 18 (2002) 82.
[129] Boscá F. *et al.,* Photochemistry and Photobiology 74 (2001) 637.
[130] Costanzo L.L. *et al.,* Photochemistry and Photobiology, 50 (1989) 359.
[131] Madhavan C. *et al.,* Journal of Hazardous Materials, 178 (2010) 202.
[132] Skoumal M. *et al.,* Electrochimica Acta, 54 (2009) 2077.
[133] Musa K.A.K. *et al.,* Journal of Medicinal Chemistry, 50 (2007) 1735.
[134] Xu M. *et al.,* Journal of Photochemistry and Photobiology A: Chemistry, 204 (2009) 52.
[135] Gonzalez M. G. *et al.,* Journal of Photochemistry and Photobiology A: Chemistry, 5(2004) 225.
[136] Eliot A., Radiation Physics and Chemistry, 34(1989)753.
[137] Hunter E.P. *et al.,* Free Radical Biology and Medicine, 6 (1989) 581.
[138] A. Rockenbauer and L. Korecz, Applied Magnetic Resonance, 10 (1996) 29.

List of publications

Publications:

Articles:

L. Meite, R. Szabo, P. Mazellier, J. De Laat
Cinétique de phototransformation de pollutants organiques émergents/ Kinetics of phototransformation of emerging contaminants in aqueous solution
Revue des Sciences de l'Eau 23(1) (2010) 31-39

R. Szabó, Cs. Megyerei, P. Mazellier*, A. Dombi, K. Gajda-Schrantz
Photolytic degradation of Ibuprofen and Ketoprofen
J. Photochem. Photobiol. A (accepted for publication)

R. Szabó, A. Dombi, P. Mazellier, K. Gajda-Schrantz,
Photosensitation of ketoprofen in presence of ibuprofen
J. Photochem. Photobiol. A (under publication)

E. Arany, R.Szabó, , K. Gajda-Schrantz, P. Mazellier, A. Dombi
Degradation of Naproxen by UV and UV/VUV Light
Chemosphere (under publication)

S. Cerrone, R. Szabó, K. Gajda-Schrantz, A. Dombi, T. Oppenländer
Degradation of ibuprofen and ketoprofen using xenon excimer lamp
Chemosphere (under publication)

Full-scale communication in conference proceedings:

R. Szabó, K. Gajda-Schrantz, P. Mazellier, A. Dombi
Degradation of pharmaceutical compounds by Advanced Oxidation Processes
The 16th International Symposium on Analytical and Environmental Problems (ISBN, 978-963-482-975-1, pg. 496-500, 2009)

R.Szabó, Cs.Megyeri, A. Dombi, P. Mazzelier, K. Gajda-Schrantz
Photolytic degradation of ibuprofen and ketoprofen/ Az ibuprofen és ketoprofen fotolitikus bomlása
Dunaújvárosi Főiskola lektorált kiadványa, Dunaújvárosi Főiskola Kiadó (ISSN 1586-8567, p. 8, 2009.)

E. Illés, R. Szabó, T. Oppenländer, A. Dombi, K. Gajda-Schrantz
Degradation of ketoprofen by ozonisation/ Ketoprofen bontása ózonozással
Dunaújvárosi Főiskola lektorált kiadványa, Dunaújvárosi Főiskola Kiadó (ISSN 1586-8567, p. 8, 2009.)

R. Szabó, Zs. Lénárt, E. Szabó, A. Dombi, K. Gajdáné Schrantz *
The role of radicals in the degradation of ketoprofen
Dunaújvárosi Főiskola lektorált kiadványa, Dunaújvárosi Főiskola Kiadó (accepted, 2010.)

E. Arany, R. Szabó, K. Gajda-Schrantz*, P. Mazellier, A. Dombi
Degradation of Naproxen by advanced Oxidation Processes
Dunaújvárosi Főiskola lektorált kiadványa, Dunaújvárosi Főiskola Kiadó (accepted, 2010.)

Chapter in Assay:

R.Szabó, Cs. Megyeri, P. Mazzellier, A. Dombi, K. Gajda-Schrantz
Photolytic degradation of ibuprofen and ketoprofen/ Az ibuprofen és ketoprofen fotolitikus bomlása
Vizek szerves szennyezőinek eltávolítása nagyhatékonyságú oxidációs módszerekkel/Removal of Organic Contaminants of waters by advanced Oxidation Processes, szerk. Dombi A. és mtsi., pp. 117-129, ISBN 978-963-06-9621-0, InnoGeo Kft, Szeged (2010)

R. Szabó, Gajda- Schrantz K., A. Dombi
Degradation of Pharmaceutical Ccompounds by Advanced Oxidation Processes
Vizek szerves szennyezőinek eltávolítása nagyhatékonyságú oxidációs módszerekkel/Removal of Organic Contaminants of waters by advanced Oxidation Processes, szerk. Dombi A. és mtsi., pp. 129-140, ISBN 978-963-06-9621-0, InnoGeo Kft, Szeged (2010)

Participation at scientific conferences:

R. Szabó, Cs. Megyeri, Cs. Ripli, A. Dombi, K. Gajda-Schrantz, P. Mazellier
Photodecomposition of pharmaceutical compounds
XXII International Conference on Photochemistry,
29. July-03. August 2007, Cologne, Germany
poster

R. Szabó, L. Meité, P. Mazellier
Phototransformation of Naproxen in dilute aqueous solution
XXII International Conference on Photochemistry
29. July-03. August 2007, Cologne, Germany
poster

T. Alapi, A. Pallagi, R. Szabó, A. Dombi,
Comparison of the UV-induced photolysis of phenol in water and acetonitrile
XXII International Conference on Photochemistry
29. July-03. August 2007, Cologne, Germany
poster

R. Szabó, K. Gajda-Schrantz, A. Dombi, P. Mazellier
Photodegradation of pharmaceutical compounds
9th European Meeting on Environmental Chemistry,
3-6. December 2008, Girona, Catalonia, Spain
oral presentation

R. Szabó, K. Gajda-Schrantz, P. Mazellier, A. Dombi
Degradation of pharmaceutical compounds by Advanced Oxidation Processes
The 16th International Symposium on Analytical and Environmental Problems,
28. September 2009, Szeged, Hungary
oral presentation

R. Szabó, K. Gajdáné Schrantz, P. Mazellier, A. Dombi
Investigation of the photochemical degradation of pharmaceuticals/ Gyógyszerhatóanyagok fotokémiai bomlásának vizsgálata
A IX. Környezetvédelmi Analitikai és Technológiai Konferencia (IX. KAT 2009)
07-09 October 2009, Sopron, Hungary
oral presentation

R. Szabó, A. Dombi, P. Mazellier, K. Gajda-Schrantz

Degradation of naproxen by Advanced Oxidation Processes/ A naproxen lebontása nagyhatékonyságú oxidációs eljárásokkal
XXXII. Kémiai Előadói Napok,
26-28. October 2009, Szeged, Hungary
oral presentation

R. Szabó, Cs. Megyeri, A. Dombi, P. Mazzelier, K. Gajda-Schrantz
Photolytic degradation of ibuprofen and ketoprofen/ Az ibuprofen és ketoprofen fotolitikus bomlása
A Magyar Tudomány Hete,
09-13. November 2009, Dunaújváros, Hungary
oral presentation

E. Illés, Z. Lénárt, R. Szabó, E. Szabó, K. Gajda-Schrantz, A. Dombi
Influence of methanolas hydroxyl radical scavenger on the photolytic degradation of ibuprofen and ketoprofen
XXIII. IUPAC Symposium on Photochemistry,
11-16. July 2010, Ferrara, Italy
poster

R. Szabó, E. Szakács, K. Gajda-Schrantz, P. Mazellier, A. Dombi
Degradation of naproxen (NSAID) by Advanced Oxydation Processes
XXIII. IUPAC Symposium on Photochemistry,
11-16. July 2010, Ferrara, Italy
poster

R. Szabó, K. Gajda-Schrantz, A. Dombi, P. Mazzelier
Degradation of pharmaceutical compounds by Advanced Oxydation Processes/ Gyógyszerhatóanyagok eltávolítása nagyhatékonyságú oxidációs eljárásokkal
XXXIII. Kémiai Előadói napok, (ISBN 978-963-315-020-7)
25-27. October 2010, Szeged, Hungary
oral presentation

R. Szabó, Zs. Lénárt, E. Szabó, A. Dombi, K. Gajda-Schrantz
The role of radicals in the degradation of ketoprofen/ Gyökök szerepe a ketoprofen bomlásában
A Magyar Tudomány Hete,
08-12. November 2010, Dunaújváros, Hungary
oral presentation

Acknowledgement

This work has been realized in a joint leadership between the University of Szeged and University of Poitiers. I would like to thank to the French Government and the CROUS Poitou-Charentes for this bourse and to the Hungarian Research Foundation OTKA T67559 and the NKFP DA_THERM TECH_08_4 for the financial support of my studies.

Especial acknowledgement goes to both department leaders, for Dr. Tamás Kiss, University of Szeged, Department Inorganic and Analytical Chemistry and Dr. Bernard Legube, University of Poitiers, ESIP, Laboratory of Water Chemistry and Microbiology for their trust in me as they welcomed in their departments to perform this thesis.

I give my special thanks for my incredible supervisors Dr. Krisztina Gajda-Schrantz, Prof. András Dombi for their enormous help, kindness, trust and encouragement, last but not least to Prof. Patrick Mazellier his help and advices during this period. I thank also to Dr. Bernard Legube for being my "poitevin" supervisor after Patrick's moving to Bordeaux.

Thanks go to my Hungarian colleagues, to Károly Mogyorósi for his kindness, special regards go to Tünde Alapi for her help with the photoreactors and István Ilisz for his high competence in analytical methods; many thanks go to Katalin Kacsala for her technical help.

I would like to extend these thanks to all the team of the LCME, to Anne Delmont for her vigilance with the HPLC.

I would like to give a great thanks to all my Ph. D. student mates in Szeged, especially to Erzsi, Mesi, Eszter, Évi, Ati, Gábor and Zsolt for the good atmosphere and happiness.

Another great thanks for "mes copines et copins" Datte, Mimi, Juju and Aurelien for their presence in my life. Thank you all the night-dinners, talking, hold up and their friendship. Thank you Bertrand everything for this three years.

I would like to thank everything for all these years to my best friends, Angi, Eszter, Kata, Endre, TomikA, Zoli, Szabolcs, Laci. Also thanks the friendship of Viki, Patrik, Dani and Gábor.

My greatest thank goes to my family; my sweetest mother and mummy for everything can't be saying by words and to my pappy who can't be with me now.