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SULFATE RADICAL ANION (SO₄^{•-}) MEDIATED DEGRADATION OF SOME OVER-THE-COUNTER NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AT NEUTRAL pH IN AQUEOUS ENVIRONMENT

Joydev K. Laha,* Neelam Manral, Sagar Badoni, Mandeep Kaur Hunjan, and Upma Gulati

Department of Pharmaceutical Technology (Process Chemistry), National Institute of Pharmaceutical Education and Research, S. A. S. Nagar, Punjab 160062, India; E-mail: jlaha@niper.ac.in

Abstract – The degradation of some common NSAIDs containing an arylacetic acid moiety via thermal oxidative decarboxylation using potassium persulfate (K₂S₂O₈) in water at 80 °C has been investigated. A neutral pH condition is critical for efficient degradation of the drugs yielding the degraded products (corresponding carbonyl compounds). The drugs remain unaffected at lower (2-3) or higher pH (9-10). Unlike the common practice of identification of pharmaceutical degradation products by LC-MS data, the current report unveils major degradation products through isolation and identification using standard analytical techniques. The mechanism of the formation of degradation products via a radical pathway is discussed. The current report on NSAIDs degradation features a rare study in the contemporary pharmaceutical degradation dispersed in the literature.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of inflammatory disorders such as rheumatoid arthritis and for relief of pain.¹ Several NSAIDs that contain arylacetic acid moiety **1**, e.g.; ibuprofen (**2**), ketoprofen (**3**), diclofenac (**4**), and indomethacin (**5**) are non-prescription drugs and are available as over-the-counter drugs (Figure 1). Due to excessive consumption of these drugs, the fate of NSAIDs in the aqueous environment especially after release through urine, faeces, and toilet flushing in water is a great concern.² Because of their resistance to biodegradation and potential to

cause adverse ecological effects, the degradation of pharmaceuticals, especially NSAIDs in water effluents have gained increasing momentum during the last decade.³

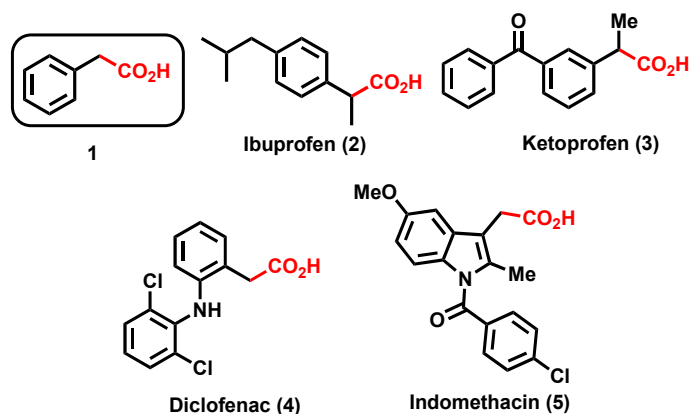


Figure 1. NSAIDs containing arylacetic acid moiety

Various advanced oxidation processes (AOPs) are reported for degradation of these NSAIDs.⁴ Recently, sulfate radical anion ($\text{SO}_4^{\cdot-}$) based oxidation is recurrently discussed as an alternative oxidative treatment for pollution control in water treatment.⁵ Potassium persulfate is largely used as the source for the generation of $\text{SO}_4^{\cdot-}$ in the presence of an activator.⁶ For example, ibuprofen removal by heating persulfate in aqueous solution⁷ and chemical oxidation of ibuprofen⁸ have been reported in the literature. Similarly, thermally activated persulfate is reported to degrade ketoprofen in aqueous solution.⁹ The degradation of diclofenac using peroxymonosulfate/cobalt(II) system¹⁰ and thermally activated persulfate¹¹ have reportedly been achieved. Removal of indomethacin using UV-VIS peroxydisulfate¹² and degradation of indomethacin using ferrous-peroxydisulfate oxidative system in aqueous solutions¹³ has successfully been endorsed. Perhaps most importantly, these reports largely discuss coverage of all degradation products that are detectable using sensible mass spectroscopy techniques and kinetics of the formation of degradation products. However, the limitations may include a) identification of the degradation products primarily using mass data, b) isolation of degradation products rarely attempted causing inability to spectroscopically characterize the degradation products, c) and often, mechanism to the formation of degradation products is debatable. More importantly, the degradation products are inaccessible for further toxicological study. The degradation products that form in significant quantities and are readily accessible in ample quantity for toxicity studies, their identification via isolation and characterization using analytical techniques, ability to produce the degradation products under green oxidative conditions are the main objectives of current study. Previously, we have studied the decarboxylation of arylacetic acids, and subsequently implemented to the synthesis of fused heterocycles and active pharmaceutical ingredients (APIs).¹⁴ Our diverse interests on various aspects of pharmaceuticals, viz. API synthesis, degradation, and

pharmaceutical biology, embarked us towards pharmaceutical degradation of certain over-the-counter drugs. Herein, we report an advanced oxidation process for the degradation of NSAIDs via thermal oxidative decarboxylation using $K_2S_2O_8$ in water. The key to the successful degradation is the neutral pH of the medium. The major degradation products are found to be the corresponding carbonyl compounds that are isolated and spectroscopically characterized. A new insight into the mechanism of the formation of degradation products is also discussed. The current report features a rare study in the contemporary NSAIDs degradation available in the literature.

RESULTS AND DISCUSSION

As discussed above persulfate mediated degradation largely focuses on the involvement of $SO_4^{\cdot-}$ which could be generated through various means.^{15,16} In our study, we were mainly focused on thermally activated persulfate for the degradation of NSAIDs and other related arylacetic acids. More precisely, oxidative decarboxylation of pharmaceuticals containing arylacetic acids at neutral pH is yet to be explored. Our objective was to demonstrate oxidative degradation of some NSAIDs (Table 1) and report their major degradation products. Firstly, the chemical oxidation of ibuprofen was investigated in the presence of thermally activated $K_2S_2O_8$ (2 equiv) using water as the solvent at neutral pH. A time course of the degradation is shown in Figure 2. The graph shows a percentage distribution of the drug and the major degradation product with time. We have carried out the analysis of degradation after 1 h, 2 h, 4 h, and 6 h. It is apparent from the plot that ca. 50% and ca. 80% of the drug was degraded after 4 h and 6 h, respectively. However, complete degradation was not observed even after prolonging the degradation time. A HPLC trace of the crude mixture of ibuprofen degradation under the optimized condition is shown in Figure 3. The HPLC trace reflects the presence of one component as the major degradation product. Thus, the degradation of ibuprofen in the presence of $K_2S_2O_8$ (2 equiv) in water at 80 °C for 6 h resulted in **2a** in 79% isolated yield. The isolated **2a** was identified by NMR spectroscopy and IR spectroscopy. Unlike the previous reports wherein identification of a degradation product is postulated based on LC-MS data of the crude reaction mixture, the major degradation product **2a** is characterized using standard analytical data. Thus, our approach of studying the degradation of NSAIDs is clearly distinct from the literature.

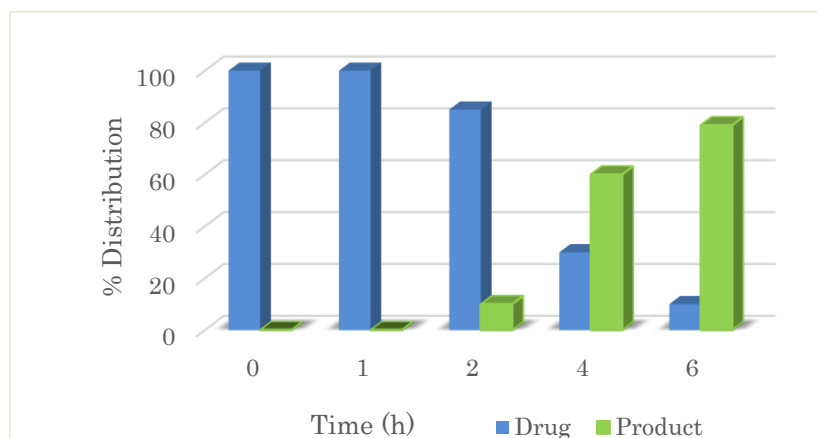


Figure 2. Time course of ibuprofen degradation to the major product

Similarly, degradation of other NSAIDs ketoprofen, diclofenac sodium, and indomethacin were also investigated using similar conditions. The HPLC chromatogram of degradation of these drugs is shown in Figure 3. Similar to the degradation of ibuprofen, a major degradation product along with some minor products were formed in these reactions. Notably, some amount of drug remained undegraded even after prolonged hours. The major degradation products were isolated and characterized in each case: **3a** in 75% yield, **4a** in 40% yield, and **5a** in 35% yield were obtained from ketoprofen, diclofenac, and indomethacin, respectively. Furthermore, these compounds were identified by NMR spectroscopy and IR spectroscopy.

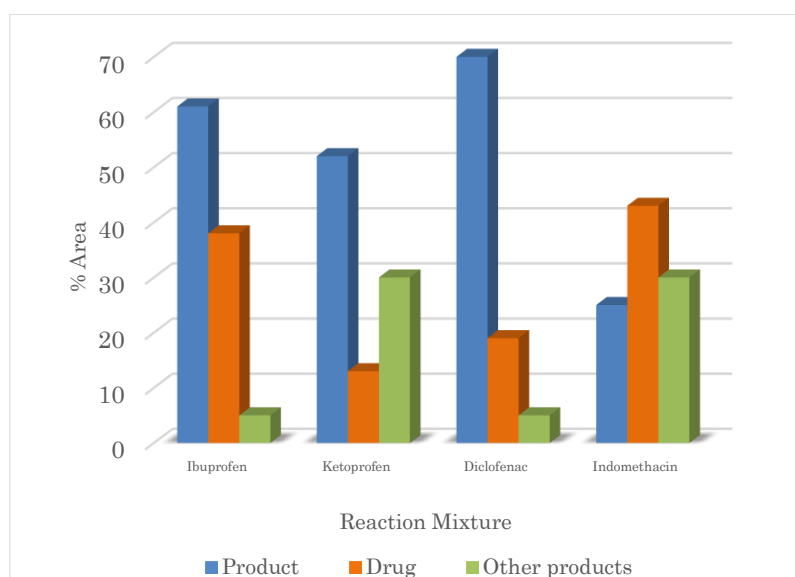


Figure 3. HPLC trace of the crude mixture of drug degradation

Table 1. Degradation of NSAIDs and other arylacetic acids

| Drugs | Major degradation product | Other arylacetic acids | Major degradation product |
|----------------------------|---------------------------|------------------------|---------------------------|
| Ibuprofen (2) | 2a 79% | 6 | 6a 89% |
| Ketoprofen (3) | 3a 75% | 7 | 7a 85% |
| Diclofenac sodium salt (4) | 4a 40% | 8 | 8a 74% |
| Indomethacin (5) | 5a 35% | 9 | 9a 40% |
| | | 10 | 10a 60% |

We were also interested to see whether the reaction was versatile to other arylacetic acids, especially those with a hydroxyl functionality as $K_2S_2O_8$ in aqueous conditions is known to hydroxylate phenols to generate *para*-di-phenols (Elbs persulfate reaction).¹⁷ So, starting with 4-hydroxyphenylacetic acid (**6**); we obtained the corresponding 4-hydroxybenzaldehyde (**6a**) in excellent yield. Also, di-substituted phenylacetic acid i.e. 3-methoxy-4-hydroxyphenylacetic acid (**7**) gave the corresponding 3-methoxy-4-hydroxybenzaldehyde (**7a**) in 85% yield. Other di-substituted phenylacetic acid, 3,4-dimethoxyphenylacetic acid (**8**) and tri-substituted phenylacetic acid, 3,4,5-trimethoxyphenylacetic acid (**9**) resulted in efficient decarboxylation affording 3,4-dimethoxybenzaldehyde (**8a**) and 3,4,5-trimethoxybenzaldehyde (**9a**) in 74% and 40% yields respectively. The optimized condition was then tried using indole-3-acetic acid (**10**), which yielded indole 3-carboxyaldehyde (**10a**) in 60% yield.

Effect of pH on drug degradation

The degradation studies were further carried out in acidic and basic conditions to see the effect of pH on persulfate activation and subsequent degradation of NSAIDs.¹⁸ The acidic condition was maintained at pH 2-3 by adding H_2SO_4 until the pH was achieved. Similarly, the basic condition was attained by adding a saturated solution of Na_2CO_3 until the pH 9-10 was reached. So, first we observed the effect of acidic and basic pH on the degradation of ibuprofen (Table 2, Entry 1). To our surprise, no degradation was observed in both cases. Then, we moved on to see the effect on other drugs, such as ketoprofen,

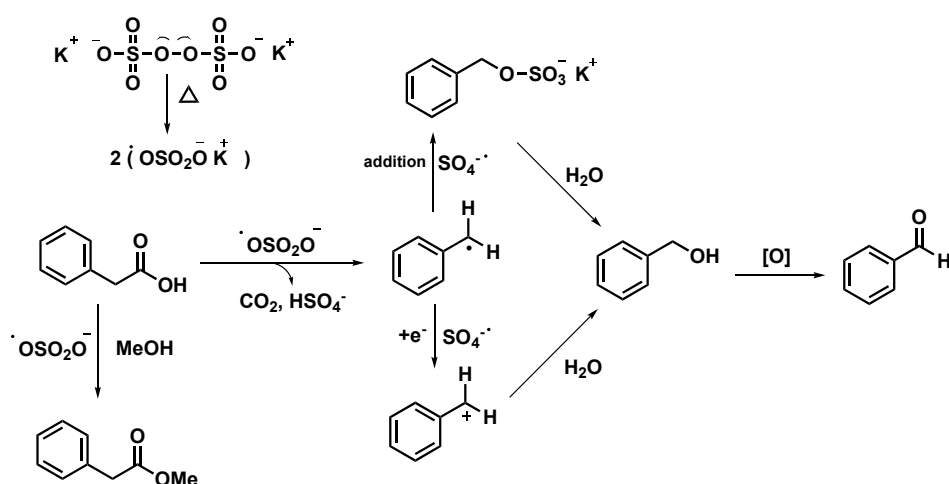
diclofenac, and indomethacin (Entries 2-4). However, no degradation was observed in any of these cases. Similar to the literature report,¹⁸ a nearly neutral pH conditions is essential in our degradation study.

Table 2. Effect of pH on drug degradation

| Entry | Drugs | Acidic Condition (H ₂ SO ₄) | Basic Condition (Na ₂ CO ₃) | Observation |
|-------|---------------------|---|---|---------------------------|
| 1 | Ibuprofen | pH (2-3) | pH (9-10) | no decarboxylation |
| 2 | Ketoprofen | pH (2-3) | pH (9-10) | |
| 3 | Diclofenac | pH (2-3) | pH (9-10) | |
| 4 | Indomethacin | pH (2-3) | pH (9-10) | |

Mechanism of oxidative degradation

Based on the literature^{6,18,19} and our own experiences working with K₂S₂O₈,¹⁴ a plausible mechanism of oxidative decarboxylation of arylacetic acids to the corresponding carbonyl compounds is shown below (Scheme 1). Thermal decomposition of K₂S₂O₈ could give SO₄^{•-},⁶ which could help promote decarboxylation of **1** to form the corresponding benzyl radical. A possibility of reaction of this benzyl radical would be to form the benzyl carbocation via transfer of one-electron to SO₄^{•-}, which upon subsequent reaction with water could form benzyl alcohol. Alternatively, the SO₄^{•-} could add to the benzyl radical to form the benzyl sulfate,^{19a} which upon nucleophilic substitution with water could give benzyl alcohol. Benzyl alcohol, thus generated is subsequently oxidized to benzaldehyde. Our experiments suggest that reaction of **2** in MeOH, or a mixture of solvents containing MeOH gave the corresponding methyl ester (**2b**), which inhibits the decarboxylation process.



Scheme 1. Plausible mechanism for the formation of carbonyl compounds

CONCLUSION

The oxidative degradation of some NSAIDs and organic arylacetic acids was studied using $K_2S_2O_8$ in water at 80 °C. The corresponding decarboxylated products (aldehydes or ketones) were isolated. The study unveils identification of the major degradation products obtained from NSAIDs through isolation and identification using standard analytical techniques. The degradation in water especially at neutral pH conditions could add value to the new protocol. The report could serve as a valuable repository of analytical data of degradation products.

EXPERIMENTAL

Materials and Methods:

All reagents were purchased from commercial sources and used as received. All drugs including ibuprofen, ketoprofen, diclofenac and indomethacin were obtained as gift samples. The substituted phenylacetic acids were purchased from commercial vendors. All the reactions were performed under screw-capped vials. The 1H NMR and ^{13}C NMR spectroscopic data were recorded with 400 MHz and 100 MHz spectrometers, respectively and are reported in δ units. The samples were dissolved in $CDCl_3$, and the coupling constants (J values) are reported in Hz. Column chromatography was performed on silica gel (100–200 or 230–400 mesh). All new compounds were characterized by using melting point (for solids), 1H NMR and ^{13}C NMR, IR data.

General Procedure for the degradation of drugs:

A solution of drug (0.25 mmol) and $K_2S_2O_8$ (0.5 mmol) was heated in water (1 mL) at 80 °C for 6 h. Water (20 mL) was added, and the reaction mixture was extracted with EtOAc (2 x 10 mL). The organic layers were combined, dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (100–200# silica, EtOAc/hexane = 3:7) to give the desired product.

1-(4-Isobutylphenyl)ethan-1-one (2a):^{19d} Colorless liquid. 1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.28 Hz, 2 H), 7.25 (d, J = 8.24 Hz, 2 H), 2.60 (s, 3 H), 2.56 – 2.54 (d, J = 7.24 Hz, 2 H), 1.96 – 1.86 (m, 1 H), 0.92 (d, J = 6.64 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 147.6, 134.9, 129.3, 128.3, 45.3, 30.1, 29.7, 26.5, 22.3; IR (cm^{-1}): 2955, 2925, 2869, 1682, 1605, 1357, 1265, 1181, 849, 795.

Methyl 2-(4-isobutylphenyl)propanoate (2b): Colorless liquid. 1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 7.96 Hz, 2 H), 7.12 (d, J = 7.92 Hz, 2 H), 3.75 – 3.72 (m, 1 H), 3.68 (s, 3 H), 2.48 – 2.47 (m, 2H), 1.92 – 1.82 (m, 1 H), 1.52 – 1.51 (m, 3 H), 0.94 – 0.92 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 140.5, 137.7, 129.3, 127.1, 51.9, 45.0, 30.1, 22.3, 18.6. The data is in agreement with that of commercially available compound.

1-(3-Benzoylphenyl)ethan-1-one (3a):^{19d} Colorless liquid. 1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1 H), 8.21 (d, J = 7.8 Hz, 1 H), 8.01 (d, J = 7.64 Hz, 1 H), 7.82 (d, J = 7.44, 2 H), 7.65 – 7.61 (m, 2 H), 7.53 (t,

$J = 7.60$ Hz, 2 H), 2.68 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.4, 195.9, 138.0, 137.1, 136.9, 134.3, 132.9, 131.8, 130.0, 129.7, 128.7, 128.5, 26.8; IR (cm^{-1}): 3366, 2927, 1686, 1659, 1597, 1447, 1358, 1286, 1239, 1146, 1020, 779, 718.

2-((2,6-Dichlorophenyl)amino)benzaldehyde (4a):^{19d} Colorless liquid. ^1H NMR (400 MHz, CDCl_3): δ 10.01 (s, 1 H), 9.81 (s, 1 H), 7.64 (dd, $J = 1.48, 7.72$ Hz, 1 H), 7.45 (d, $J = 8.08$ Hz, 2 H), 7.39 – 7.35 (m, 1 H), 7.21 (t, $J = 8.08$ Hz, 1 H), 6.91 (t, $J = 7.04$ Hz, 1 H), 6.37 (d, $J = 8.44$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 194.5, 147.5, 136.1, 135.3, 134.3, 128.8, 127.7, 117.7, 113.3; IR (cm^{-1}): 3263, 2848, 1661, 1586, 1507, 1455, 1204, 1162, 1118, 1014, 824, 753.

1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-carbaldehyde (5a):^{19d} Colorless liquid. ^1H NMR (400 MHz, CDCl_3): δ 10.34 (s, 1 H), 7.84 – 7.83 (m, 1 H), 7.74 – 7.72 (m, 2 H), 7.53 – 7.51 (m, 2 H), 6.75 (d, $J = 1.52$ Hz, 2 H), 3.89 (s, 3 H), 2.7 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 185.8, 168.2, 157.1, 148.6, 140.9, 132.0, 131.7, 131.2, 129.5, 129.1, 126.9, 114.3, 113.9, 103.2, 55.7, 12.6; IR (cm^{-1}): 3313, 2943, 2832, 2297, 1682, 1659, 1449, 1115, 1021, 750.

4-Hydroxybenzaldehyde (6a):²⁰ Light yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.88 (s, 1 H), 7.84 (d, $J = 8.04$ Hz, 2 H), 7.01 (d, $J = 8.04$ Hz, 2 H), 6.67 (bs, 1 H).

4-Hydroxy-3-methoxybenzaldehyde (7a):²⁰ Light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.70 (s, 1 H), 7.28 – 7.23 (m, 2 H), 6.90 (d, $J = 8.0$ Hz, 1 H), 3.39 (s, 3 H).

3,4-Dimethoxybenzaldehyde (8a):²¹ White solid. ^1H NMR (400 MHz, CDCl_3): δ 9.87 (s, 1 H), 7.48 (dd, $J = 1.88, 8.2$ Hz, 1 H), 7.43 (d, $J = 1.8$ Hz, 1 H), 7.00 (d, $J = 8$ Hz, 1 H), 3.99 (s, 3 H), 3.96 (s, 3 H).

3,4,5-Trimethoxybenzaldehyde (9a):²² Light yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.89 (s, 1 H), 7.15 (s, 2 H), 3.95 (s, 9 H).

Indole-3-carboxaldehyde (10a):²³ White solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.15 (bs, 1 H), 9.95 (s, 1 H), 8.29 (s, 1 H), 8.12 – 8.09 (m, 1 H), 7.52 (d, $J = 7.7$ Hz, 1 H), 7.28 – 7.20 (m, 2 H).

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