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RESEARCH PAPER

Reactions of Ketorolac and Its Isopropyl Ester in 35% Isopropyl Alcohol

Michael Brandl* and Adina Magill

Roche Bioscience, Palo Alto, California 94303

ABSTRACT

The pH-rate profiles for the esterification and hydrolysis of ketorolac and the isopropyl ester of ketorolac have been measured in 35% isopropyl alcohol at 22, 60, and 80°C. The data showed that pH has a large effect on the rate of esterification in the pH region below pH 5. Additional studies on the hydrolysis of the isopropyl ester of ketorolac showed that acetate buffer catalyzes the hydrolysis reaction.

INTRODUCTION

Ketorolac tromethamine (Toradol®) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (1). Due to its high potency it has been considered for topical use to relieve local pain. Prototype ketorolac topical gel formulations contain ketorolac tromethamine dissolved in a solution of 35% isopropyl alcohol. The formulation also contains ethylene diamine tetraacetic acid, butylated hydroxytoluene, tromethamine, diisopropyl adipate, and Carbomer 940, and is adjusted to pH 4.

The stability of ketorolac has been studied in solution (2,3) and in the solid state (4) where oxidation is the major degradation pathway. However, in the ketorolac topical gel formulation the isopropyl ester of ketorolac was the major degradation product (Fig. 1). Formation of the isopropyl ester of ketorolac in the topical gel formulation is a regulatory concern since the ester may have different permeability properties from the parent compound (5). Studies on the rate of formation and hydrolysis of the isopropyl ester of ketorolac have been conducted in 35% isopropyl alcohol to determine conditions at which stable formulations can be prepared. This report describes the results of these studies.

EXPERIMENTAL

Material

Ketorolac free acid was prepared by the Institute of Organic Chemistry, Syntex Research. Isopropyl alcohol was from Burdick and Jackson. Butylated hydroxytoluene was NF grade. Buffer salts were analytical grade.

Preparation of Ketorolac Isopropyl Ester

Ketorolac free acid (10 g) was dissolved in isopropyl alcohol (100 ml) containing 2 ml sulfuric acid (conc.). The solution was stirred at ambient temperature for 2

*To whom correspondence should be addressed.

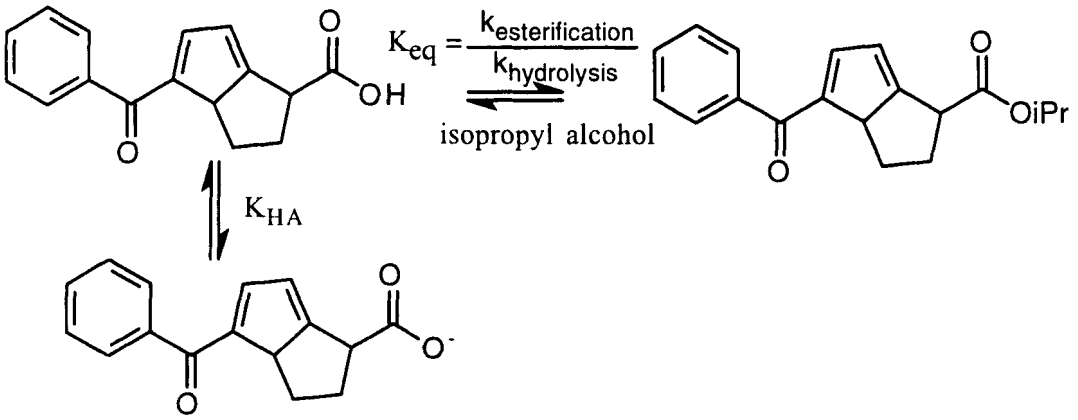

Figure 1. Equilibrium equations in the formation of the isopropyl ester of ketorolac.

days under nitrogen. HPLC analysis showed that 95% conversion to ester had occurred. The reaction mixture was diluted with three parts of water and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate (anhydrous). Ethyl acetate was removed by rotary evaporation at 50°C. Methylene chloride was added to azeotropically remove traces of solvent under high vacuum. To the remaining oil, 25 ml of hexane was added and the mixture was heated to approximately 50°C for several minutes. While the solution was still warm the hexane was decanted from the undissolved oil and allowed to cool slowly. The resulting oil crystallized, yielding 5.3 g of off-white crystals (53%). The purity by HPLC analysis was 99.5% and the melting point was 48.0°C.

Measurement of the Dissociation Constant of Ketorolac in Isopropyl Alcohol Solutions

Approximately 7 mg of ketorolac free acid was accurately weighed and dissolved in 10 ml of isopropyl alcohol:water (35%, 30%, and 20% w:v). The pH meter was standardized at pH 7.0, 4.0, and 1.69 with 100% aqueous standard buffer solutions. The samples were titrated with 0.105 M potassium hydroxide. The data were fitted to Eq. (1) with the nonlinear curve-fitting program in Kaleidagraph (Synergy Software, Reading PA) to determine the pK_a values. Measurements were made in duplicate.

$$\text{Equivalents of base} = \frac{10^{(pH - pKa)}}{1 + 10^{(pH - pKa)}} \quad (1)$$

Preparation of Kinetic Solutions

pH 1.4, 2.4, and 3.4 solutions were prepared from 0.1 M HCl and 35% isopropyl alcohol (w:v) stock solution containing 0.03% butylated hydroxytoluene (w:v) as an antioxidant. Solutions of pH 4.6 and 5.6 contained 0.1 M acetate buffer and the isopropyl alcohol–butylated hydroxy toluene stock solution. To these solutions ketorolac free acid or ketorolac isopropyl ester were added at a final concentration of 1 mg/ml. The effect of sodium acetate buffer on the rate of hydrolysis of the isopropyl ester of ketorolac was studied in pH 5.10, 5.30, and 5.50 acetate buffer containing 35% isopropyl alcohol (w:v). The drug concentration in these samples was 75 μg/ml and butylated hydroxy toluene was not added to these samples. Aliquots of 1 ml were placed in clear 2-ml ampules and flame sealed. Several ampules of each solution were placed at -20°C to serve as "time zero" controls. The remainder of the samples were stored at 22, 60, and 80°C. At selected time intervals, samples were removed from the elevated-temperature ovens and either stored at -20°C or analyzed immediately by an HPLC method that allowed for simultaneous assay of ketorolac and the isopropyl ester of ketorolac. Reactions were followed for a period of up to 6 months or less depending on reaction rate.

First-order data for the disappearance of ketorolac or the isopropyl ester of ketorolac were analyzed by fitting the percent ketorolac or percent isopropyl ester versus time data to Eq. (3). Rate constants were verified with the rate of formation data using Eq. (4). Percentages were corrected for a small loss due to oxidation.

HPLC Methods

The HPLC system consisted of an SP 8700 ternary solvent delivery system from Spectra Physics and a Micromeritics model 725 autoinjector equipped with a 25-μl loop, and a Kratos 757 variable-wavelength detector. The detector was interfaced to a Macintosh SE computer and the data analyzed with Dynamax® software from Rainin.

The method used an Zorbax Rx C8 column (250 × 4.6 mm i.d.) with an isocratic mobile phase consisting of water:acetonitrile:formic acid (60:40:0.5). A flow rate of 1.2 ml/min and detection at 310 nm were used.

RESULTS AND DISCUSSION

Determination of the pK_a of Ketorolac in 35% Isopropyl Alcohol

Ketorolac reacts with isopropyl alcohol in acidic solutions to form the isopropyl ester. The amount of ester that forms, as well as the rate of formation, depends on the percent isopropyl alcohol in solution and the pH of the solution (Fig. 1). The equilibrium value for ester formation reduces dramatically above the pK_a of the carboxylate group [Eq. (2)].

$$\frac{[\text{isopropyl ester}]}{[\text{ketorolac}]} = \frac{K_{eq}[\text{isopropyl alcohol}][H^+]}{[\text{water}]\{K_{HA} + [H^+]\}} \quad (2)$$

Addition of alcohols to aqueous solutions is known to increase the pK_a of carboxylic acids (6). The effect of isopropyl alcohol on the pK_a of ketorolac is shown in Fig. 2. In this study, ketorolac or the isopropyl ester was reacted in 35% isopropyl alcohol (w:v) to model the topical gel formulation. At this concentration of isopropyl alcohol the pK_a of ketorolac is 4.9, suggesting that the ketorolac will be largely non-ionized if formulated below this pH.

Effect of pH on the Kinetics of Esterification

Ketorolac and the isopropyl ester were degraded in aqueous buffers of pH 1.4–5.6 containing 35% isoproyl alcohol (w/v) at 22, 60, and 80°C. The kinetics of degradation were analyzed by reversed-phase HPLC. Typical plots of the approach to equilibrium starting from the ketorolac or the isopropyl ester of ketorolac are shown in Fig. 3. The rate of approach to equilibrium was determined from the degradation of compound or the formation of product using Eq. (3) or Eq. (4), respectively.

$$k_{deg} = 1\Big/\frac{(t \times \ln 100 - \%R_{inf})}{\%R_t - \%R_{inf}} \quad (3)$$

$$k_{form} = 100 - 1\Big/\frac{(t \times \ln 100 - \%R_{inf})}{\%R_t - \%R_{inf}} \quad (4)$$

In these equations, $\%R_t$ is the percent drug or product at time t and $\%R_{inf}$ is the percent remaining at infinity.

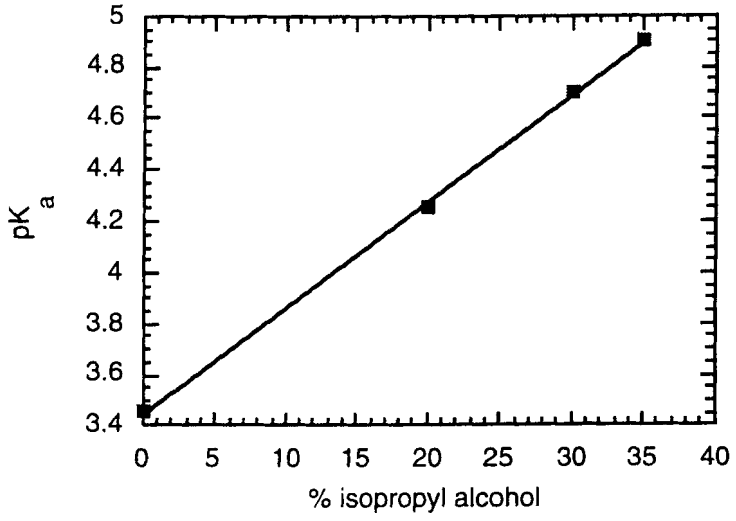

Figure 2. Plot of the pK_a of ketorolac versus the percent isopropyl alcohol (w:v).

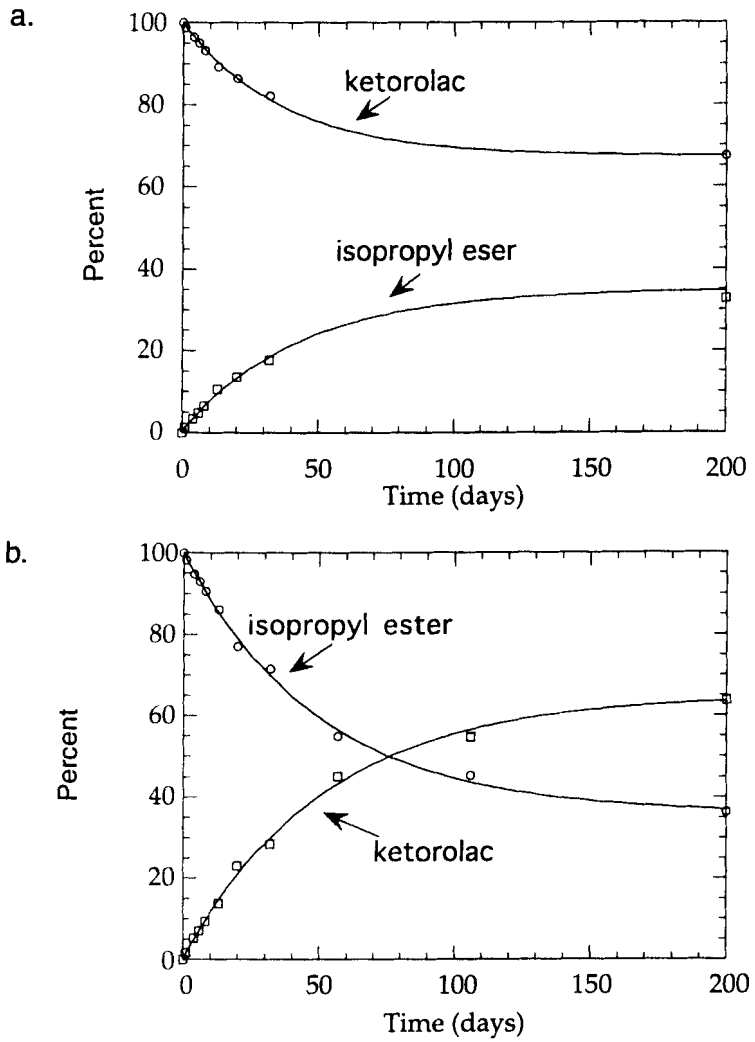

Figure 3. Degradation and formation profiles for reactions in 35% isopropyl alcohol (w:v) at 80°C. a) Solutions of ketorolac. b) Solutions of the isopropyl ester of ketorolac.

Equilibrium values were measured or approximated using Eq. (5).

$$k_{obs} = \frac{K_{eq}[H^+]}{K_{HA} + [H^+]} \quad (5)$$

K_{eq} is the equilibrium constant at pH values were ketorolac is entirely in the free acid form ($K_{eq} = 0.5$) and K_{HA} is the dissociation constant of ketorolac in 35% isopropyl alcohol ($K_{HA} = 1.2 \times 10^{-5}$ M). The rates of reaction at the various pH conditions and temperatures, and the equilibrium percentages used to calculate the rate constants are summarized in Table 1. Since the ester formation and ester hydrolysis reactions are an approach to the same equilibrium value from the opposite directions, the observed rate constants for both reactions are the sum of the rate constants for the esterification and hydrolysis reaction (7) and thus the same within experimental error.

$$k_{obs} = k_{esterification} + k_{hydrolysis} \quad (6)$$

The values for the observed rate constants at 60 and 80°C can be fitted to an equation containing a second-order specific acid rate constant, k_{H+}, and a water term, k_w, using a nonlinear regression method.

$$k_{esterification} = k_{H+}[H+] + k_w \quad (7)$$

The k_w term also includes a component due to catalysis by 0.1 M acetate buffer (see below). A similar equation to Eq. (7) applies to the formation reactions. The

Table 1

Observed First-Order Rate Constants for the Approach to Equilibrium for the Esterification of Ketorolac and Hydrolysis of the Isopropyl Ester of Ketorolac in Aqueous Buffers Containing 35% Isopropyl Alcohol[a]

Compound	pH	K_{obs}	k_{obs}, sec^{-1} 22°C	60°C	80°C
Ketorolac	1.41	0.50	7.2×10^{-7}	1.0×10^{-5}	3.2×10^{-5}
	2.40	0.50	5.1×10^{-8}	1.1×10^{-6}	3.4×10^{-6}
	3.26	0.49	9.8×10^{-9}	7.9×10^{-8}	3.1×10^{-7}
	4.70	0.31	[b]	9.6×10^{-9}	3.0×10^{-8}
Isopropyl ester	1.41	0.50	5.3×10^{-7}	9.6×10^{-6}	3.2×10^{-5}
	2.43	0.50	4.3×10^{-8}	9.5×10^{-7}	3.2×10^{-6}
	3.41	0.49	6.5×10^{-9}	9.1×10^{-8}	2.3×10^{-7}
	4.79	0.29	1.4×10^{-10}	8.1×10^{-9}	2.2×10^{-8}
	5.75	0.06	1.7×10^{-10}	5.6×10^{-9}	2.1×10^{-8}

[a]Rate constants were determined from kinetic data from 6 months or less.
[b]Rate constant was too slow to determine.

curves drawn in Fig. 4 were constructed from the microscopic rate constants summarized in Table 2. The degradation of ketorolac in solutions of pH greater than 4 was less than 5% after 200 days at 22°C, therefore, k_w could not be determined. Only the k_{H+} was obtained at this temperature.

Activation energies for the reaction of ketorolac and the isopropyl ester are 15 $kcal/mol^{-1}$. The rate constants

Table 2

Effect of Temperature on the Microscopic Rate Constants for the Esterification of Ketorolac and Hydrolysis of the Isopropyl Ester of Ketorolac

Compound	T, °C	k_{H+} $M^{-1} \cdot sec^{-1}$	k_w sec^{-1}
Ketorolac	22	6.2×10^{-6}	a
	60	8.6×10^{-5}	1.0×10^{-10}
	80	2.7×10^{-4}	1.0×10^{-9}
Isopropyl ester	22	$9.1 + 10^{-6}$	8.0×10^{-11}
	60	1.6×10^{-4}	4.0×10^{-9}
	80	5.5×10^{-4}	1.0×10^{-8}

[a]Too slow to determine.

Table 3

Predicted Rate and Equilibrium Constants and T_{95} Values for Ketorolac in 35% Isopropyl Alcohol at 25°C

pH	k_{obs} 10^9 sec^{-1}	K_{obs} M^{-1}	T_{95} years
3.8	4.0	0.46	1.4
4.0	2.7	0.44	2
4.2	2.0	0.42	3
4.4	1.2	0.38	5
4.6	1.0	0.33	7
4.8	0.8	0.28	10
5.0	0.7	0.22	14

Table 4

Hydrolysis of the Isopropyl Ester of Ketorolac in Acetate Buffer

	% Ketorolac Ester[a]								
	pH 5.48 [acetate], M			pH 5.30 [acetate], M			pH 5.11 [acetate], M		
T, °C	0.133	0.066	0.033	0.133	0.066	0.033	0.133	0.066	0.033
60	3.1	1.5	1.0	3.0	1.5	1.1	3.3	1.5	1.3
80	11.2	5.8	4.2	10.8	5.6	4.2	11.3	5.5	5.0

[a]Percent formed when reacted for 60 days at 80°C.

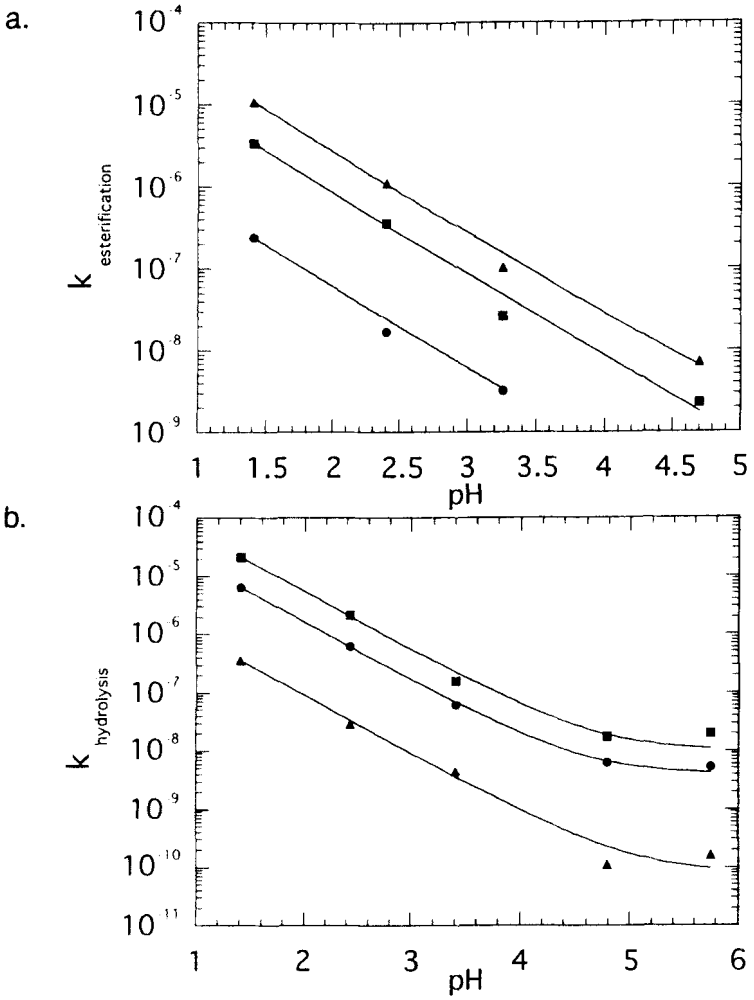

Figure 4. pH-rate profile for reactions in 35% isopropyl alcohol (w:v) at 22, 60, and 80°C. a) The microscopic rate constant for esterification of ketorolac. b) The microscopic rate constant for hydrolysis of the isopropyl ester of ketorolac.

for 25°C (Table 3) were obtained by interpolation of the curves in Fig. 3 at pH 4–5 from the data obtained for the rates of degradation at 22, 60, and 80°C. Values for k_{obs}, K_{obs}, and t_{95} at various pH values are listed in Table 3. The data show that pH values >4 are necessary to obtain an adequate shelf life.

Effect of Buffer on the Hydrolysis of the Isopropyl Ester of Ketorolac

Table 4 shows the percent ketorolac formed from the hydrolysis of the isopropyl ester in 35% isopropyl alcohol (w:v) after 60 days at pH 5.11–5.48 and 60 and 80°C. The data show little pH dependence; however, acetate buffer appears to strongly catalyze the reaction. The extent of the catalysis by acetate appears to be independent of pH in the region studied. These results suggest that viscosity-increasing agents that contain carboxylates may accelerate the approach to equilibrium and should be tested before being included in the formulations.

REFERENCES

1. J. Muchowski, S. Unger, J. Ackrell, P. Cheung, G. Cooper, J. Cook, P. Callegra, O. Halpern, R. Koehler, A. Kluge, A. Van Horn, Y. Antonio, H. Carpio, F. Franco, E. Galeazzi, I. Garcia, R. Green house, A. Guzman, J. Iriate, A. Leon, A. Pena, V. Perez, D. Valdez, N. Ackerman, S. Ballaron, D. Murthy, J. Rovioto, A.

Tomolonis, J. Young, and W. Rooks, J. Med. Chem., 28, 1037–1049 (1985).
2. L. Gu, H. Chiang, and A. Becker, Int. J. Pharm., 41, 95–104 (1988).
3. L. Gu, H. Chiang and D. Johnson, Int. J. Pharm., 41, 105–113 (1988).
4. M. Brandl, A. Magill, V. Rudraraju, and M. S. Gordon, J. Pharm. Sci., 84, 1151–1153 (1995).
5. S. D. Roy and E. Manoukian, J. Pharm. Sci., 83, 1548–1553 (1994).
6. A. Albert and E. P. Serjeant, *The Determination of Ionization Constants*, Chapman and Hall, New York, 1984, pp. 35–36.
7. A. Frost and R. Pearson, *Kinetics and Mechanism*, 2nd ed., John Wiley Publishing, 1961, p. 186.