Alkaline Hydrolysis of Ethiofencarb: Kinetic Study and Mechanism Degradation

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ABSTRACT: The present paper deals with the hydrolysis of ethiofencarb [2-ethylthiomethyl(phenyl)-N-methylcarbamate] in alkaline solution. The reaction kinetics has been investigated using spectrophotometric and liquid chromatographic techniques. The rate constants were determined following a proposed first-order kinetic model. The positive activation entropy $\Delta S^{\neq} = +100.07\ J\ mol^{-1}\ K^{-1}$ and the absence of general basic catalysis indicated an E1cB hydrolytic mechanism, involving the formation of methyl isocyanate. This result was confirmed by the fact that ethiofencarb fits well into Brönsted and Hammett lines, obtained for a series of substituted N-methylcarbamate whose decomposition in aqueous media was established to follow an E1cB mechanism. © 2012 Wiley Periodicals, Inc. Int J Chem Kinet 45: 118–124, 2013

INTRODUCTION

Ethiofencarb [2-ethylthiomethyl(phenyl)-*N*-methylcarbamate] is a carbamate insecticide, popularly known as Croneton [1,2]. It is used as an agricultural spray to control aphids on fruits, vegetables, and corn [3]. A great number of papers have been published about the toxicity of ethiofencarb: The oral LD_{50} for rats is about 200 mg/kg body weight [4].

A recent study showed that this pesticide and the product derived from its degradation give rise to residues that may spread through the environment and are particularly frequent contaminants in surface water, ground water, soil, and food products [5]. Analyses of aged solutions of ethiofencarb by LC-MS showed the formation of a unique degradation product corresponding to a 2-ethylthiomethylphenol (R-OH) derivative as described by Asensio et al. [6]. The photodegradation of ethiofencarb in solar light is very rapid, and sulfoxide and sulfone are the main degradation products [5]. Kopf and Schwack investigated the photodegradation of ethiofencarb by UV light ($\lambda > 280$ nm) and natural sunlight in the presence of different solvents, in an attempt to model its photolysis on plant surfaces [7]. Different products were obtained depending on the solvent and light sources: Ethiofencarb sulfoxide was the main product of irradiation in cyclohexane, whereas photo-oxidation, hydrolysis, and addition product formation were observed when the photolysis took place in isopropanol. The determination of residues of ethiofencarb in surface water [8], grain, fruits, and vegetables was reported [9–15]. Analyses were

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performed using HPLC with ultraviolet or fluorescence detection and gas chromatography (GC) in combination with nitrogen phosphorus detection after a derivatization step.

The degradation of carbamate derivatives is possible through chemical, microbiological, and photochemical processes. A detailed study of voltammetric behavior of ethiofencarb was reported using a glassy carbon electrode and a hanging mercury drop electrode [16]. The photodegradation of ethiofencarb was investigated in aqueous media. Half-lives were measured, and photoproducts were assessed by GC with mass spectrometry as a detector, allowing the establishment of a cleavage mechanism [6].

A kinetic study of the hydrolysis of ethiofencarb in pure water and in aqueous solutions at different pH values and different temperatures has been carried out using a gas chromatographic nitrogen phosphorus detection method. The values of the first-order rate constants for the degradation reaction were found to be dependent on pH and temperature [17]. Zamy et al. studied the hydrolysis of four organophosphorus pesticides and two *N*-methylcarbamate derivatives (oxamyl and ethiofencarb). At pH 8, ethiofencarb was found stable ($t_{1/2} < 1$ month). A degradation product was identified by LC-MS [18]. The corresponding mechanism involves either an addition of OH^- onto the carbonyl with a further elimination of the RO^- leaving group or an abstraction of the hydrogen of the methyl carbamate moiety again evolving with the elimination of the RO^- group.

Since no systematic studies on the mechanistic aspect of the hydrolysis of ethiofencarb in aqueous solution had been reported in the literature, the objective of this study was to determine the mechanism of the hydrolysis of ethiofencarb employing spectrophotometric UV and liquid chromatographic methods.

EXPERIMENTAL

Materials

A Beckman DU 640B spectrophotometer fitted with a thermostated multiple cell compartment is used for all spectroscopic measurements.

The liquid chromatography diode array detection (LC-DAD) system consists of a gradient model pump from Varian G 1600 A, a rehodyne six-port injection valve model 7125 with a 20-μL loop. A model Pro Star 330 photodiode array detector was connected to a computer station. Separations were performed using a Symmetry C18, 150 × 4.6 mm i.d., 3-μm particulate size analytical column.

The mobile phase was acetonitrile–water (45:55 v/v). It was set at a flow rate of 2 mL min^{-1}. The measured wavelength was 200 nm.

Standards and Reagents

Ethiofencarb and 2-ethylthiomethylphenol were obtained from Supelco (Saint-Quentin Fallavier, France). Standard stock solutions were prepared as 1000 μg mL^{-1} in methanol at 4°C. Working solutions were prepared by sequential dilution at 20 μg mL^{-1} in various buffer and in sodium hydroxide solutions ranging from pH 9.80 to 11.71. Ionic strength (I) made up 1 with KCl at 25°C.

These aqueous solutions were prepared with deionized water, which was distilled over permanganate and sodium hydroxide. Nitrogen was bubbled through the distilled water used for the preparation of sodium hydroxide solutions.

Acetonitrile and methanol were of HPLC grade. Borax ($Na_2B_4O_7 \cdot 10\ H_2O$), $NaHCO_3$, KH_2PO_4, HCl, NaOH, and KCl were purchased from Fluka (Saint-Quentin Fallavier, France).

Kinetics Measurements

Spectrophotometric Method. The changes in concentration of ethiofencarb were followed spectrophotometrically by recording changes in the absorbance corresponding to the appearance of a hydrolysis product ($\lambda = 295$ nm).

All reactions exhibited first-order kinetics with respect to the substrate. The absorbance versus time plots (Fig. 1) gave the pseudo–first-order rate constants graphically using the experimental infinity value. The observed rate constants k_{obs} were obtained by plotting $\log (A_\infty - A_t)$ versus time, where A_∞, and A_t are the absorbance at infinity and at time t, respectively:

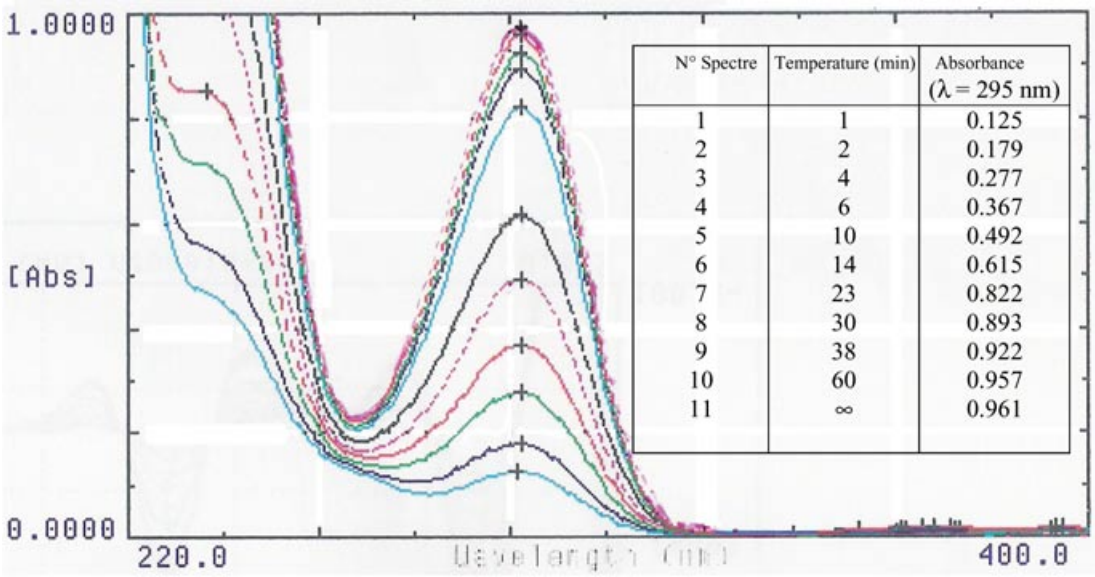
$$\log (A_\infty - A_t) = -\frac{k_{obs}}{2,3}\, t + \log (A_\infty - A_0) \qquad (1)$$

Liquid Chromatographic Method. We followed by reversed-phase liquid chromatography the evolution of 2-ethylthiomethylphenol chromatogram (peak 2) versus time during the hydrolysis of ethiofencarb (peak 1) in alkaline solution (Fig. 2).

The observed rate constants k_{obs} were obtained by plotting $\log (A_\infty - A_t)$ versus time, where A_∞, and A_t are the peak area at infinity and at time t, respectively (Eq. (1)).

Entropy Activation

The logarithms of the observed rate constants were plotted versus $1/T$, a straight line was observed, and



N° Spectre	Temperature (min)	Absorbance (λ = 295 nm)
1	1	0.125
2	2	0.179
3	4	0.277
4	6	0.367
5	10	0.492
6	14	0.615
7	23	0.822
8	30	0.893
9	38	0.922
10	60	0.957
11	∞	0.961

Figure 1 Ultraviolet spectra versus time for the hydrolysis of ethiofencarb in alkaline solution (10^{-4} M, pH 11.31) at $T = 25°C$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

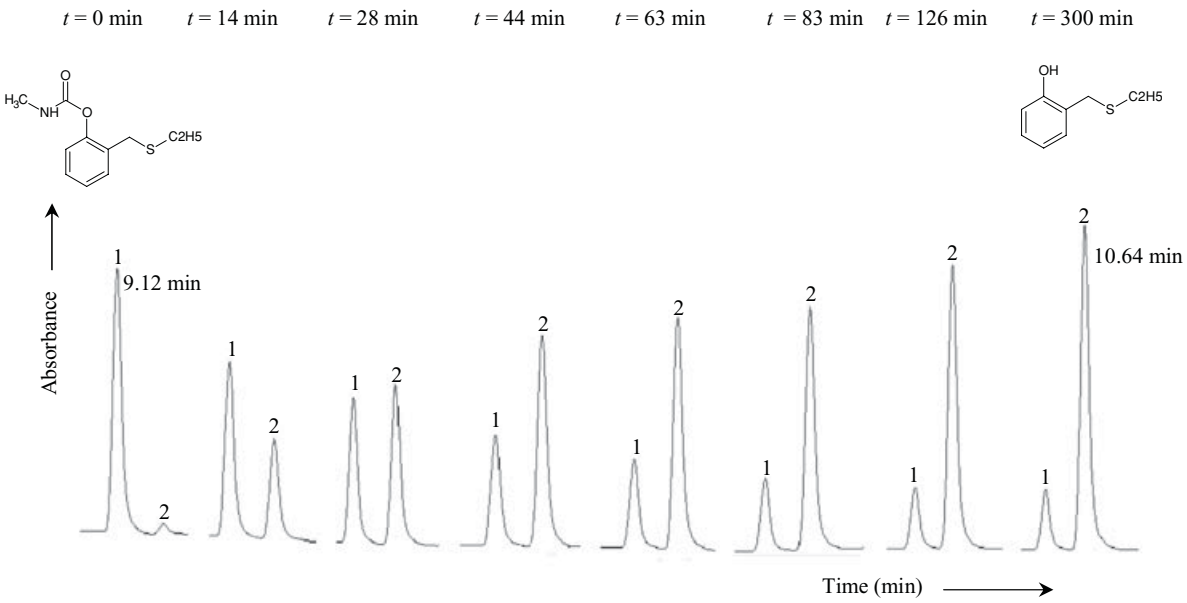


Figure 2 Chromatogram versus time for the hydrolysis of ethiofencarb in alkaline solution (10^{-4} M, pH 10.60) at $T = 25°C$.

the slope of which, multiplied by $-2.3R$ gave the Arrhenius activation energy E_a. The entropy activation $\Delta S^{\neq}$ was obtained from the following equation:

$$\frac{\Delta S^{\neq}}{(2.3R)} = \log k_{obs} - \log \frac{eK_B}{h} - \log T + \frac{E_a}{2.3RT}$$

where h and K_B are the Planck and Boltzmann constants, respectively, and R is the gas constant, $\log(eK_B/h) = 10.755$.

pK_a Measurement

The ultraviolet spectra of the studied carbamate in aqueous media show an increase with the pH in the region 280–300 nm. In 1 M NaOH, the maximum observed at 295 nm is consistent with the formation of a phenolate ion [19]. The pK_a was obtained from the intercept of the graph.

$$\log \frac{A - A_{AH}}{A_{A^-} - A} = f(\text{pH})$$

where A_A^-, A_{AH}, and A are, respectively, the absorbances of the phenolate ion in 1 M NaOH, of the nonionized carbamate in 1 M HCl and of the mixture of the two species in buffer solutions ranging from pH 10.45 to 11.95. The pK_a value of 2-ethylthiomethylphenol is 11.45 (25°C, $I = 1$, KCl).

RESULTS AND DISCUSSION

Determination of the Hydrolysis Product

An aliquot of an ethiofencarb hydrolysis reaction in a buffer solution was analyzed by spectrophotometric UV and reversed phase liquid chromatography in an acetonitrile–water mixture. The hydrolysis product was identified by comparing retention times and UV spectra with those of authentic samples.

Effect of pH

The rates constants of ethiofencarb hydrolysis were measured in various buffers and in sodium hydroxide solutions ranging from pH 9.80 to 11.71. The spectrophotometric and liquid chromatographic methods indicate the same rate constants k_{obs}. The values of first-order rate constants k_{obs}, respectively, determined by spectrophotometric and liquid chromatographic methods at pH 10.60 and $T = 25$°C were 1.84×10^{-2} min^{-1} and 1.80×10^{-2} min^{-1}. The plot of log $k_{obs} = f$ (pH) is shown in Fig. 3. It can be observed that higher rates were obtained at higher pH values.

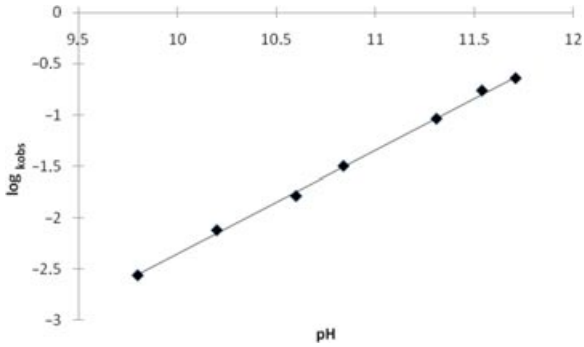


Figure 3 Plot of log k_{obs} versus pH for the hydrolysis of ethiofencarb at 25°C.

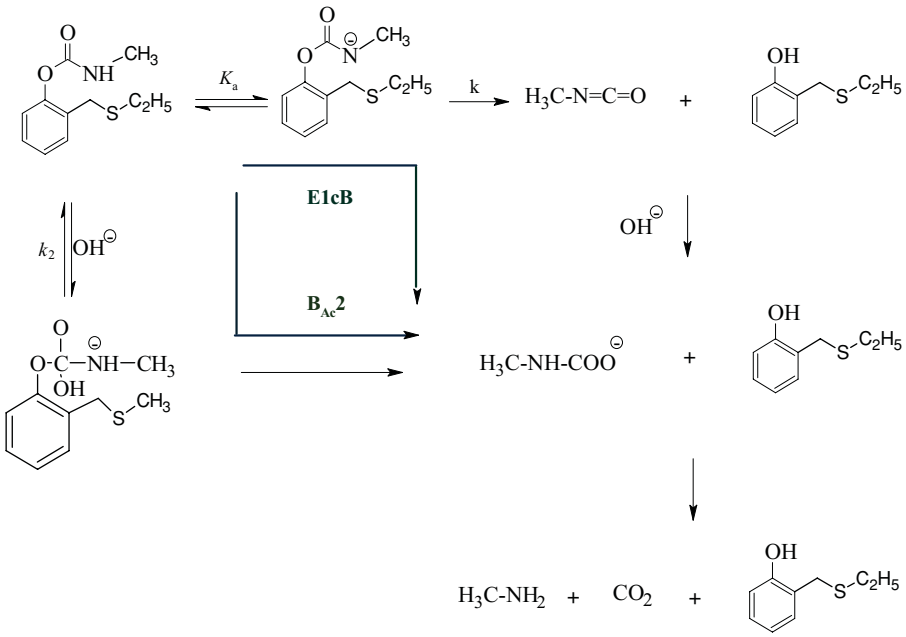
Furthermore, it can be pointed out that the ethiofencarb hydrolysis reaction presents a straight line of slope unity (log $k_{obs} = 1.008$, pH $- 12.44$, $R^2 = 0.999$).

This slope value is in agreement with the limit forms obtained for $a_H \gg K_a$ and $a_H \ll K_a$ of Eqs. (2) and (3).

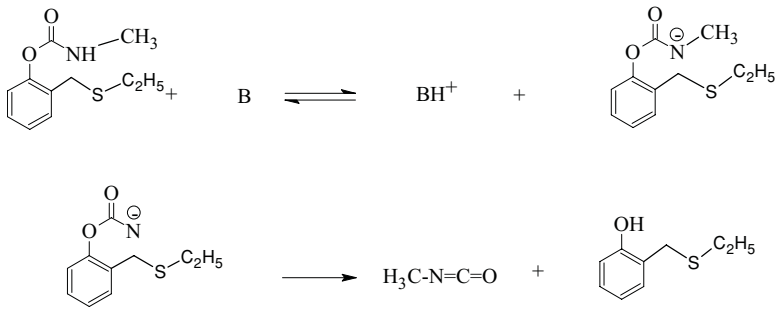
$$k_{obs} = \frac{k_1 K_a}{K_a + a_H} \tag{2}$$

$$k_{obs} = K_2[OH^-] \tag{3}$$

These correspond to the E1cB and $B_{Ac}2$ mechanisms (Scheme 1), respectively, both of which are possible



Scheme 1 Hydrolysis of ethiofencarb according to E1cB and $B_{Ac}2$ mechanisms.



Scheme 2 A bimolecular elimination mechanism E2.

hydrolysis pathways with N-monosubstituted carbamates [20,21]. Both mechanisms E1cB and $B_{Ac}2$ differ mainly by the formation of methyl isocyanate. The detection of this intermediate in the reaction medium is very difficult because of its extreme transience. Indeed methyl isocyanate quickly reacts with the hydroxyl ion to form *N*-methylcarbamic, which by decarboxylation leads to methylamine [22].

Possibility of Mechanism E2: Research of General Basic Catalysis

Although E1cB and $B_{Ac}2$ are the only mechanisms that have been given for the hydrolysis of aryl or alkyl carbamates, it is possible to propose a bimolecular elimination mechanism E2 (Scheme 2). Such a mechanism involves a transfer of protons that should be translated by a general basic catalysis. The rate constants were measured in phosphate buffer solutions (pH 11.31) at different concentrations (Table I). It is noted that rate constants remain fixed, and the mechanism E2 is rejected.

Effect of Temperature

Equations (1) and (2) are equivalent, so we cannot differentiate between the two mechanisms. By the consequence to elucidate the mechanism of carbamate hydrolysis, we need to evaluate the activation entropy $\Delta S^{\neq}$. Indeed, the two mechanisms present a very different activation entropy: The $B_{Ac}2$ mechanism shows a $\Delta S^{\neq}$ value of between -42 and -167 J mol^{-1} K^{-1},

Table I Rates of Hydrolysis of Ethiofencarb at Different Phosphate Buffer Concentrations (pH 11.31) at 25°C

$[HPO_4^{2-}]$ ($\times 10^{-2}$ mol L^{-1})	1	0.75	0.5	0.25
k_{obs}($\times 10^2$ min^{-1})	9.11	9.06	9.00	9.02

Table II Effect of temperature on hydrolysis of Ethiofencarb in Phosphate Buffer Solution at pH 11.54

Temperature (°C)	15	20	25	30	35
k_{obs} ($\times 10^2$min^{-1})	3.3	6.90	17.18	29.78	64.28

largely due to the addition of the hydroxyl ion [23], whereas the E1cB mechanism involves a positive or a slightly negative value of activation entropy that can be attributed to the dissociation of the anionic species $\Delta S^{\neq} = -24.2$, $+79.4$, and $+66.88$ J mol^{-1} K^{-1} for aldicarb, penmedipham, and desmedipham hydrolysis, respectively [21,24,25]. The rate constants of the hydrolysis reaction of ethiofencarb, measured at temperatures ranging from 15 to 35°C, are reported in Table II.

The energy of activation E_a calculated from the equation $\log k_{obs} = -5.78/T + 18.49$ is 110.10 kJ mol^{-1}. The activation entropy of the hydrolysis reaction of ethiofencarb is then deduced $\Delta S^{\neq} = +100.07$ J mol^{-1}K^{-1}. This large positive value indicates that an E1cB mechanism is involved.

Brönsted Relationship

The Brönsted relationship, which relates k_{OH} to the pK_a of the leaving group, also provides useful information as to the differentiation of the two reaction mechanisms [21,23,26]. The pK_a value of 11.45 for 2-ethylthiomethylphenol was measured as described previously. The point corresponding to ethiofencarb was introduced into the graph $\log k_{OH} = f\ (pK_a)$ of a precedent study on E1cB hydrolysis of substituted phenyl *N*-phenylcarbamates [27] (Fig. 4). The slope, which is less than -1 ($\beta = -1.15$; $r = 0.971$), is characteristic of a reaction mechanism involving elimination of the leaving group as the rate-limiting step. The fact that ethiofencarb fits into the correlation supports the argument that its hydrolysis follows an E1cB reaction mechanism.

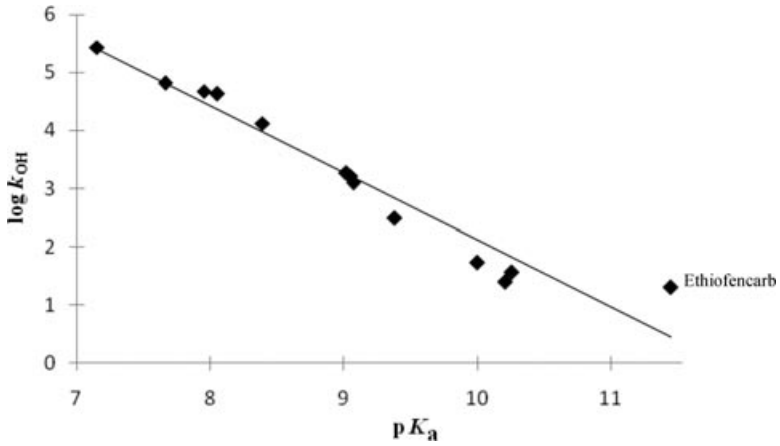


Figure 4 Brönsted plot of log k_{OH} versus pK_a of the leaving group for the hydrolysis of aryl and alkyl *N*-phenylcarbamates at 25°C.

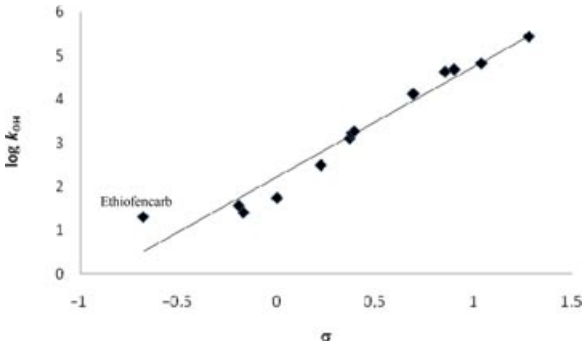


Figure 5 Hammett plot of log k_{OH} versus σ of the leaving group for the hydrolysis of aryl and alkyl *N*-phenylcarbamates at 25°C.

Hammett Relationship

The Hammett relationship $\log k_{OH} = 2.865\sigma + 2.04$ established by Williams for the hydrolysis of a series of phenyl-*N*-phenylcarbamates is in favor of an E1cB mechanism [27]. The electronic parameter $\sigma = -0.68$ on the leaving group 2-ethylthiomethylphenol was calculated from the equation $pK_a = 9.92 - 2.23\ \Sigma\sigma$ [28]. The experimental point corresponding to ethiofencarb ($\log k_{OH} = 1.3$, $\sigma = -0.68$) is positioned perfectly on the Hammett line (Fig. 5).

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