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## Light degradation of ketorolac tromethamine

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### Summary

Aqueous and ethanol solutions of ketorolac tromethamine were found to decompose rapidly under laboratory black light (350 nm) to yield CO<sub>2</sub>, 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 ≥ 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.

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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. =  $15 \pm 1$  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<sub>2</sub>O (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 ( $\pm$ )-5-benzoyl-2,3-dihydro-1-hydroxy-3H-pyrrolo[1,2a]pyrrole: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.53–2.91 (2H, m, C–CH<sub>2</sub>–C), 4.52 (2H, m, N–CH<sub>2</sub>), 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<sub>14</sub>H<sub>13</sub>NO<sub>2</sub>: 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 ( $\pm$ )-5-benzoyl-2,3-dihydro-1-hydroperoxy-3H-pyrrolo[1,2a]pyrrole: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\alpha$  2.73–2.85

(2H, m, C–CH<sub>2</sub>–C), 4.52 (2H, m, N–CH<sub>2</sub>), 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<sub>14</sub>H<sub>13</sub>NO<sub>3</sub>: 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 <sup>1</sup>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: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.57 (2H, p, –C–CH<sub>2</sub>–C), 2.90 (2H, t, –CH<sub>2</sub>–C), 4.44 (2H, t, N–CH<sub>2</sub>–), 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<sub>14</sub>H<sub>13</sub>NO: C, 79.59, H, 6.20; N, 6.63. Found: C, 79.59; H, 6.36; N, 6.52.

#### Yield of CO<sub>2</sub>

A titration method (Niewenberg and Hegge, 1951) was used in selected runs to determine the yield of the gaseous product CO<sub>2</sub>. First, the culture tubes were fitted with a gas inlet–outlet device. Sample solutions were then purged with CO<sub>2</sub> 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<sub>2</sub>-free Ba(OH)<sub>2</sub> solution. The trapped CO<sub>2</sub> was then quantitated by titration of the Ba(OH)<sub>2</sub> 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<sub>8</sub> Ultrasphere (Altex) 5- $\mu$  column (14.6 mm  $\times$  250 mm) and a mobile phase of CH<sub>3</sub>CN/H<sub>2</sub>O/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  $\mu$ g. The correlation coefficients and relative molar response factors thus obtained using 8 sample solutions are summarized

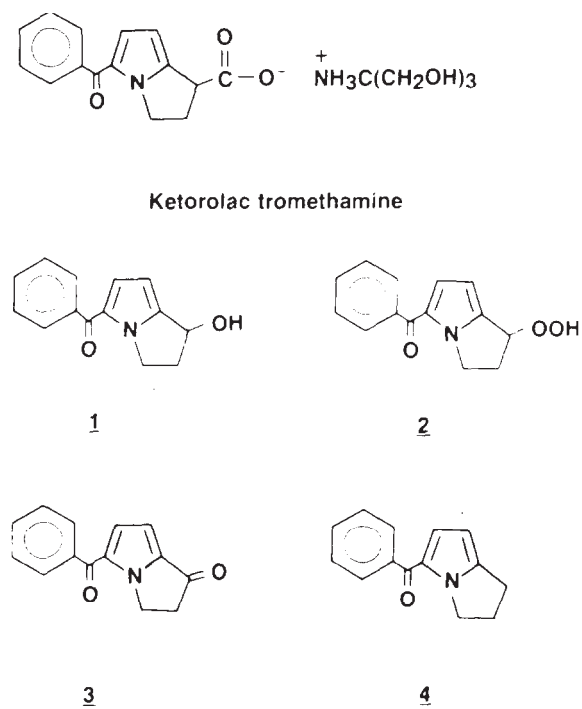
in Table 1. Hydroperoxide **2** was unstable in mobile phase and degraded to 52% remaining after 24 h at room temperature. Thus, the molar response factor for **2** (Table 1) was established using only two sample solutions (5.2 and 10.4  $\mu\text{g}/\text{ml}$ , respectively).

HPLC method B was used mainly for collection of degradation products. It employs a semi-preparative  $\text{C}_8$  Ultrasphere 5- $\mu$  column (10 mm  $\times$  250 mm) and a mobile phase identical to that used in method A.

## Results

### Material balance studies

Photolysis of ketorolac tromethamine was studied in  $\text{H}_2\text{O}$ ,  $\text{H}_2\text{O}/\text{EtOH}$  (9/1) and  $\text{EtOH}$  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.



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  $\text{EtOH}$ , 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  $\sim 30\%$  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  $\text{H}_2\text{O}$ , 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 <sup>a</sup>	Molar response factor <sup>b</sup>
Ketorolac tromethamine	0.9999	1.00
<b>1</b>	0.9998	0.91
<b>2</b>	– <sup>c</sup>	0.98
<b>3</b>	0.9999	1.42
<b>4</b>	0.9999	1.02

<sup>a</sup> Eight concentrations and triplet injections.

<sup>b</sup> Relative to ketorolac tromethamine.

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

<sup>a</sup> The desired atmosphere was purged into the photolysis media for at least 10 minutes prior to irradiation.

<sup>b</sup> t means trace.

<sup>c</sup> 0.025 M phosphate buffer.

<sup>d</sup> pH = 2.05.

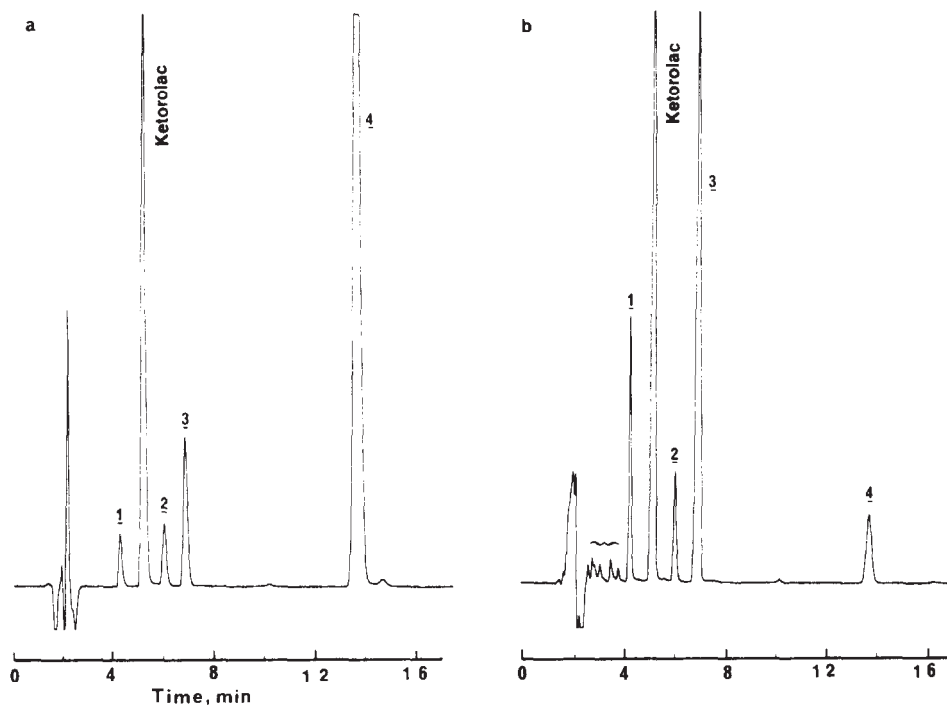


Fig. 1. HPLC chromatograms of photodegraded samples of ketorolac tromethamine in air-saturated (a) EtOH (30% remaining) and (b) H<sub>2</sub>O at pH 7.0 (36% remaining).

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<sub>2</sub>

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<sub>2</sub> was conducted in deaerated EtOH and H<sub>2</sub>O solutions, and the results are summarized in Table 3. In both solutions approximately 67% of the expected CO<sub>2</sub> 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  $\leq 2.0$   $\mu\text{g}/\text{ml}$  (see Fig. 2a). However, at concentrations  $\geq 10$   $\mu\text{g}/\text{ml}$  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 reac-

TABLE 3

CO<sub>2</sub> formation from photolysis of ketorolac tromethamine

Solvent <sup>a</sup>	Conc.	% Remaining	% of CO <sub>2</sub> <sup>b</sup>
EtOH	1.0 mg/ml	50	67
pH 7.0 H <sub>2</sub> O <sup>c</sup>	0.10 mg/ml	78	66

<sup>a</sup> Purged with CO<sub>2</sub>-free argon.

<sup>b</sup> Based on the loss of ketorolac.

<sup>c</sup> Phosphate buffer.

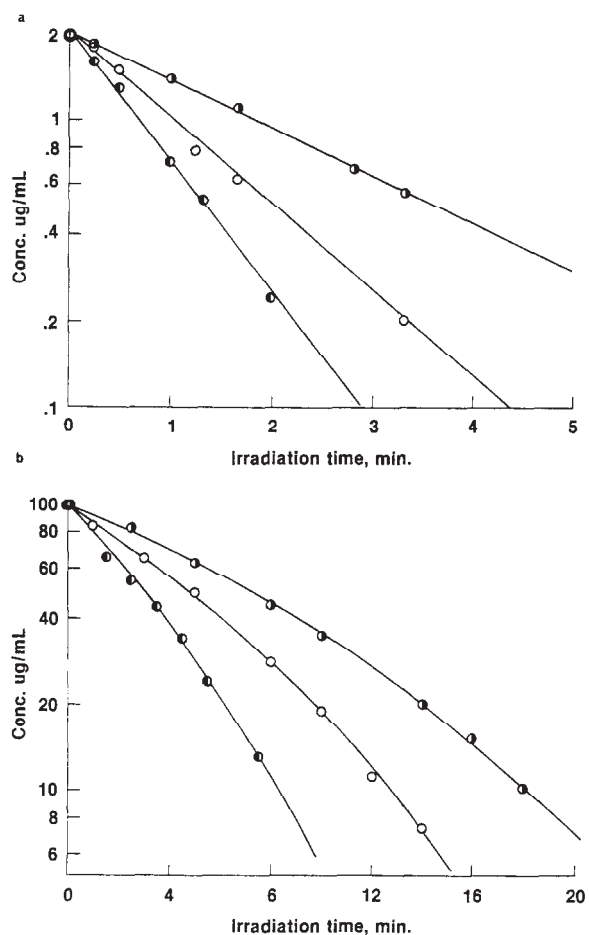


Fig. 2. Photolysis kinetics of ketorolac tromethamine in EtOH under argon (●), air (○) or oxygen (●) atmosphere at (a) 2.0  $\mu\text{g}/\text{ml}$  and (b) 100  $\mu\text{g}/\text{ml}$  drug concentrations.

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

The effect of oxygen concentration on the rate of the reaction in H<sub>2</sub>O 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.

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