International Journal of Pharmaceutics, 41 (1988) 105–113
Elsevier

IJP 01378

Light degradation of ketorolac tromethamine

Leo Gu, Hi-Shi Chiang and David Johnson

Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304 (U.S.A.)

(Received 2 December 1986)
(Accepted 20 July 1987)

Key words: Ketorolac tromethamine; Stability; Autoxidation; Light degradation; Mechanism

Summary

Aqueous and ethanol solutions of ketorolac tromethamine were found to decompose rapidly under laboratory black light (350 nm) to yield CO_2, decarboxylation product **4** and 3 oxidation products, **1**, **2**, and **3**. Complete material balance of these 4 products in ethanol was found while the material balance in aqueous solutions was poor and decreased with the extent of the reaction. A mechanism which involves an initial decarboxylation of the triplet excited state of ketorolac, followed by oxidation, is proposed to account for the observed oxygen concentration-dependent kinetics and the product distribution of the reaction.

Introduction

Drug substances stored either as pure raw material, in the solid or liquid dosage forms, or during the manufacturing processes, are subject to various degrees of irradiation by sunlight and fluorescent room light. Drugs with absorption greater than 280 nm have the potential for decomposition in sunlight and drugs with absorption maxima greater than 400 nm have the potential for degradation in both sunlight and room light.

Direct sunlight and room light experiments are time-consuming and often result in inconsistent data due to the day-to-day variation in the light intensity. Different light model systems have been used to simulate the light degradation of drug substances (Lachman et al., 1960; Lin and Lachman, 1969; Grünert and Wollman, 1978). One of these consists of a Rayonet Photochemical Reactor equipped with laboratory black lights (350 nm). This system accelerates the degradation by ~ 150 times compared to typical north window sunlight and by $\geq$ 75,000 times compared to typical laboratory fluorescent light. It has been used successfully in evaluating the light reactivities of a series of compounds with different functionalities in this laboratory. This paper reports the light stability studies of ketorolac tromethamine, a potent non-narcotic analgesic agent (Muchowski et al., 1985; Bloomfield et al., 1984; Yee et al., 1984, 1985), in various aqueous and ethanol solutions in a Rayonet Photochemical Reactor (see Scheme 1).

Materials and Methods

Materials

Ketorolac tromethamine was obtained from the Institute of Organic Chemistry, Syntex Research.

Correspondence: L. Gu, Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304, U.S.A.

Ethanol was USP grade and buffers were reagent grade. High-performance liquid chromatography (HPLC) grade acetonitrile and nanopure water were used to prepare the mobile phase.

Kinetics

Photolysis of ketorolac tromethamine was performed in a Rayonet model RPR 1000 Photochemical Reactor equipped with sixteen 350-nm black-light lamps. Sample solutions of ketorolac tromethamine in various media were prepared and transferred into a set of clear pyrex culture tubes (i.d. = 15 ± 1 mm) before photolysis. For irradiation under oxygen or argon, sample solutions in culture tubes were purged with solvent-saturated gas for at least 10 min before sealing with Teflon-lined caps. A stability-specific HPLC method (see below) was used to follow the extent of the reaction.

*Preparation of degradation products **1–4***

A stock solution containing 100 mg ketorolac tromethamine in EtOH/H_2O (1/9, v/v) was prepared and transferred into eight 20 ml culture tubes. The solutions were purged with oxygen for 5 min, sealed with Teflon-lined caps and irradiated with 350 nm lamps in a Rayonet Photochemical Reactor at 0 °C (maintained using an ice bath) to ~ 80% completion. The reaction mixtures were combined, evaporated to dryness, and stored in a freezer before analysis. Samples were then dissolved in mobile phase and separated by semi-preparative HPLC (see HPLC methods below) to give ~ 4–6 mg of each of the degradation products **1–4**.

Compound **1** was identified to be (±)-5-benzoyl-2,3-dihydro-1-hydroxy-3H-pyrrolo[1,2a]pyrrole: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53–2.91 (2H, m, C–CH_2–C), 4.52 (2H, m, N–CH_2), 5.27 (1H, dd, –CH–OH), 6.18–6.85 (2H, dd, pyrrolic), 7.47–7.83 (5H, m, Ph); EIMS (70 eV, m/e) 227 (m/b), 210, 105, 77; HRMS, Calcd. for $C_{14}H_{13}NO_2$: 227.0946. Found: 227.0946. Anal. calcd.: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.71; H, 5.82; N, 6.45.

Compound **2** was identified to be (±)-5-benzoyl-2,3-dihydro-1-hydroperoxy-3H-pyrrolo[1,2a]-pyrrole: ^{1}H NMR (300 MHz, $CDCl_3$) α 2.73–2.85 (2H, m, C–CH_2–C), 4.52 (2H, m, N–CH_2), 5.47 (1H, dd, –CH–OOH), 6.27–6.99 (2H, dd, pyrrolic), 7.47–7.83 (5H, m, Ph), 7.95 (1H, bs, –OOH); EIMS (80 eV, m/e) 243(m), 227, 210, 105(b), 77. Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.92; H, 5.17; N, 5.91.

Compound **3** was identified to be 5-benzoyl-2,3-dihydro-1-oxopyrrolo[1,2a]pyrrole. The ^{1}H NMR, MS and CHN analysis data have been reported elsewhere (Gu et al., 1987).

Compound **4** was identified to be 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2a]pyrrole: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (2H, p, –C–CH_2–C), 2.90 (2H, t, –CH_2–C), 4.44 (2H, t, N–CH_2–), 5.94–6.81 (2H, dd, pyrrolic), 7.44–7.82 (5H, m, Ph); EIMS (80 eV, m/e) 211 (m/b), 210, 182, 134, 105, 77. Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59, H, 6.20; N, 6.63. Found: C, 79.59; H, 6.36; N, 6.52.

Yield of CO_2

A titration method (Niewenberg and Hegge, 1951) was used in selected runs to determine the yield of the gaseous product CO_2. First, the culture tubes were fitted with a gas inlet–outlet device. Sample solutions were then purged with CO_2 free (trapped by concentrated NaOH solution) argon gas for 10 min before irradiation. Argon gas was continuously passed through the reaction mixture into a CO_2-free $Ba(OH)_2$ solution. The trapped CO_2 was then quantitated by titration of the $Ba(OH)_2$ solution with standard HCl solution after photolysis was complete.

Analytical methods

The details of the reverse phase HPLC methods are described elsewhere (Gu et al., 1987). Method A (used mainly for kinetic analysis) employed a C_8 Ultrasphere (Altex) 5-μ column (14.6 mm × 250 mm) and a mobile phase of CH_3CN/H_2O/HOAc (45/55/0.5). The flow rate was controlled at 1.0 ml/min and the wavelength of detection at 314 nm. Excellent linearities by area integration were obtained for ketorolac tromethamine and compounds **1**, **3** and **4** (isolated pure materials were used as authentic materials) with injection sizes in the range of 0.015–1.0 μg. The correlation coefficients and relative molar response factors thus obtained using 8 sample solutions are summarized

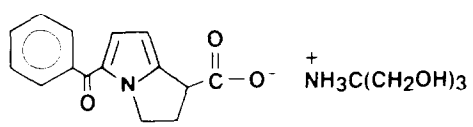
in Table 1. Hydroperoxide **2** was unstable in mobile phase and degraded to 52% remaining after 24 h at room temperature. Thus, the molar response factor for **2** (Table 1) was established using only two sample solutions (5.2 and 10.4 μg/ml, respectively).

HPLC method B was used mainly for collection of degradation products. It employs a semi-preparative C_8 Ultrasphere 5-μ column (10 mm × 250 mm) and a mobile phase identical to that used in method A.

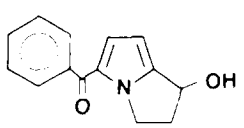
Results

Material balance studies

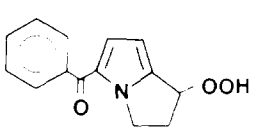
Photolysis of ketorolac tromethamine was studied in H_2O, H_2O/EtOH (9/1) and EtOH with laboratory black light (350 nm). Four decomposition products, **1–4**, were isolated from HPLC (method B). Their structures were identified as shown in Scheme 1.



Ketorolac tromethamine



1



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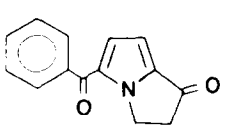

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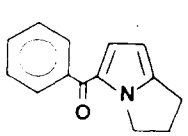

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Scheme 1

The material balance of the reaction as a function of solvent and extent of reaction was determined using HPLC method A and the response factors of each degradation product shown in Table 1. The results are summarized in Table 2.

When the photolysis was conducted in EtOH, 94–101% of the reacted ketorolac was accounted for regardless of the initial drug concentration, the extent of the reaction or the oxygen concentration. In deoxygenated samples, decarboxylation product **4** was the only observed product whereas under aerobic conditions, oxidation products **1–3** accounted for ~ 30% of the degraded ketorolac (see Fig. 1a and Table 2). The relative yield of hydroperoxide **2** decreased with the extent of the reaction while the relative yields of **1** and **3** increased suggesting that **2** decomposed under the reaction conditions to **1** and **3**.

When the photolysis was conducted in H_2O, the distribution and the material balance of products **1–4** were pH-dependent. At pH 2.0, where ketorolac exists mainly as a neutral species (free acid), the decarboxylated product, compound **4** was the predominant product regardless of whether oxygen was present or not and > 80% of reacted ketorolac was accounted for by compounds **1–4**. At pH 7.0 where ketorolac exists mainly as an anion, oxidation products **1–3** became more predominant as the reaction proceeded in air or oxygen saturated solutions. The yields of products **1–4** at this pH decreased with the extent of the

TABLE 1

Linearity and molar response factors for ketorolac tromethamine and its degradation products at 314 nm

Compound	Linearity correlation coefficient [a]	Molar response factor [b]
Ketorolac tromethamine	0.9999	1.00
1	0.9998	0.91
2	– [c]	0.98
3	0.9999	1.42
4	0.9999	1.02

[a] Eight concentrations and triplet injections.
[b] Relative to ketorolac tromethamine.
[c] Not determined due to the instability of the compound.

TABLE 2

Results of laboratory black light (350 nm) photolysis of 10 μg/ml ketorolac tromethamine solutions at various kinetic time points

Solvent	Atmosphere [a]	Remaining (%)	Products distribution (%)				Material balance (%)
			1	2	3	4	
EtOH	Air	85	2	9	4	85	100
		10	4	3	9	85	101
	O_2	92	6	13	11	70	100
		10	10	4	13	73	96
	Argon	89	–	t [b]	–	99	94
		13	t	t	t	98	95
pH 7.0 H_2O [c]	Air	90	18	8	51	23	76
		11	19	3	70	8	46
	O_2	86	5	7	41	47	60
		23	10	3	67	20	60
	Argon	90	25	–	6.5	59	55
	Vacuum	55	–	–	–	100	48
0.010 N HCl [d]	Air	88	4	6	10	80	83
		7	7.5	4.5	11	77	80
	Argon	91	t	t	t	99	85

[a] The desired atmosphere was purged into the photolysis media for at least 10 minutes prior to irradiation.
[b] t means trace.
[c] 0.025 M phosphate buffer.
[d] pH = 2.05.

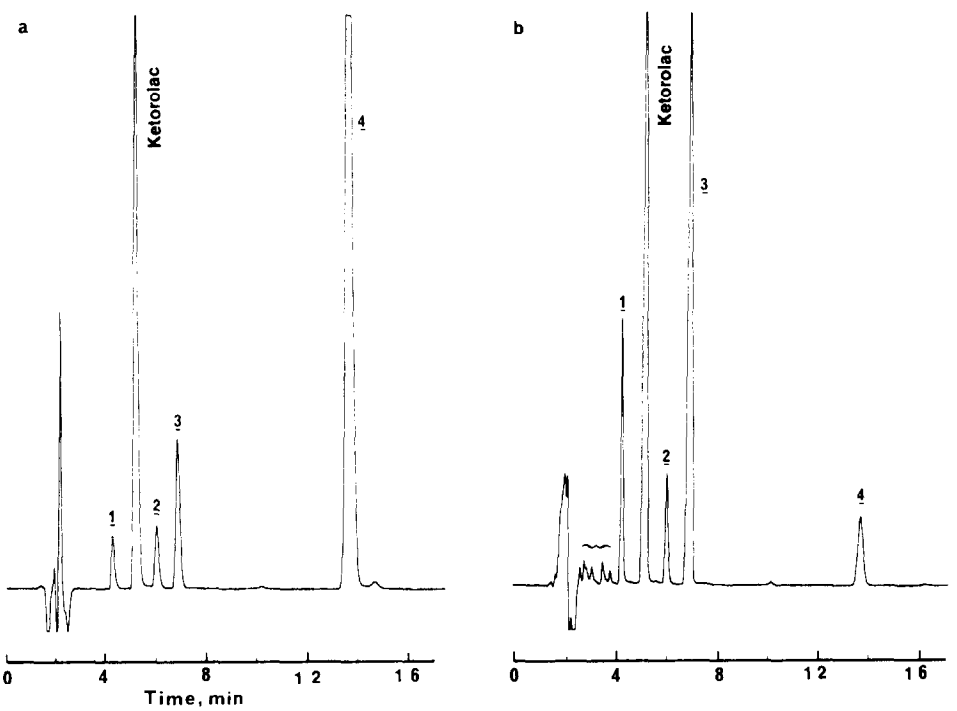


Fig. 1. HPLC chromatograms of photodegraded samples of ketorolac tromethamine in air-saturated (a) EtOH (30% remaining) and (b) H_2O at pH 7.0 (36% remaining).

reaction with as low as 46% accounted for after 89% degradation in air. At pH 7.0, HPLC analysis of the degraded samples showed that additional degradation products which eluted near the solvent front were also found (Fig. 1b). These apparently polar products were not identified in this study.

It was noted that small amounts of **1** and **3** were formed in argon-purged aqueous solutions at pH 7.0, presumably because argon purging of the aqueous solution did not remove all the available oxygen. After residual oxygen was removed by several freeze-thaw cycles, compound **4** was the only observed product in aqueous solutions.

Yield of CO_2

From the products isolated (Scheme 1), it was apparent that the decarboxylation of ketorolac is a major photoreaction pathway. Quantitative determination of the expected product CO_2 was conducted in deaerated EtOH and H_2O solutions, and the results are summarized in Table 3. In both solutions approximately 67% of the expected CO_2 was accounted for.

Kinetics

When EtOH was used as the solvent, an apparent first-order reaction was observed when the concentration of the tromethamine salt was ≤ 2.0 μg/ml (see Fig. 2a). However, at concentrations ≥ 10 μg/ml where the photolysis solution was no longer optically thin (o.d. of the solution is < 0.03), the kinetics were non-first-order (Fig. 2b) and the t_{90} (time to reach 90% remaining) increased with increasing drug concentration. This concentration effect on the rate of photolysis agrees qualitatively with theoretical predictions (Mendenhall, 1984).

In EtOH, oxygen appeared to quench the reaction significantly at all concentrations studied, as evidenced by the decreasing rate obtained in going from argon to air to oxygen saturated solutions (Fig. 2).

TABLE 3

CO_2 formation from photolysis of ketorolac tromethamine

Solvent [a]	Conc.	% Remaining	% of CO_2 [b]
EtOH	1.0 mg/ml	50	67
pH 7.0 H_2O [c]	0.10 mg/ml	78	66

[a] Purged with CO_2-free argon.
[b] Based on the loss of ketorolac.
[c] Phosphate buffer.

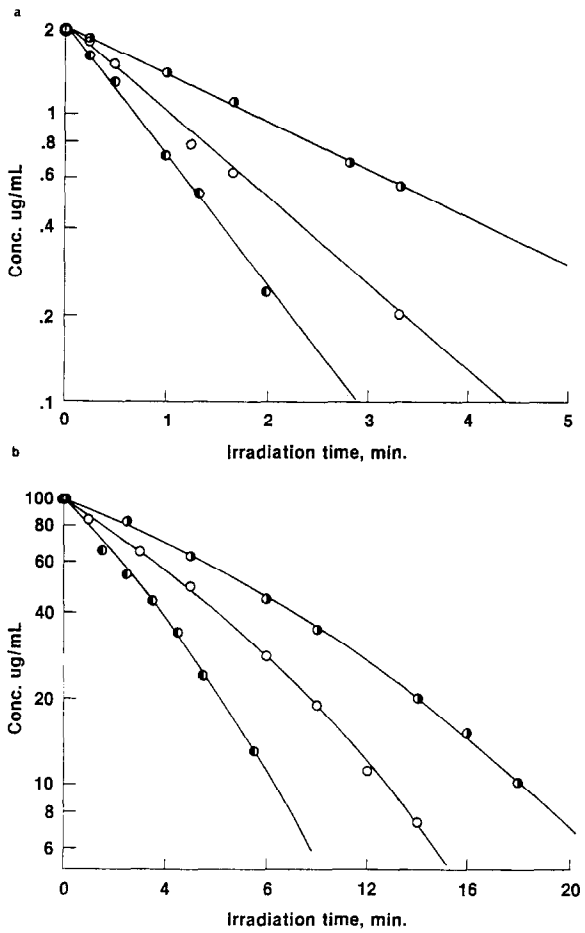


Fig. 2. Photolysis kinetics of ketorolac tromethamine in EtOH under argon (◐), air (○) or oxygen (◑) atmosphere at (a) 2.0 μg/ml and (b) 100 μg/ml drug concentrations.

The effect of oxygen concentration on the rate of the reaction in H_2O was markedly different from that observed in EtOH. For example, at pH 7.0 the initial photolysis rate in air or oxygen saturated solutions was similar to that in argon-saturated solution (see Fig. 3). However, at $< 90\%$ remaining, an autocatalysis reaction was observed in the air-saturated solutions which was not apparent in oxygen or argon-saturated solutions. The autocatalytic kinetic behavior was also observed in air-saturated aqueous solutions at pH 2.0.

Discussion

Photodecarboxylation of aryl acetic acids and their salts has been reviewed extensively (Epling and Lopes, 1977; Coyle, 1978; Givens and Levi, 1979). The primary photoprocess for the acid is believed to involve the singlet excited state of the acid which undergoes an α-bond (C–C(O)) cleavage to yield an alkyl radical:

$$ArCH_2COOH \xrightarrow{h\nu} (ArCH_2COOH)^1$$

$$\rightarrow ArCH_2^{\cdot} + {}^{\cdot}CO_2H \qquad (1)$$

Evidence for the radical mechanism include the detection of both alkyl and $\cdot CO_2H$ radicals from flash photolysis studies (Mittal et al., 1973; Meiggs et al., 1972) and the formation of radical coupling products (Epling and Lopes, 1977; Meiggs et al., 1972).

Although the singlet excited state of the salts was also believed to be involved, the primary photoreaction for the salts is less clear. Meiggs et al. (1972) have detected solvated electrons from flash photolysis of phenylacetic acid in water at pH 8.4 and thus indicated a radical pathway:

$$PhCH_2COO^- \xrightarrow{h\nu} PhCH_2\cdot + CO_2 + e^- \qquad (2)$$

However, when sodium phenylacetate was photolyzed in the absence of oxygen in $H_2O/(CH_3)_2CDOH$ (99/1), 95% of the quantitative product, toluene, was not deuterium-incorporated. Since hydrogen abstraction by benzyl radical would occur primarily at the C–D bond of the $(CH_3)_2CDOH$ an ionic mechanism involving a benzyl anion followed by protonation appeared to be the dominating pathway (Epling and Lopes, 1977).

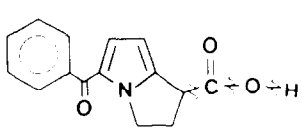
$$PhCH_2COO^- \xrightarrow{h\nu} PhCH_2^- + CO_2 \qquad (3)$$

$$PhCH_2^- \xrightarrow[(99/1)]{H_2O/(CH_3)_2CDOH} \underset{95\%}{PhCH_3} + PhCH_2D \qquad (4)$$

Photolysis of ketorolac tromethamine showed significant differences from simple aryl acetic acids and their salts in many ways. First, the benzoylpyrrole structure in ketorolac has a similar conjugation system to that of benzophenone which has a quantum yield of unity for the intersystem crossing (Φst) from singlet-excited state to triplet-excited state (Turro, 1979). The triplet energy (E_T) for benzophenone is 69 kcal/mol (Turro, 1979). If we assume that the E_T for ketorolac is close to 69 kcal/mol, then this energy is capable of breaking the C–C(O) (~ 68 kcal/mol) bond of ketorolac but not the C(O)–O (~ 106 kcal/mol) or O–H bond (~ 104 kcal/mol) (Weast, 1972–1973) (Scheme 2).

Thus, unlike most simple aryl acetic acids and salts the decarboxylation of ketorolac probably results from the triplet-excited state. This suggestion is supported by the experimental observation that the initial photolysis rate of ketorolac in EtOH and aqueous solutions was slower in the presence of oxygen (Fig. 2), which is an efficient triplet quencher (Foote, 1968).

To test if the photolysis products of ketorolac, compounds **1**–**3** were formed from the secondary decomposition of the decarboxylated product **4** (Crosby and Tang, 1969), compound **4** was subjected to the identical photolysis conditions as those used for ketorolac. Table 4 summarizes the results. No degradation could be found after photolysis of **4** in EtOH for 10 min. Under identical conditions ketorolac tromethamine decomposed to 25% remaining. Less than 2% degradation of **4** was observed after photolysis in H_2O for 21 min while ketorolac tromethamine decomposed to 88% remaining. We therefore conclude that compound **4** is not an intermediate in the formation of the oxidation products **1**–**3**. A mechanism which is consistent with all the experimental observations is outlined in Scheme 3.



Scheme 2

TABLE 4

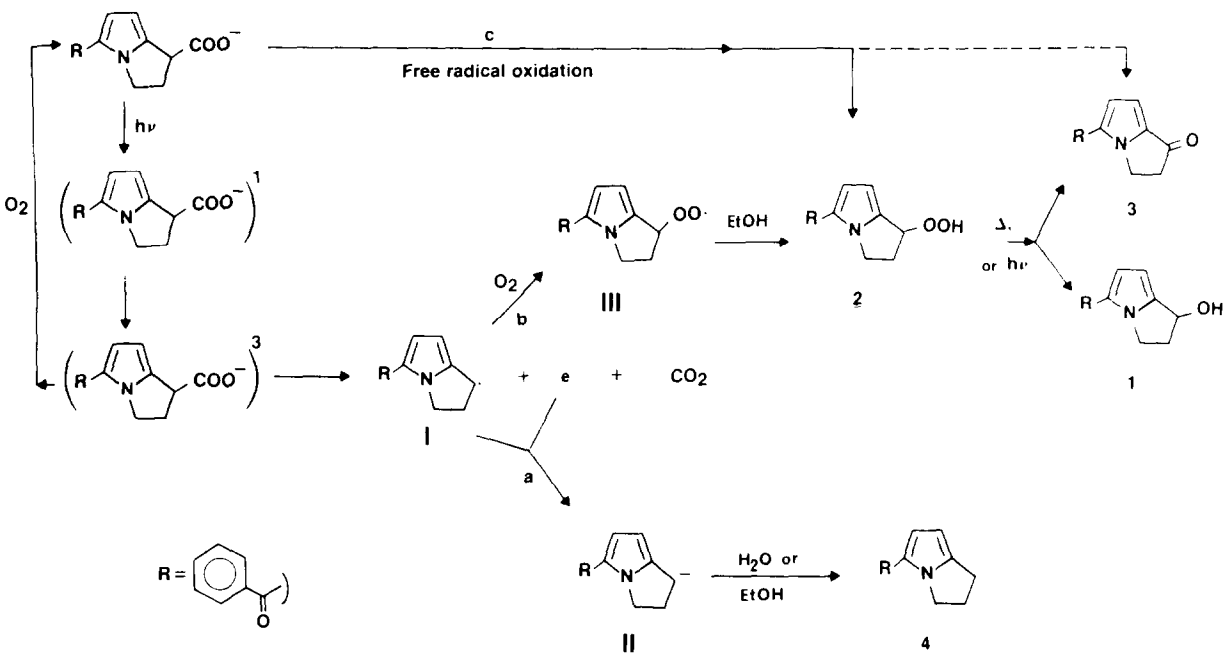
Results of photolysis of ketorolac tromethamine and decarboxylation product **4** [a]

Compound	Solvent	Photolysis time (min)	Remaining (%)
Ketorolac tromethamine	EtOH	10	25
4	EtOH	11	100
Ketorolac tromethamine	pH 7.0 H_2O [b]	21	88
4	pH 7.0 H_2O [b]	21	99

[a] Substrate concentration = 100 μg/ml; ambient air.
[b] Phosphate buffer.

The discharge of an electron from the triplet-excited state of ketorolac anion followed by the cleavage of α(C–C(O)) bond leads to the formation of CO_2 and alkyl radical **I**. In the absence of oxygen, the solvated electron can recombine with radical **I** to yield carbanion **II** (route a) which protonates rapidly in the presence of H_2O or EtOH to give **4** as the major product. Thus, the proposed mechanism involves both radical and ionic pathways. Oxygen has a dichotomous effect on the photolysis rate. Oxygen can slow down the reaction by quenching the triplet-excited state of ketorolac anion, but it can also react with alkyl radical **I** to form peroxy radical **III** (route b). When a good hydrogen donor solvent such as EtOH is used, peroxy radical III can abstract a hydrogen from EtOH to give hydroperoxide **2** which can decompose thermally or photochemically (Lundberg 1961) to alcohol **1** and ketone **3**. When a poor hydrogen donor solvent such as H_2O is used peroxy radical **III** aggregates and eventually initiates the free radical chain oxidation of ketorolac (route c). This thermal chain free radical oxidation is different from that base-catalyzed ionic autoxidation of ketorolac observed at elevated temperatures (Gu et al., 1987) and yields mainly **1**–**3** and some unidentified polar products. Thus, autocatalysis kinetics were observed in air-saturated aqueous solutions but not in EtOH.

Quenching of triplet ketorolac by oxygen in oxygen-saturated aqueous solutions should be 5 times more efficient than those in air-saturated solutions. Therefore, the accumulation of free



Scheme 3

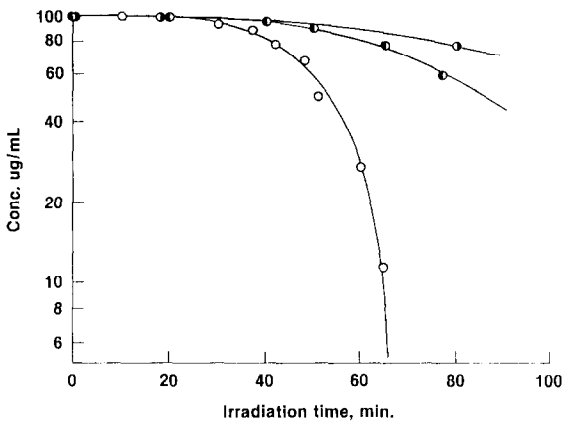


Fig. 3. Photolysis kinetics of 100 μg/ml ketorolac tromethamine in H_2O at pH 7.0 under argon (◑) air (○) or oxygen (◐) atmosphere.

radicals in solutions is expected to be slower and autocatalysis was observed only with prolonged photolysis time (Fig. 3).

Finally, it can be suggested that protonation of carboanion **II** is more favorable in acidic solutions (Crosby and Tang, 1969) and compound **4** remains to be the major product at pH 2 in the presence of oxygen (Table 2).

Conclusions

The pronounced effect of oxygen on the photolysis kinetics and product distribution of ketorolac tromethamine has led to the identification of both radical and ionic reaction pathways. The results presented in this study may be applied to other acidic non-steroidal analgesic/anti-inflammatory agents containing substituted arylacetic acid structure (e.g., naproxen, indomethacin, ibuprofen, ketoprofen, etc.).

Acknowledgements

The authors thank Mrs. J. Nelson for obtaining the ^1H NMR spectra, Dr. L. Partridge for obtaining the mass data and Mr. M. Chung for obtaining the CHN analysis data. Helpful discussions from Drs. W. Lee, and M. Powell are appreciated.

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