International Journal of Pharmaceutics, 41 (1988) 95–104
Elsevier

IJP 01384

Kinetics and mechanisms of the autoxidation of ketorolac tromethamine in aqueous solution

Leo Gu, Hi-Shi Chiang and Allyn Becker

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; Degradation product; Autoxidation; Mechanism; Kinetics

Summary

The thermal reactivity of ketorolac tromethamine (**1**) in aqueous buffer solutions was studied at 60 °–100 °C from pH 1.1 to 12.4. Four products (**2**–**5**) were formed and their distribution was pH dependent. The apparent degradation was both acid- and base-catalyzed and the rate depended on the oxygen concentration in a linear fashion at pH > 4.8. At low pH (2.15), however, no significant difference in rate was observed when solutions were saturated with either air or oxygen. Mechanisms involving either base-catalyzed deprotonation or uncatalyzed hydrogen abstraction at the tertiary carbon (α to the carboxylic group of ketorolac) followed by reaction with O_2 are proposed to account for the observed kinetics and product distribution at pH > 4.8.

Introduction

Ketorolac tromethamine (Scheme 1) is a potent non-narcotic analgesic agent (Muchowski et al., 1985). In a number of efficacy studies, oral doses of 10 mg ketorolac tromethamine have exhibited equal or better analgesia than 650 mg aspirin (Bloomfield et al., 1984) and were indistinguishable from naproxen sodium 550 mg or morphine sulfate 10 mg (Yee et al., 1984). An intramuscular (i.m.) dose of 10 mg was found to be more effective to relieve post-surgery pain than an i.m. dose of 6 mg morphine sulfate (Yee et al., 1985).

Ketorolac tromethamine contains substituted arylacetic acid ($ArCR_1R_2COOH$) found in many acidic non-steroidal analgesic/anti-inflammatory agents (e.g. naproxen, indomethacin, ibuprofen, ketoprofen, etc.). The chemical reactivity of this substituted acetic acid structure in aqueous solution however is relatively unknown. In this paper, the detailed kinetics, products and mechanisms of the thermal degradation of ketorolac tromethamine in aqueous solutions are explored.

Materials and Methods

Materials

Ketorolac tromethamine and the ketorolac decarboxylate analog **6** were obtained from the Institute of Organic Chemistry, Syntex Research. Ethanol was USP grade. Ethylenediaminetetraacetic acid (EDTA) and buffer reagents were reagent grade. High-performance liquid chromatographic (HPLC) grade acetonitrile, reagent grade acetic acid and nanopure water were used to pre-

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

pare the mobile phase. Standard 0.10 N HCl and KOH solutions (Baker) were used as received.

Kinetics

Acetate, phosphate, and carbonate buffer solutions containing 0.025 M total buffer concentration were prepared and KCl was added to adjust the total ionic strength to 0.20 M. The pH of each solution was measured at the reaction temperature using a Radiometer Model PHM 64 research meter equipped with a Radiometer Model GK 2410C combination electrode.

In a typical kinetic experiment, 500 μl (or 250 μl for HCl buffers) of a 15.0 mg/ml ketorolac tromethamine aqueous stock solution was added to 250 ml of freshly prepared buffer solution. This solution was stirred for 10 min under ambient air and aliquots (10 ml) were removed and placed in 10 ml type I amber glass ampules. For solutions stored under ambient atmosphere, the ampoules were sealed immediately. For samples purged with oxygen or argon, water-saturated gas was bubbled through the solutions for 10 min prior to sealing the ampoules. The sealed ampoules were then stored in constant temperature water baths or ovens at the specified temperatures.

Degradation products 2, 3, 4, and 5

A stock solution containing 100 mg ketorolac tromethamine in 100 ml 0.010 N KOH was prepared and transferred into 50-ml culture tubes. The solution was purged with oxygen for 10 min, sealed with a Teflon-lined cap and stored in a 100 °C oven. After the reaction was complete, the mixture was acidified to pH 2 with 1.0 N HCl and extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$ and evaporated to dryness. Semi-preparative HPLC (see HPLC methods below) of the residue yielded ~ 5 mg each of the major degradation products **2**, **3**, **4**, and **5**.

Compound **2** was identified as *N*-carboxymethylene-5-benzoylpyrrole-2-carboxylic acid: ^{1}H NMR (300 MHz, d_4-MeOH) δ 5.71 (2H, s, N–CH_2), 6.63–6.84 (2H, dd, pyrrolic), 7.47–7.77 (5H, m, Ph); EIMS (70 eV, rapid heating, from room temperature to 300 °C in 5 s, m/e) 237(m), 228(b), 215, 183, 105, 77. To further confirm the proposed structure, compound **2** was derivatized with CH_2N_2/MeOH to its dimethyl ester: ^{1}H NMR (300 MHz, d_4-MeOH) δ 3.79 (3H, s, –OCH_3), 3.86 (3H, s, –OCH_3), 5.72 (2H, s, N–CH_2), 6.71–6.99 (2H, dd, pyrrolic), 7.47–7.82 (5H, m, Ph); EIMS (70 eV, m/e) 301(m), 242(b), 228, 183, 105, 77; HRMS, Calcd. for $C_{16}H_{15}O_5N$: 301.0950. Found: 301.0940.

Compound **3** was identified as 5-benzoylpyrrole-2-carboxylic acid: ^{1}H NMR (300 MHz, d_4-MeOH) δ 6.81–6.86 (2H, dd, pyrrolic), 7.53–7.88 (3H, m, Ph); EIMS (70 eV, m/e) 215(m/b), 170, 138, 120, 105, 77; HRMS, Calcd. for $C_{12}H_9NO_3$: 215.0582. Found: 215.0569.

Compound **4** was identified as 2-acetyl-5-benzoylpyrrole: ^{1}H NMR (300 MHz, d_4-MeOH) δ 2.52 (3H, s, –CH_3), 6.84–7.05 (2H, dd, pyrrolic), 7.54–7.88 (5H, m, Ph); EIMS (70 eV, m/e) 213(m/b), 198, 170, 136, 105, 77; HRMS, Calcd. for $C_{13}H_{11}NO_2$: 213.0790. Found: 213.0783.

Compound **5** was identified as 5-benzoyl-2,3-dihydro-1-oxopyrrolo[1,2a]pyrrole: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (2H, t, –CH_2–C(O)–), δ 4.76 (2H, t, N–CH_2–), 6.73–7.00 (2H, dd, pyrrolic), 7.52–7.89 (5H, m, Ph); EIMS (80 eV, m/e) 225(m/b), 120, 105, 77. Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.99; H, 4.50; N, 6.25. Found: C, 75.06; H, 4.67; N, 6.17.

Analytical methods

HPLC was performed on a Spectra-Physics Model 8700 instrument equipped with a Kratos 757 variable wavelength UV detector, a Micromeritics 728 autosampler and a Spectra-Physics 4100 computing integrator.

HPLC Method A was used mainly for the quantitation of ketorolac tromethamine and its degradation products (**2–5**). This method employed a C_8 Ultrasphere® 5 μ column (4.6 mm × 250 mm) and a mobile phase of CH_3CN/H_2O/HOAc (45/55/0.2). The flow rate was 1.0 ml/min and the detection wavelength was 314 nm. Excellent linearities by area integration for ketorolac tromethamine and compounds **2–5** (isolated pure materials were used as authentic samples) were obtained with injection amounts between 0.015 μg to 1.0 μg. The correlation coefficients and relative molar response factors thus obtained are summarized in Table 1.

The precision of method A for 3 duplicate injections was usually within 2% for amounts as low as 0.015 μg injected. This low limit for 2% precision at 314 nm increased to 0.040 μg when detected at 254 nm. The specificity of Method A was supported by observing a complete disappearance of **1** when a totally degraded sample was injected. HPLC method B was used mainly for collection of degradation products. It employed 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

The aqueous stability of ketorolac tromethamine was studied in buffer solutions from pH 1.1 to pH 12.4. Because the reaction at room temperature was slow, the degradation was studied at 60 °C, 80 °C and 100 °C. A stability-specific HPLC method (method A) was used to follow the extent of the reaction. Four major decomposition product were isolated from the highly degraded 0.01 N KOH aqueous sample solutions using the semi-preparative HPLC method B. The structures of these 4 products are summarized in Scheme 1.

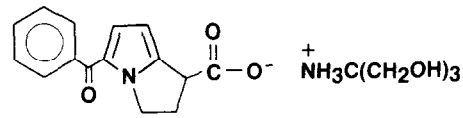
The distribution of these products and the material balance determined by HPLC response factors (Table 1) were found to be pH-dependent (Table 2). At pH 11.4, the 4 products accounted for 80% of the reacted ketorolac tromethamine

TABLE 1

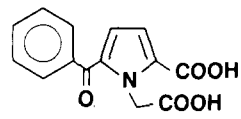
Linearity and molar response factors for ketorolac tromethamine and its degradation products

Compound	Linearity correlation coefficient [a]	Molar response factor [b]
Ketorolac tromethamine	0.9999	1.00
2	0.9999	0.93
3	0.9999	0.91
4	0.9998	1.44
5	0.9999	1.42

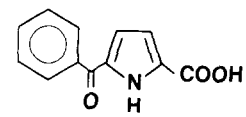
[a] Eight concentrations and triplet injections.
[b] Relative to ketorolac tromethamine at 314 nm.



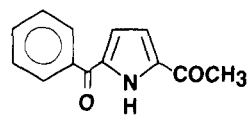
Ketorolac tromethamine, 1



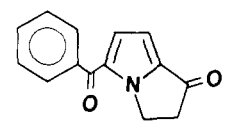
2



3



4



5

Scheme 1

and compounds **2**, **3** and **4** were the major products (Fig. 1a). Several minor and polar products were also detected by HPLC (Fig. 1a). However, their structures were not identified. At pH 7.4, the main decomposition product, **5**, accounted for 84% of the products. In very acidic solutions such as 0.10 N HCl, however, the material balance was very poor (16%) and **5** was the only product observed (Fig. 1b).

Kinetics

First-order kinetics were observed down to < 20% remaining at the pH extremes where the reaction was rapid. At intermediate pHs (5–8), the kinetics were analyzed by initial rates assuming first-order kinetics. Since very low buffer concentrations were used (0.025 M), corrections were not made for possible buffer catalysis. Fig. 2 summarizes the pseudo first-order rate constants obtained at all pHs and temperatures.

Effect of EDTA and oxygen

The effect of EDTA (4.0×10^{-5} M) on the rate of reaction at 80 °C was studied at pH 1.1, 3.0 and

TABLE 2

Material balance studies of ketorolac tromethamine autoxidation at 80 °C and representative pHs

Solvent [a]	pH at 80 °C	Product distribution (%)				Material balance [b] (%)
		2	**3**	**4**	**5**	
0.10 N KOH	11.4	42	24	35	4.2	80
0.01 N KOH	10.5	37	19	30	14	92
Phosphate buffer [c]	7.4	8	*t* [d]	–	91	84
0.10 N HCl	1.1	–	–	–	100	16

[a] Ionic strength was adjusted to 0.2 M.
[b] Based on reacted ketorolac tromethamine.
[c] [Buffer] = 0.025 M.
[d] *t* denotes trace amount.

11.4 and was found to be insignificant. The presence of oxygen in the sealed ampoules played a significant role on the rate of degradation. For example, from pH 4.8 to pH 12.4 the degradation of **1** in oxygen saturated solutions was consistently 3.1–4.4-fold faster than that in air saturated samples. When the same reaction solutions were deaerated with argon, the degradation rates were extremely slow (Table 3). This dramatic effect of oxygen on the degradation rate of **1** in 0.10 N KOH at 80 °C is also given in Fig. 3. It is noted that pseudo-first-order drug loss was obtained in

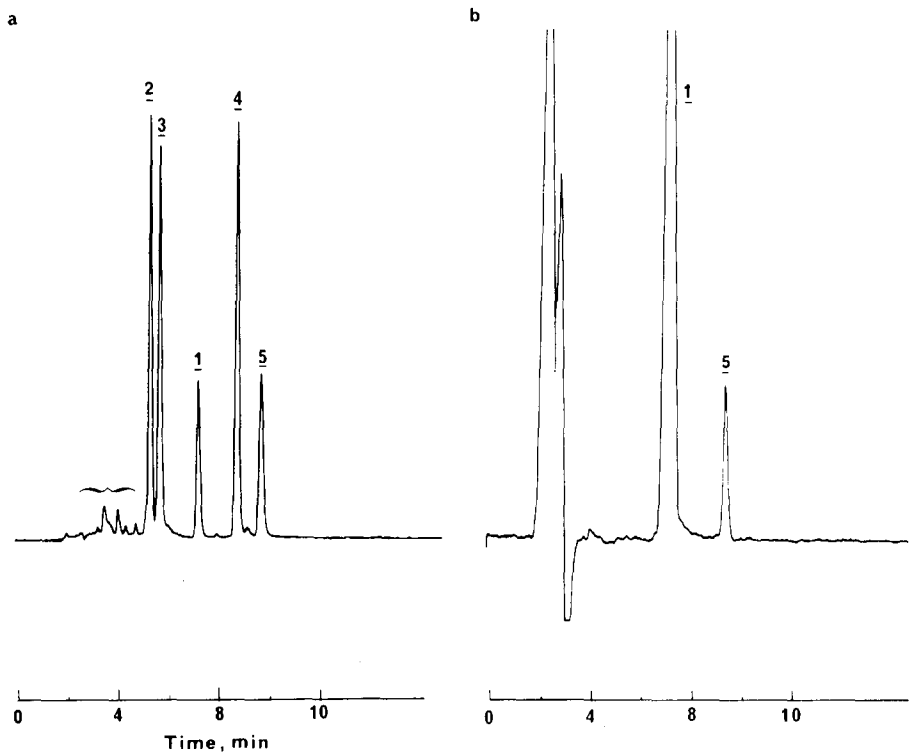


Fig. 1. HPLC chromatograms of samples of partially degraded ketorolac tromethamine in H_2O at (a) pH 11.4, and (b) pH 1.1. The peaks elute before **2** in (a) are unidentified minor products.

TABLE 3

Effect of oxygen concentration on the degradation rate of ketorolac tromethamine at 80 °C

pH [a]	Relative rate constants		
	Air	O_2	Argon
11.4	1	4.4	< 0.1
9.7	1	4.3	< 0.1
4.8	1	3.1	0.5
1.1	1	1.1	0.8

[a] Measured at 80 °C.

solutions saturated with either ambient air or oxygen. This is due to the large excess of oxygen available in the sealed ampoules relative to the drug used (2.7×10^{-5} M). HPLC analyses of the degraded samples demonstrated that there was no change in degradation product profiles by increasing oxygen concentration at these pHs. Thus, it is safe to conclude from these results that the reaction rate at pH $\geq$ 4.8 is proportional to the oxygen concentration. At pH 1.1, however, oxygen saturation resulted in only a 1.1-fold increase in rate, suggesting a different mechanism might be operating in this region.

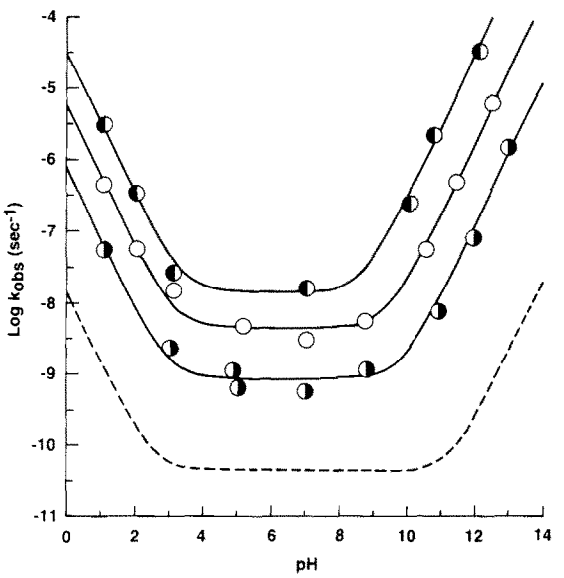


Fig. 2. Log(rate)–pH profiles for the degradation of ketorolac tromethamine at 60 °C (◑), 80 °C (○) and 100 °C (◐). The solid lines are the non-linear regression fit using Eqn. 3. The dashed line is the calculated log(rate)–pH profile at 25 °C using the Arrhenius equation and is included for the estimation of shelf-life.

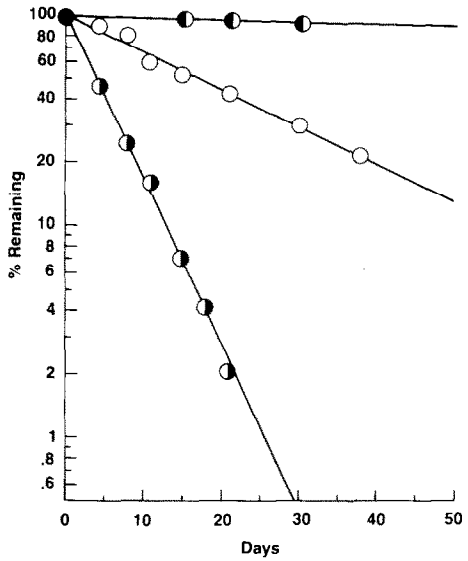


Fig. 3. Pseudo-first-order kinetics of autoxidation of ketorolac tromethamine in 0.10 N KOH at 80 °C in an oxygen- (◑), air- (○), or argon- (◐)-saturated atmosphere.

Discussion

Effect of pH and temperature

The effect of pH on the decomposition kinetics of **1** in air-saturated solutions can best be depicted by the log(rate)–pH profiles shown in Fig. 2. The *U*-shape profile indicates the occurrence of specific acid-catalyzed (k_H), neutral or water catalyzed (k_0), and specific base-catalyzed (k_{OH}) processes according to the following rate expression:

$$\text{Rate} = k_{obs}[\text{ketorolac}]_t \quad (1)$$

and

$$k_{obs} = k_H a_H + k_0[O_2] + k_{OH}[O_2]a_{OH} \quad (2)$$

where $[\text{ketorolac}]_t$ is the total concentration of the drug, and a_H and a_{OH} are the hydrogen ion and hydroxide ion activity, respectively, at the reaction temperature. Equation 2 has included an oxygen

TABLE 4

Kinetic analysis of aqueous degradation of ketorolac tromethamine according to Eqn. 3

Temp. (°C)	Rate constants		
	k'_H, $M^{-1} s^{-1}$	k'_0, s^{-1}	k'_{OH}, $M^{-1} s^{-1}$
100	$3.13 \pm 0.70 \times 10^{-5}$	$1.36 \pm 0.44 \times 10^{-8}$	$5.20 \pm 0.10 \times 10^{-5}$
80	$5.84 \pm 1.02 \times 10^{-6}$	$4.35 \pm 0.63 \times 10^{-9}$	$7.00 \pm 1.01 \times 10^{-6}$
60	$7.79 \pm 2.51 \times 10^{-7}$	$8.47 \pm 1.48 \times 10^{-10}$	$1.26 \pm 0.27 \times 10^{-6}$
25	1.39×10^{-8} [a]	4.24×10^{-11} [a]	2.00×10^{-8} [a]

[a] Extrapolated from the Arrhenius plot using the rate constants obtained at 100, 80 and 60 °C.

concentration term, $[O_2]$, in the rate equation. Although $[O_2]$ in water as a function of oxygen pressure in an open system at 60 °C, 80 °C and 100 °C is available (Mendenhall, 1984), similar data for a closed system, e.g. in a sealed ampoule is not. The rate constants plotted in Fig. 2 were fit to the following simplified equation using a non-linear regression curve fitting method (Bevington, 1969).

$$k_{obs} = k'_H a_H + k'_0 + k'_{OH} a_{OH} \quad (3)$$

where $k'_H (= k_H)$, k'_0 $(= k_0[O_2])$ and $k'_{OH} (= k_{OH}[O_2])$ are the apparent acid-catalyzed, neutral or water-catalyzed and base-catalyzed rate constants. The solid curves in Fig. 2 were constructed using the rate constants summarized in Table 4. All the apparent rate constants were found to follow the Arrhenius equation (Fig. 4) and the activation energies derived for k'_H, k'_0 and k'_{OH} were 23, 21 and 19 kcal/mol, respectively. The rate constants at 25 °C obtained by extrapolation were substituted into Eqn. 3 affording the pH dependence on the rate of degradation at 25 °C (dashed line in Fig. 2). This extrapolation results in a predicted shelf-life (t_{90}) at 25 °C of ketorolac tromethamine in aqueous solutions in excess of 75 years in pH 4–8.

Mechanism in basic pH region

The effect of oxygen on the rate of ketorolac tromethamine decomposition and product distribution indicates that the major reaction occurring at pH > 4.8, where ketorolac tromethamine ($pK_a = 3.43$) exists mainly as the carboxylate anion, is autoxidation. Below pH 2.0, the reaction is independent of oxygen concentration and thus appears to react by a different mechanism. Although autoxidation of various organic molecules has been the subject of extensive studies over several decades (Lundberg, 1961; Connors et al., 1979; Stewart and Rucker, 1985; Mendenhall, 1984) autoxidation involving decarboxylation of $ArCHRCOO^-$ compounds has not been reported. In order to elucidate the possible intermediates of the reaction, the stabilities of the degradation products **2–5**, were each examined in 0.10 N KOH at 80 °C (Table 5). Compounds **2–4** were virtually inert (99.8–101.2% remaining) after 8 days. Com-

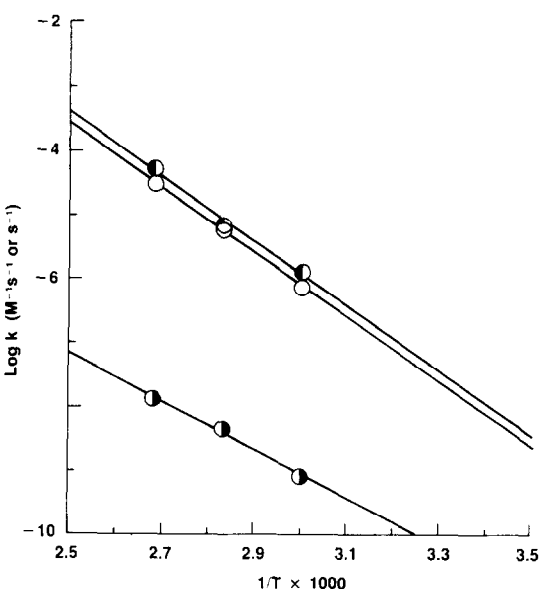
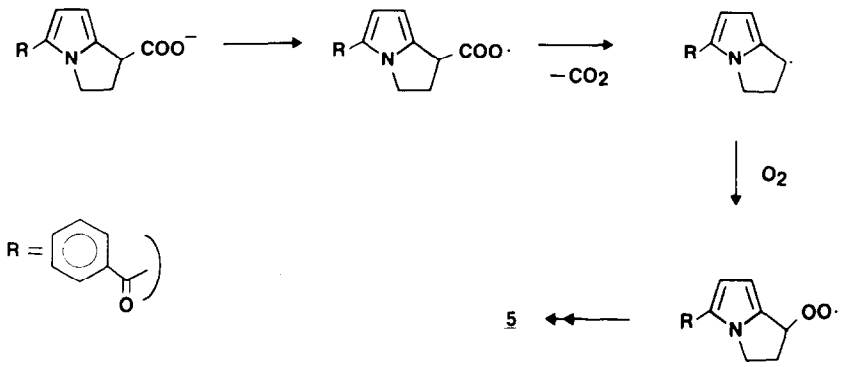


Fig. 4. Arrhenius plots of the degradation of ketorolac tromethamine. The rate constants k_H (○), k_0 (◑) and k_{OH} (◐) are taken from Table 4.

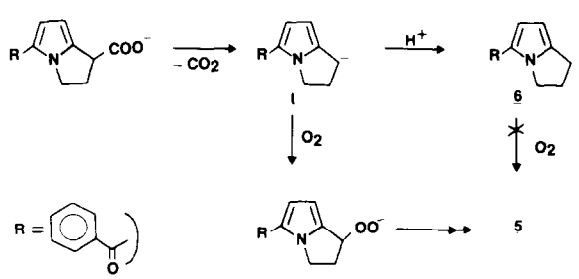


Scheme 2

pound **5**, however, degraded completely (0% remaining) within 4 days to yield mainly **4** and some **2** and **3**. This suggests that the thermal degradation of ketorolac tromethamine yields the primary product, compound **5**, which then partially degrades under the reaction conditions to form secondary products **2**–**4**.

Several mechanisms can be suggested to explain the formation of **5**. First, the degradation reaction may be initiated by a homolytic free radical reaction between ketorolac anion and traces of impurity and/or metal ions (Scheme 2) which may be either from the raw material or leached into the reaction mixture from the amber glass used (Sanga, 1979).

This mechanism is unlikely however, because the presence of EDTA, an efficient metal ion quencher (Schwarzenbach, 1957), had no effect on the rate of degradation. Also, there is no apparent need for OH^- in this mechanism, in contrast to the observed base-catalyzed reaction (Fig. 2). This latter result also excludes the possible α-hydrogen abstraction initiation reaction as observed in simple fatty acids (Bascetta, 1984). Alternatively, since many carboxylic acids and their salts are known to decarboxylate thermally (March, 1977), compound **5** may result from oxidation of initially formed carboanion (I) as shown in Scheme 3.



Scheme 3

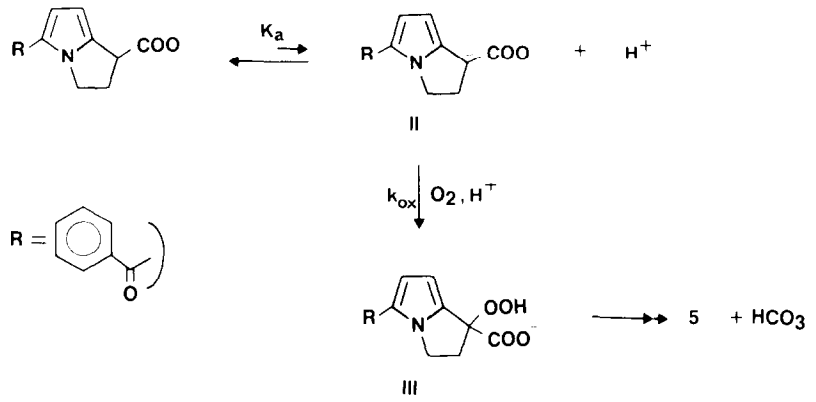
This mechanism however predicts the formation of ketorolac decarboxylate analog **6**, undetected in the reaction mixture, via protonation of carbanion I. Further, a control experiment showed that compound **6** was stable under alkaline conditions used to degrade **1** (Table 5). Thus, decarboxylation of ketorolac was not a primary degradation pathway and therefore is not involved in the formation of the primary product **5**. The racemization reaction of optically pure ketorolac was recently studied by Conley (1984) in aqueous solution. The observed racemization rates

TABLE 5

Stability of ketorolac, ketorolac degradation products (2–5) and ketorolac decarboxylate analog 6 in 0.10 N KOH

Compound [a]	Conc. (μg/ml)	Temp. (°C)	Reaction time (days)	Results	
				% Remaining	Products observed
1	10.0	80	8	72.5	2–5
2	5.0	80	8	101.2	–
3	4.8	80	8	100.2	–
4	4.6	80	8	99.8	–
5	4.0	80	4	0.0	2–4
6	10.0	100	8	97.5	–

[a] See Schemes 1 and 2 for structures.



Scheme 4

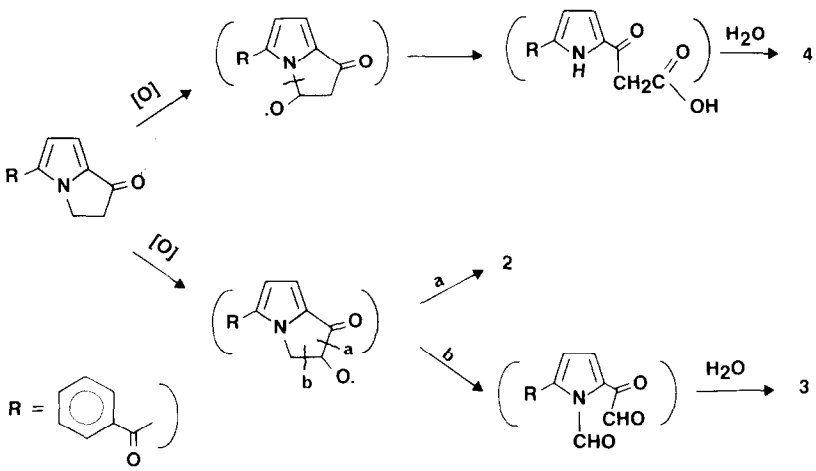
were > 10-fold faster than the autoxidation rate found in this study. Thus, the tertiary hydrogen in ketorolac is acidic and the dianion (II) formed could react with O_2 to yield hydroperoxide (III) in multiple steps (Howard, 1973) followed by rapid decomposition (Lundberg, 1961) to **5** as shown in Scheme 4. The rate expression for the autoxidation for the base-catalyzed process according to Scheme 4 is

$$k_{obs} = \frac{K_a k_{ox} a_{OH} [O_2]}{K_w} \tag{4}$$

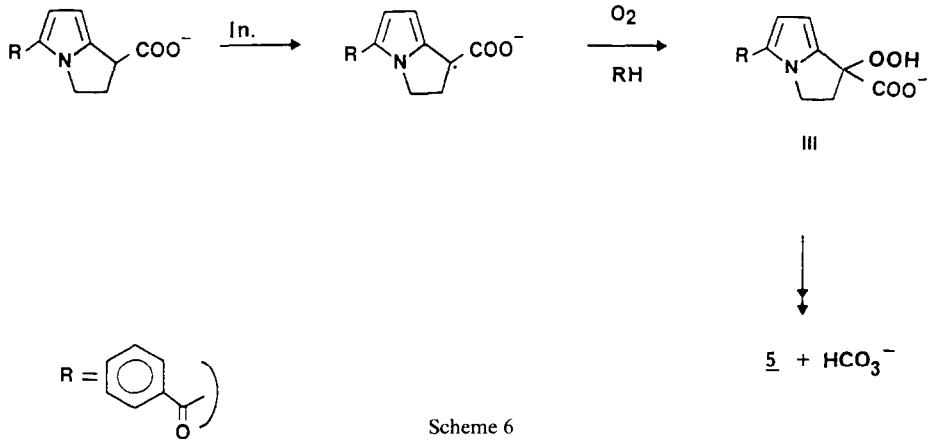
where K_a is the acid dissociation constant of ketorolac carboxylate anion (II), k_{ox} is the rate constant of oxygen addition reaction and K_w is the ion product constant for water. Comparing Eqns. 3 and 4 for the base-catalyzed reaction we obtain Eqn. 5.

$$k'_{OH} = \frac{K_a k_{ox} [O_2]}{K_w} \tag{5}$$

At 25 °C, $[O_2]$ in water under ambient air is approximately 2.5×10^{-4} M (Mendenhall, 1984), K_w is 1.0×10^{-14} M (Skoog, 1979) and k'_{OH} is 2.0×10^{-8} M^{-1} s^{-1} (Table 4). If we assume the oxygen addition reaction in water is diffusion-controlled (e.g., $k_{ox} = 1 \times 10^9$ M^{-1} s^{-1}) (Howard, 1973), then the pK_a of ketorolac carboxylate an-



Scheme 5



Scheme 6

ion is estimated to be $\simeq 27$ according to Eqn. 5. This pK_a value for anion I is that expected for slightly acidic hydrocarbons (Streitwieser, 1965), and this further supports the proposed autoxidation mechanism.

Finally, the formation of **2–4** from **5** can be explained by a series of oxidation-hydrolysis reactions (Scheme 5). It should be noted, however that proof for these mechanisms (Gu, 1987) can not be obtained from the present data alone.

Mechanism in neutral pH region

At pH values between 4.0 and 8.0, the observed autoxidation becomes pH-independent (Fig. 2) and compound **5** is the major product (Table 2). Because base is no longer required in this pH region, a simple free radical mechanism involving α hydrogen abstraction as the initiation step can be suggested (Scheme 6).

Unfortunately, no autocatalytic kinetics, typical for a free radical chain mechanism (Lundberg, 1961; Mendenhall, 1984), can be identified in the present study. This is probably because the observed reactions in neutral pH region are very slow (Fig. 2) and followed only to $< 80\%$ remaining.

Conclusion

The major degradation pathway for ketorolac tromethamine in aqueous solution is autoxidative decarboxylation. The main reaction site for either base-catalyzed or uncatalyzed autoxidation is the arylic position. This indicates that autoxidation rates for arylacetic acids should change according to the acidity and lability of the α(C–H) at the arylic position. Fortunately, for either base-catalyzed or uncatalyzed autoxidation, removal of oxygen appeared to be an effective way of preventing the degradation in this case.

Acknowledgements

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

References

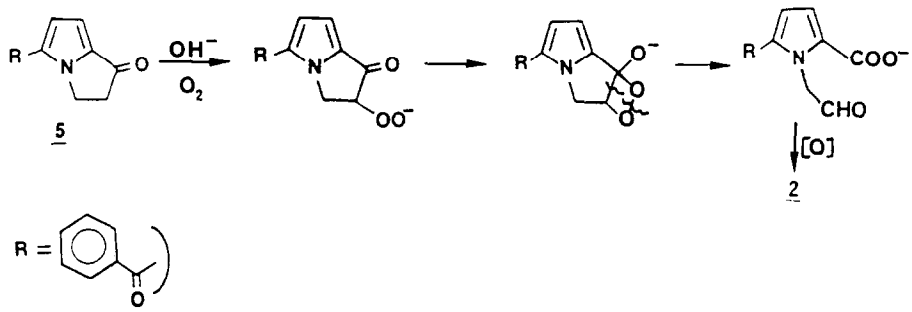
Bascetta, E., Gunstone, F.D., and Walton, J.C., An electron spin resonance study of fatty acids and esters. Part 2. Hydrogen abstraction from saturated acids and their derivatives. *J. Chem. Soc., Perkin Trans.*, II (1984) 401–406.

Bevington, P.R., *Data Reduction and Error Analysis for the Physical Sciences*, McGraw-Hill, New York, 1969.

Bloomfield, S.S., Mitchell, J., Cissell, G., and Borden, T.P., RS-37619 and aspirin analgesia for post-partum uterine cramps. *Clin. Pharmacol. Ther.*, 35 (1984) 228.

Conley, D., *The Isomerization of Ketorolac Tromethamine*, M.S. Thesis, California State University, San Jose, 1984.

Connors, K.A., Amidon, G.L., and Kennon, L., *Chemical Stability of Pharmaceuticals*, Wiley, New York, 1979, pp. 80–98.



Gersmann, H.R. and Bickel, A.F., Autoxidation of ketones and esters in basic solution. *J. Chem. Soc.* (B) (1971), 2230–2237.

Gu, L., (1987) Unpublished results; an alternative ionic mechanism can be suggested (Gersmann 1971) to the formation of **2** from **5** as follows:

Howard, A.J., Homogeneous Liquid-Phase Autoxidations. In Kochi, J.K. (Ed), *Free Radicals, Vol. II*. New York, 1973, pp. 37.

Lundberg, W.O., *Autoxidation and Antioxidants, Vol. I & II*, Wiley, New York, 1961.

March, J., *Advanced Organic Chemistry: Reactions, Mechanism, and Structure*, 2nd edn., McGraw-Hill, 1977, pp. 569–572.

Mendenhall, D.W., Stability of Parenterals, Drug Dev. Ind. Pharm, 10 (1984) 1297–1342.

Muchowski, J.M., Unger, S.H., Ackrell, J., Cheung, P., Cooper, G.F., Cook, J., Gallegra, P., Halpern, O., Koehler, R., Kluge, A.F., Van Horn, A.R., Antonio, Y., Carpio, H., Franco, F., Galeazzi, E., Garcia, I., Greenhouse, R., Guzman, A., Iriate, J., Leon, A., Pena, A., Perez, V., Valdez, D., Ackerman, N., Ballaron, S.A., Murthy, D.V.K., Rovito, J.R., Tomolonis, A.J., Young, J.M. and Rooks, II, W.H., Syntheses and antiinflammatory and analgesic activity of 5-aroyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acids and related compounds. *J. Med. Chem.*, 28 (1985) 1037–1049.

Sanga, S.V., Review of glass types available for packaging parenteral solutions. *J. Parenter. Drug Assoc.*, 33 (1979) 61–67.

Schwarzenbach, G., *Complexometric Titrations*, Chapman & Hall, New York, 1957, pp. 8.

Skoog, D.A. and West, D.M., *Analytical Chemistry*, 3rd edn., 1979, p. 27.

Stewart, P.J. and Tucker, I.G., Prediction of drug stability - Part 3: oxidation and photolytic degradation. *Aust. J. Hosp. Pharm.*, 15 (1985) 111–117.

Streitwieser Jr., A. and Hammons, J.H., Acidity of hydrocarbons. *Prog. Phys. Org. Chem.*, 3 (1965), 41–80.

Yee, J., Brown, C.R., Allison, C. and Wildman, K., Analgesia from intramuscular ketorolac tromethamine compared to morphine (MS) in "severe" pain following "major" surgery. *Clin. Pharmacol. Ther.*, 37 (1985) 239.

Yee, J., Brown, C.R., Sevelius, H. and Wild, R.N., The analgesic efficacy of (±)-5-benzoyl-1,2-dihydro-3H-pyrrole[1,2a]pyrrole-1-carboxylic acid, tromethamine salt (B) in post-operative pain. *Clin. Pharmacol. Ther.*, 35 (1984) 285.