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Kinetics and Mechanism of Cymoxanil Degradation in Buffer Solutions

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The kinetics and mechanism(s) of the hydrolytic degradation of a compound are needed to evaluate a compound's abiotic degradation in the environment. In this paper, the hydrolysis of cymoxanil [2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino) acetamide] was investigated in dark sterile aqueous solutions under a variety of pH conditions (pH 2.8−9.2) and temperatures (15−50 °C). Hydrolysis of cymoxanil was described by first-order kinetics, which was dependent on pH and temperature. Cymoxanil degraded rapidly at pH 9 (half-life = 31 min) and relatively slowly at pH 2.8 (half-life = 722 days). The effect of temperature on the rate of cymoxanil degradation was characterized using the Arrhenius equation with an estimated energy of activation of 117.1 kJ mol^{-1}. An increase in temperature of 10 °C resulted in a decrease in half-life by a factor of ∼5. Three competing degradation pathways are proposed for the hydrolysis of cymoxanil, with two of the pathways accounting for ∼90% of cymoxanil degradation. These two pathways involved either initial cyclization to 1-ethyldihydro-6-imino-2,3,5(3*H*)-pyrimidinetrione-5-(*O*-methyloxime) (**1**, **Figure 1**) or direct cleavage of the C-1 amide bond to form cyano(methoxyimino) acetic acid (**7**). The third pathway of degradation involved initial cyclization to 3-ethyl-4-(methoxyimino)-2,5-dioxo-4-imidazolidinecarbonitrile (**8**), which rapidly degrades into 1-ethyl-5-(methoxyimino)-2,4-imidazoline-2,4-dione (**9**). All three pathways eventually lead to the formation of the polar metabolite oxalic acid.

KEYWORDS: Cymoxanil; hydrolysis; half-life; pH; temperature; kinetics

INTRODUCTION

Cymoxanil-based fungicides have been in use for over 25 years. Today, cymoxanil is registered in over 50 countries and used on over 10 million hectares worldwide for 17 different crops. Cymoxanil is used primarily to control downy mildew diseases and is key in controlling the fungal pathogens *Plasmopara viticola* (grape downy mildew) and *Phytophthora infestans* (tomato and potato late blight). Despite cymoxanil's long and intensive history of use, there have been no reports of emerging resistance to the compound mixtures when applied according to good agricultural practice (preventive applications) (*1*−*4*). Credit for the continued sensitivity of pathogens to cymoxanil following its intensive use has been due in large part to its complex mode of action and exclusive use in mixtures (*1*).

The environmental profile of cymoxanil has been cited as another possible reason for its continued efficacy (*1*). However, there is little or no information in the literature concerning cymoxanil's environmental characteristics to verify this assumption. Consequently, information on the environmental characteristics of cymoxanil is needed to predict its fate and behavior in the environment. These data can be used to evaluate what role, if any, cymoxanil's environmental profile has in its continued efficacy toward target pathogens.

Previous metabolism studies of cymoxanil have shown that it readily degrades into naturally occurring compounds, with glycine being the major metabolite in both animal (*5*) and plant (*6*) test systems. However, abiotic degradation mechanisms are expected to contribute more to cymoxanil's degradation in the natural environment. In fact, abiotic degradation mechanisms can be the dominating agents of degradation below the root zone (*7*), aquatic systems (groundwater and surface water) (*8*), and systems in which microbial activity is greatly reduced (*9*). Abiotic transformation processes, in particular, hydrolysis, are the most important naturally occurring reactions in the environment and represent the most important degradation pathways for many pesticides (*8*, *10*, *11*).

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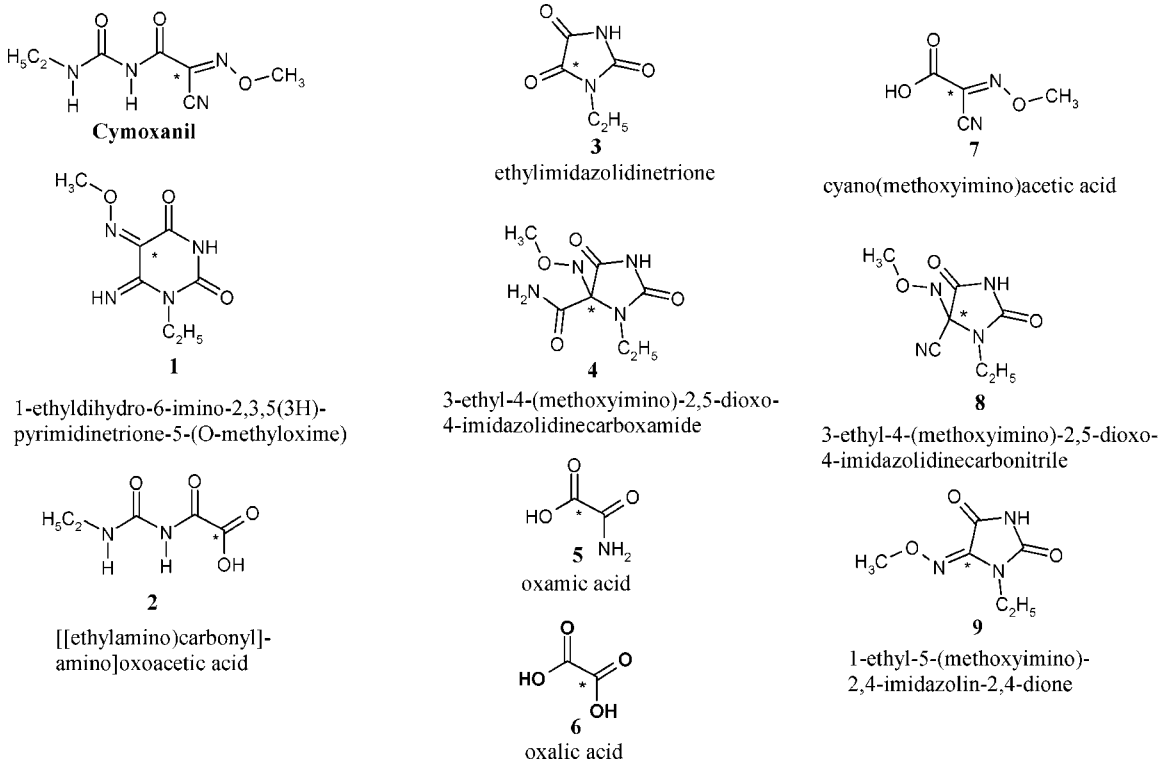

Figure 1. Structures of cymoxanil and cymoxanil degradates.

Hydrolysis studies in buffer test systems serve as simplified models for understanding the chemical degradation mechanisms occurring in both aquatic and soil solutions. The purpose of this paper is to investigate the kinetics and mechanisms of cymoxanil degradation in sterile aqueous solutions and how these properties are influenced by both pH and temperature. The experiments are important for the identification of hydrolysis metabolites that may differ from biological products.

MATERIALS AND METHODS

Chemicals. Non-radiolabeled cymoxanil and its potential metabolites (names and structures are given in **Figure 1**) were synthesized either by DuPont Crop Protection, USA, or by University of Napoli "Federico II", Italy. Radiolabeled [*cyanoacetamide*-2-^{14}C]cymoxanil was synthesized at NEN (Boston, MA). [*cyanoacetamide*-2-^{14}C]Cymoxanil had a radiochemical purity of >95% and a specific activity of 2.79 MBq/mg of cymoxanil. All organic solvents used were of HPLC grade.

Ten buffer solutions of varying pH values were used to study the aqueous hydrolysis of cymoxanil, and **Table 1** shows the procedures followed for their preparation. Prior to use, all buffer solutions were filter sterilized using either a Millex GS/AP20 0.22 μm (Millipore, Bedford, MA) or Corning 0.22 μm cellulose acetate (Corning Inc., Corning, NY) filter.

Hydrolysis Experiments. Experiments were conducted using either non-radiolabeled or radiolabeled cymoxanil. In both the non-radiolabeled and radiolabel studies, glassware was sterilized by autoclaving for at least 20 min at 121 °C prior to use. Aseptic techniques were adopted to maintain sterility. The effectiveness of the aseptic procedures performed was confirmed by microbial tests, which demonstrated no contamination by microorganisms at the end of each respective study.

Non-radiolabeled Experiments. Hydrolysis rates in non-radiolabeled experiments were determined by monitoring the disappearance of cymoxanil in aqueous buffer solutions within the pH range 2.8−9.2 (**Table 1**). A stock solution containing 200 μg mL^{-1} of cymoxanil in acetonitrile was prepared. Triplicate 50.0 mL samples, each containing 4.0 μg mL^{-1} of cymoxanil, were obtained by diluting aliquots of 1.0 mL of the stock solution to 50 mL with the appropriate buffer solution. The treated buffer solutions were stored in the dark at ambient temperature (25 ± 2 °C) in centrifuge glass tubes. Another set of triplicate 50.0 mL distilled water samples at pH 6.6, containing 4.0 μg/mL of cymoxanil, was stored in the dark at 15, 28, 44, and 50 °C to test the effects of temperature on hydrolysis. One milliliter from each test vessel was aseptically removed at appropriate time intervals ranging from 20 min for cymoxanil solutions at higher temperatures to weeks (120 days) for solutions at pH <4 for HPLC analysis. In all trials, the pH of each sample was periodically measured and did not vary by >0.1 unit. If samples were not analyzed immediately, they were store at −20 °C until analyzed.

Table 1. Buffer Solutions Prepared for the Aqueous Hydrolysis of Cymoxanil

buffer solution	pH	preparation for 100 mL of buffer solution
A	2.8	98 mL of 0.2 M KCl + 2 mL of 0.2 M HCl
B	3.6	5.0 mL of 1.0 M NaOH + 65 mL of 1.0 M CH_3COOH
C	4.5	100 mL of 0.07 M KH_2PO_4
D[a]	5.0	14.8 mL of 0.02 M acetic acid + 35.2 mL of 0.02 M sodium acetate
E	5.9	16 mL of 0.5 M KH_2PO_4 + 1.4 mL of 0.5 M Na_2HPO_4
F	6.6	8 mL of 0.5 M KH_2PO_4 + 4 mL of 0.5 M Na_2HPO_4
G[a]	7.0	19.5 mL of 0.02 M NaH_2PO_4 + 30.5 mL of 0.02 M Na_2HPO_4 (0.02 M) (adjusted with 1.0 M HCl)
H	7.4	2 mL of 0.5 M KH_2PO_4 + 6 mL of 0.5 M Na_2HPO_4
I[a]	9.0	100 mL of 0.01 M boric acid (adjusted to pH with 50% w/w NaOH)
J	9.2	5 mL of 5 M HCl + 5.5 mL of 2 M NH_3

[a] Buffers used in radioactive experiments.

Radiolabeled Experiments. The hydrolysis rate and mechanism of degradation were determined in aqueous buffer solutions (see **Table 1**). The test solution concentration of [^{14}C]cymoxanil in pH 5.0 buffer solution was 25 μg of active ingredient (ai) mL^{-1}, whereas in the pH 7.0 and 9.0 buffer solutions, the concentration of the compound was 50 μg of ai mL^{-1}. The treated buffer solutions were maintained in the dark at 25 ± 2 °C with samples prepared in duplicate. At predetermined time intervals, the total amount of radioactivity in each test vessel was determined by liquid scintillation counting (LSC) of aliquots. Following total radioactivity analysis, aliquots of the test solutions were removed and analyzed immediately by HPLC to determine the distribution of [^{14}C]cymoxanil and its hydrolysis products. Material balance was

Table 2. HPLC Methods Used for Profiling Buffer Solutions

HPLC Method 1
(Profiling of Cymoxanil-Treated Buffer Solutions)

column/guard column	Prodigy C18 250 × 4.6 mm, 5 μm/ Prodigy C18 20 × 4 mm, 5 μm
flow rate	1.0 mL min^{-1}
detection	240 nm, MS-ESI
injection volume	20 μL
isocratic	acetonitrile/water (30:70 v/v)

HPLC Method 2
(Profiling of [^{14}C]Cymoxanil-Treated Buffer Solutions)

column/guard column	Zorbax C8 250 × 4.6 mm, 5 μm/ Zorbax C8 20 × 4 mm, 5 μm	
column temp	40.0 °C	
flow rate	1.0 mL min^{-1}	
detection	210 and 254 nm, radiochemical detection, fraction collection, and LSC	
injection volume	20–25 μL	
wavelength	254 nm	
gradient	% 0.2% formic aid	% methanol
0 min	100	0
30 min	95	5
30.5 min	75	25
45 min	70	30
55 min	35	65

HPLC Method 3
(Profiling of Polar Degradates in [^{14}C]Cymoxanil-Treated Buffer Solutions)

column/guard column	Supelcogel C-610H 7.8 mm × 5 μm	
column temp	30.0 °C	
flow rate	0.5 mL min^{-1}	
detection	254 nm, radiochemical detection, fraction collection and LSC	
injection volume	20–25 μL	
wavelength	254-nm	
gradient	% 0.2% formic acid/0.1% H_3PO_4	% acetonitrile
0 min	100	0
20 min	100	0
20.1 min	80	20
30 min	80	20

excellent [86.9−135% applied radioactivity (AR)], averaging 101.6 ± 4.8% AR (data not shown).

Analytical Procedures. *Non-radiolabeled Analyses.* The HPLC analyses were performed on a Waters HPLC system (Milford, MA) with details of the method supplied in **Table 2** (HPLC method 1). Samples were injected directly into the HPLC (no extraction or purification steps). The isocratic elution allowed a satisfactory chromatographic separation. Blanks of buffer solutions did not exhibit any peak that interfered with the detection of cymoxanil and/or its degradates. Standard solutions in acetonitrile of both cymoxanil and its potential degradates were prepared fresh every week and stored at 4 °C in the dark until use. Identification of the degradates was performed by HPLC-MS (LCQ, Finnigan Corp., San Jose, CA) using authentic standards for comparison. MS detection was performed with electrospray ionization (ESI), in positive and negative modes.

Quantitation of cymoxanil was based on calibration curves in the range of 0.025−5.00 μg mL^{-1} ($r^2 > 0.99$). The limit of detection (LOD) (estimated to be 3 times the background noise) was 25 μg L^{-1} for cymoxanil. The limit of quantitation (LOQ) (estimated to be 10 times the background noise) was 83 μg L^{-1} for cymoxanil. No significant difference in background noise was observed between the analyses of the standards in acetonitrile and those of the matrices analyzed.

Radiolabeled Analysis. The total radioactivity of each sample was determined by LSC analysis (Tracor Mark III liquid scintillation counter, TM Analytic, Elk Grove, IL) of triplicate aliquots. Samples were directly analyzed by HPLC to determine the distribution of cymoxanil and its hydrolytic degradates. Analysis was performed on a Waters Maxima 820 with details of the method supplied in **Table 2** (HPLC method 2). Quantitation of radioactivity was determined either using an in-line radiochemical detector (Ramona, Raytest Inc., Pittsburgh, PA) or by fraction collecting (typically 0.5−1 min fractions) using an ISCO Foxy fraction collector (ISCO Inc., Lincoln, NE) followed by LSC. The polar degradates of cymoxanil (degradates **4**, **5**, and **6**) were defined by HPLC method 2 as the peaks eluting from the column between 2 and 7 min and identified using HPLC method 3 (**Table 2**) on an Agilent Technologies series II 1090 HPLC. Positive confirmation of cymoxanil's major degradates were by LC-MS (Finnigan MAT TSQ 700, Finnigan Corp.) using electrospray ionization based on authentic standards for comparisons.

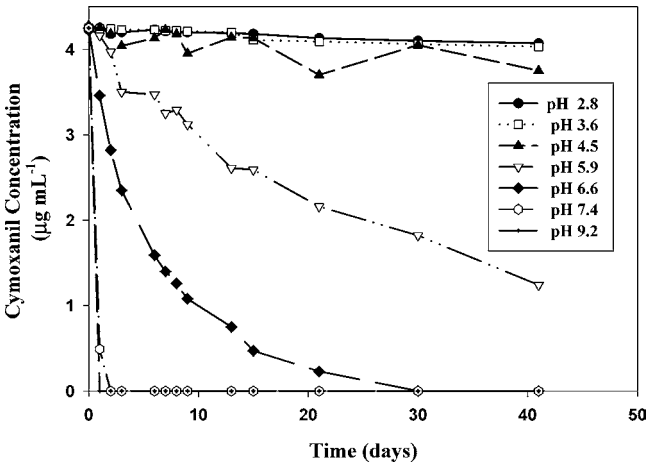

Figure 2. Disappearance of cymoxanil at different pH values in aqueous solution in the dark at ambient temperature (25 ± 2 °C).

Hydrolysis Rate. The degradation rate of cymoxanil expressed as fraction of parent compound remaining in the buffer solutions over time was estimated by first-order linear regression analysis. Linear regression analysis was performed on the data using the computer software program Microsoft Excel 97 SR2 (Microsoft Corp., Redmond, WA).

RESULTS AND DISCUSSION

Hydrolysis Kinetics. The hydrolysis of cymoxanil, monitored at different temperatures and pH values, was modeled using first-order kinetics. A plot of the observed data for cymoxanil degradation at various pH values is given in **Figure 2**. The high r^2 values (0.987−0.999) for the data fit indicate that degradation of cymoxanil in sterile buffer solutions (pH 2.8−9.2) approximates first-order kinetics.

Hydrolysis rates of cymoxanil degradation were pH dependent, with increasing k values being associated with higher pH values. The observed rate constant, k, and calculated half-lives ($t_{1/2} = \ln 2/k$) are shown in **Table 3**. At pH 9.0 ± 0.1 cymoxanil degradation was >1000-fold faster than at pH 5.9 ± 0.1 (half-lives were 31.2 min and 24 days, respectively). The half-lives of cymoxanil at pH 2.8, 3.6, and 5.0 were estimated to be 722, 576, and 144 days, respectively, and were extrapolated from their respective regression curves.

The increase in cymoxanil degradation with increasing pH may perhaps be explained by base-catalyzed hydrolysis. Cymoxanil has acidic properties on both the N−A and N−B nitrogens because the negative charge of the conjugate base is delocalized over the carbonyl groups (**Figure 3**). The pK_a of cymoxanil is 9.7 (*12*), and in basic solution the compound may convert to the anion form, which cyclizes due to nucleophilic attack on the imine and nitrile carbons, which results in the formation of the ring structures **1** and **8** (**Figure 1**). Although the N−B nitrogen is more acidic than the N−A nitrogen, cyclization to either a three- or four-member ring is not favorable (less stable), whereas formation of five- and six-member rings

Table 3. Determination of Rate Constant (k) and Half-Life ($t_{1/2}$) for the Hydrolysis of Cymoxanil

	k (days^{-1})	r^2	$t_{1/2}$ (days)
pH			
2.8 ± 0.1[a]	0.0010	0.904	722[d]
3.6 ± 0.1[a]	0.0013	0.920	576[d]
4.5 ± 0.1[a]	0.0082	0.647	96
5.0 ± 0.1[b]	0.0047	0.992	148[d]
5.9 ± 0.1[a]	0.0296	0.986	24
6.6 ± 0.1[a]	0.2646	0.999	2.62
7.0 ± 0.1[b]	0.4890	0.993	1.42
7.4 ± 0.1[a]	1.6458	0.992	0.42
9.0 ± 0.1[b]	32.0	0.995	0.02
9.2 ± 0.1[a]	10.04	0.999	0.07
temperature[c]			
15 ± 2 °C	0.0400	0.9902	17.33
28 ± 2 °C	0.4066	0.9991	1.70
44 ± 2 °C	2.7560	0.9967	0.25
50 ± 2 °C	10.3690	0.9952	0.07

[a] Hydrolysis of cymoxanil in aqueous solution (C_i = 4.0 mg/L) in the dark at ambient temperature (25 ± 2 °C). [b] Hydrolysis of cymoxanil using radiolabeled test material. [c] Hydrolysis of cymoxanil in aqueous solution (C_i = 4.0 mg/L) in the dark at pH 6.6 ± 0.1. [d] Extrapolated by the regression curve.

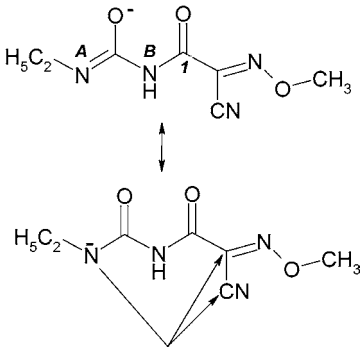

Figure 3. Proposed anion structure of cymoxanil in basic solution and mechanism of base-catalyzed reaction.

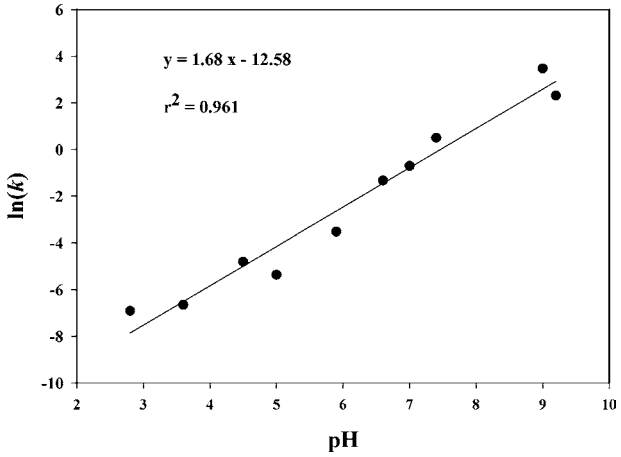

Figure 4. Variation of ln(k) with pH for the hydrolysis of cymoxanil in aqueous solution in the dark at ambient temperature (25 ± 2 °C).

with the N−A nitrogen is relatively stable. The higher proportion of **1** to **8** is due to steric hindrance.

To better characterize the effects of pH on the hydrolysis of cymoxanil, the rate constant (ln k) was plotted against pH. As can be seen in **Figure 3**, the k values increase at increasing pH. Using this relationship, ln k versus pH was plotted and its linear regression determined (**Figure 4**). This regression equation was used to estimate cymoxanil hydrolytic degradation in aquatic

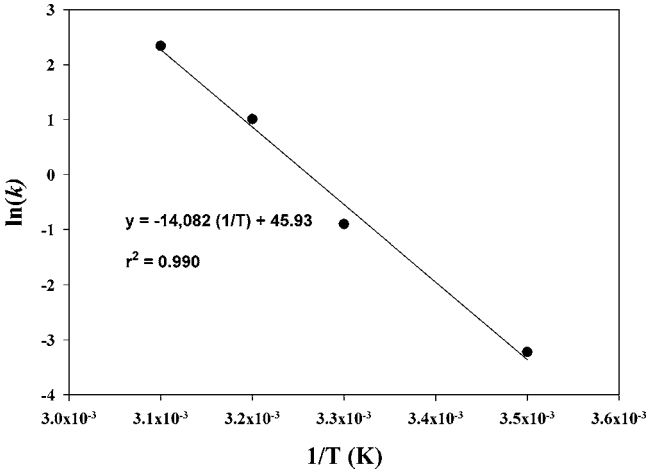

Figure 5. Variation of ln(k) with temperature for the hydrolysis of cymoxanil (pH 6.6 ± 0.1).

environments. Because typical pH values for aquatic environments range from 5.5 to 8.0 (*13*, *14*), cymoxanil's expected hydrolytic half-life at 25 °C was estimated to range between 0.3 and 19.6 days, which compares well to the measured values of 0.42 (pH 7.4) and 24 days (pH 5.9). However, it should be pointed out that the actual rate of degradation in the aquatic environment is expected to be faster because cymoxanil is susceptible to photochemical (*12*) and biological degradation (*5*, *6*). In fact, under laboratory conditions, cymoxanil's photochemical degradation rate is >85 times the hydrolytic degradation rate in pH 5.0 buffer solutions (*12*).

The hydrolysis of cymoxanil at pH 6.6 (±0.1) was monitored in the temperature range of 15−50 °C and showed a marked effect of temperature on degradation rate and half-life (**Table 2**). A change in temperature from 15 to 28 °C increased the half-life of cymoxanil by a factor of ∼10. The effects of temperature on the rate of cymoxanil hydrolysis were characterized by the Arrhenius equation:

$$\ln k = \ln A - E_a/RT$$

where A is the pre-exponential factor typical of cymoxanil hydrolysis reaction, E_a is the activation energy (J mol^{-1}), R is the universal gas constant (8.314 J K^{-1} mol^{-1}), and T is the absolute temperature (K).

As can be seen in **Figure 5**, a linear regression line fitted the experimental points, as expected for the Arrhenius equation. The activation energy (E_a), calculated from the slope of the linear regression multiplied by R, was 117.1 kJ mol^{-1}. This value is greater than the average estimated value (28−58 kJ mol^{-1}) for most organic compounds (*15*), but still similar to those of other compounds having pH-dependent degradations (*16*). However, it should be pointed out that cymoxanil degradation is not controlled by any one limiting step, but rather proceeds via three different pathways (see discussion on Pathways of Degradation), which are strongly controlled by the parent compound transforming to degradation product **1**. Consequently, the E_a value generated in this study is actually an effective or apparent E_a at the measured pH, which should hold true for pH values of <7 because the major route of degradation is pathway I (see discussion on Pathway of Degradation). The E_a estimate for cymoxanil calculates to a Q_{10} value of ∼5.2, which is double the expected value of 2.5 for most organic compounds (*15*).

Pathway of Degradation. A list of major degradation products (>10% AR) in various pH studies along with

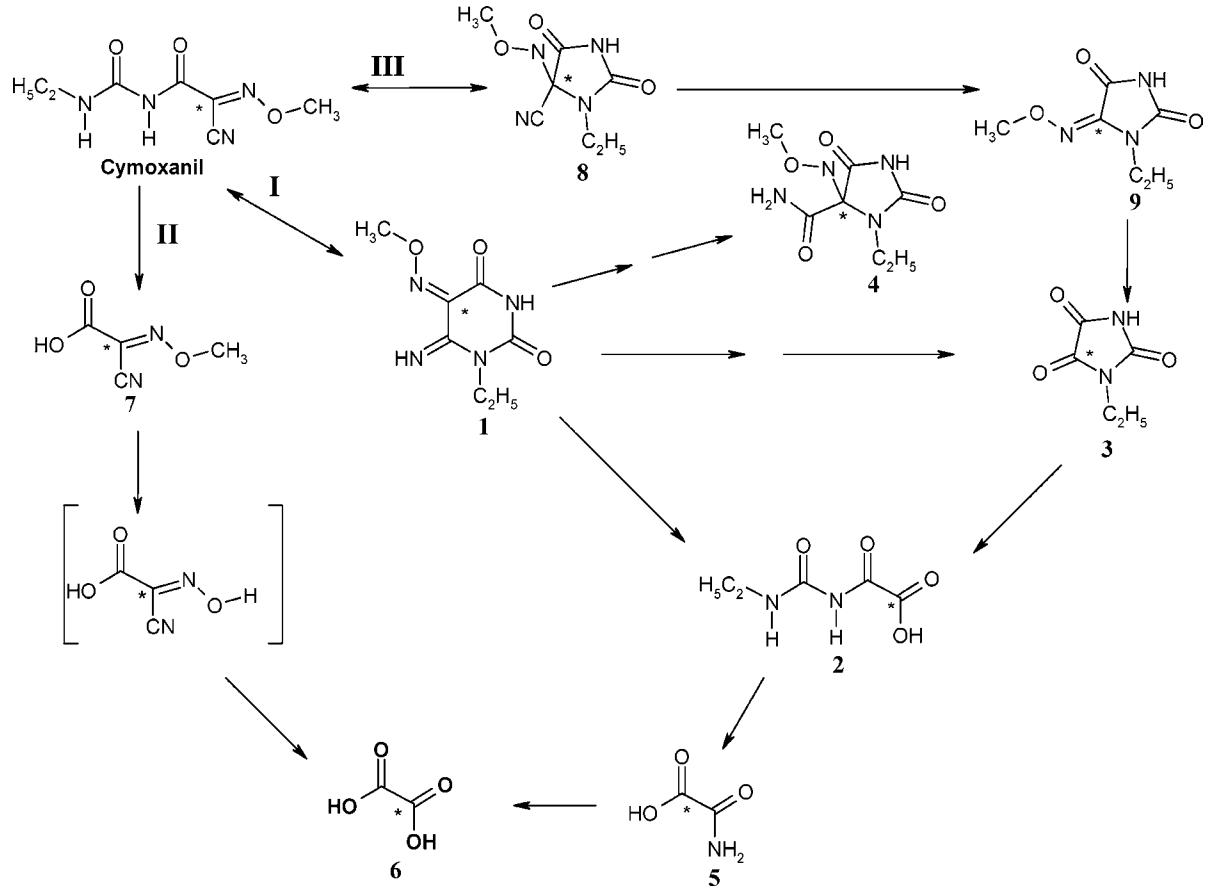

Figure 6. Proposed degradation pathway of cymoxanil in aqueous solutions.

Table 4. Major Degradation Products of Cymoxanil and Peak Levels of Detection

degradation product	pH	max level detected [% appl radioactivity (AR)]	sampling interval (days)
1	5	9.1	7
	7	52.7	2
	9	60.8	4 (h)
2	5	ND[a]	NA[b]
	7	57.0	30
	9	31.6	10
3	5	ND	NA
	7	5.4	10
	9	9.8	1
4	5	ND	NA
	7	9.0	30
	9	13.5	7
7	5	2.3	30
	7	16.2	15
	9	39.0	3
8	5	1.8	7
	7	5.0	28 (h)
	9	9.0	3 (h)
9	5	0.9	30
	7	10.2	15
	9	7.2	7

[a] Not detected (detection <0.1% AR). [b] Not applicable.

maximum levels of detection is given in **Table 4**. The overall hydrolytic degradation pathway for cymoxanil is described in **Figure 6**. Hydrolysis of cymoxanil involves three different initial pathways with the two main pathways accounting for ~90% of its degradation. Pathway I involves the cyclization of cymoxanil to **1**, which rapidly degraded to **2** and subsequently to **6**. Additional hydrolysis studies with **1** revealed that along with **2** the degradation products **3** and **4** formed in significant quantities. The degradation product **3** rapidly degraded to undetectable levels in both the pH 7 and 9 studies. In contrast, **4** was stable at all pH values tested. Pathway I accounted for an estimated 78 and 70% of cymoxanil's degradation in pH 5 and 7 buffer solutions, respectively, whereas in pH 9 buffer solutions it accounted for 55% of its degradation. Non-radiolabeled studies at pH 6.6 and 50 °C confirm that pathway I is the main degradation pathway in the pH range 5−7. As can be seen in **Figure 7**, the decreases in cymoxanil concentration correspond to the appearance of **1** first, with an increase of **2** over time.

Pathway II of cymoxanil degradation is direct cleavage of the amide bond on the C-1 carbon of cymoxanil to form **7**. This degradation product subsequently hydrolyzed slowly to more polar degradation products, but its degradation was considered insignificant. Pathway II in pH 5 and 7 buffer solutions accounted for an estimated 12 and 18%, respectively, of cymoxanil's degradation, whereas in pH 9 buffer solutions this pathway accounted for 35% of its degradation. The increase in the formation of degradate **7** at higher pH values may be a consequence of the C-1 amide bond being more susceptible to nucleophilic attack with increasing hydroxyl ion concentrations.

Pathway III involves the cyclization of cymoxanil to **8**. This degradate rapidly converted to **9**, which in turn slowly degraded to **3** as demonstrated in additional studies with **8** alone in pH 7 and 9 buffer solutions. Pathway III accounted for an estimated 10, 9, and 12% of cymoxanil's degradation in pH 5, 7, and 9 buffer solutions, respectively.

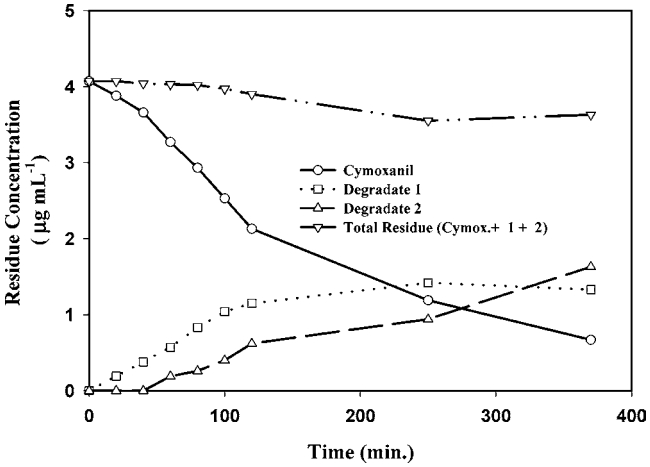

Figure 7. Hydrolysis of cymoxanil at pH 6.6 ± 0.1 and 50 ± 2 °C: formation of degradates 1 and 2 (values for 1 and 3 were converted to parent molar equivalents).

Conclusions. The results indicate that the rate of cymoxanil hydrolysis was strongly dependent on both pH and temperature. At typical pH values of aquatic environments, cymoxanil exhibits a relatively fast aqueous degradation (half-lives ranging from 1.4 to 24 days, 25 °C), whereas at typical aqueous temperatures (10−15 °C) cymoxanil degradation is expected to be moderate (half-lives ranging from 17.3 to 36.5 days, pH 6.6). Due to the hydrolytic degradation profile of cymoxanil and because it is susceptible to photochemical degradation, its presence in the environment is expected to be minimal, which supports the assertion that selective pressure of cymoxanil on target organisms will be negligible.

At all pH and temperature values tested, cyclization of cymoxanil to **1** was the main pathway of degradation. Conversion of cymoxanil to **1** (pathway I) was enhanced with increasing alkalinity of the test solution. However, cleavage of the C-1 amide bond of cymoxanil to form **7** (pathway II), although not the primary mode of degradation, accounted for a significantly larger portion of the degradation at higher pH values.

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