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Relative Stability of Formamidine and Carbamate Groups in the Bifunctional Pesticide Formetanate Hydrochloride

CHRISTOPHER B. DIVITO, SHAWN DAVIES, SOLMAZ MASOUDI, AND CLARE N. MUHORO*

Department of Chemistry, Fisher College of Science and Mathematics, Towson University, Towson, Maryland 21252

Formetanate hydrochloride is a bifunctional pesticide with remarkable solubility, high toxicity, and potential mobility in aqueous environments. The relative stability of the formamidine and carbamate groups in this compound can be used to predict the identity of its degradation products in water. The reported NMR and UV−vis spectroscopic studies revealed that the formamidine group is more labile than the carbamate group under strongly basic conditions, as well as under predetermined field conditions. The half-life of the formamidine group was determined to be 3.9 h under strongly basic conditions (pH 12.6) and 14.4 h under mildly basic conditions (pH 7.6). The longevity of the carbamate group may exceed 6 months due its resistance to base-promoted degradation. These results may be used in the design of more specific remediation technology for formetanate-contaminated surface water.

KEYWORDS: Formetanate hydrochloride; formamidines; carbamates; pesticide fate

INTRODUCTION

Formetanate hydrochloride [*m*-(((dimethylamino)methylene)-amino)phenylmethylcarbamate hydrochloride] is a highly effective acaricide and insecticide used on citrus (*1*−*3*) and seed fruits (*4*−*6*) in tropical and temperate agriculture, with demonstrated activity on organophosphate- and carbamate-resistant pests (*7*, *8*). Formetanate hydrochloride possesses two functional groups, and the compound is classified as both a formamidine acaricide and a carbamate insecticide (*9*, *10*). The formamidine group is a competitive inhibitor to the neurotransmitter octopamine (*11*−*13*), and the carbamate group functions as an inhibitor to the neurotransmitter-regulating enzyme acetylcholinesterase (*14*−*18*). Both groups act by permitting constant impulse transmission at synapses leading to convulsions in insects. Undesired side effects of formamidine and carbamate pesticides have been observed in higher animals (*19*−*22*), raising concerns over the occurrence of these compounds and their residues in the environment.

Like other formamidine and carbamate insecticides, and additionally because it is an ionic compound, formetanate hydrochloride is exceedingly soluble in water (>50 g 100 mL^{-1}) (*23*). The low octanol−water partition coefficient of formetanate hydrochloride [K_{ow} (formetanate hydrochloride) = 0.602] (*24*) and poor soil adsorption (*25*) may combine to give the compound a high contamination potential. Furthermore, the high toxicity of formetanate hydrochloride [LD_{50} (rat) = 14.8 mg kg^{-1}] (*23*) and its known harmful effects on nontarget organisms (*26*, *27*) mean that its presence in water may have a negative impact on human and ecosystem health. Importantly, the presence of two functional groups means that selective degradation of only one group may yield decomposition products with an intact pesticide-active site.

The only comparative degradation study of formetanate hydrochloride was conducted by Cegan and co-workers at elevated temperatures in dioxane−water solutions (*28*). Although a variety of product mixtures were identified by paper chromatographic methods over a wide pH range, the relative stability of the two moieties under aquatic environmental conditions remains unclear.

The focus of our study was to contrast the aqueous chemical fate of each functional group in formetanate hydrochloride under various conditions. We report herein studies on formetanate hydrochloride hydrolysis that reveal that at high pH values degradation is rapid, regioselective, and likely to occur in aquatic environments.

MATERIALS AND METHODS

Reagents. Deuterium oxide (99.9% D) was purchased from Aldrich Chemical Co. and was the sole solvent used in NMR spectroscopy. Doubly distilled water was used as the solvent in UV−visible spectroscopy. Buffer solutions were prepared in distilled water with Na_2HPO_4 and $NaHPO_4$ obtained from Fisher Scientific Corp. Formetanate hydrochloride (99 ± 0.5% purity) was purchased from Chem Service Inc. Unless specified otherwise, reagents obtained from commercial suppliers were used without further purification. Determinations of pH were conducted using glass electrode/reference electrode combinations calibrated with buffer solutions obtained from Fisher Scientific Corp.

* Corresponding author [telephone (410) 704-4827; fax (410) 704-4265; e-mail cmuhoro@towson.edu].

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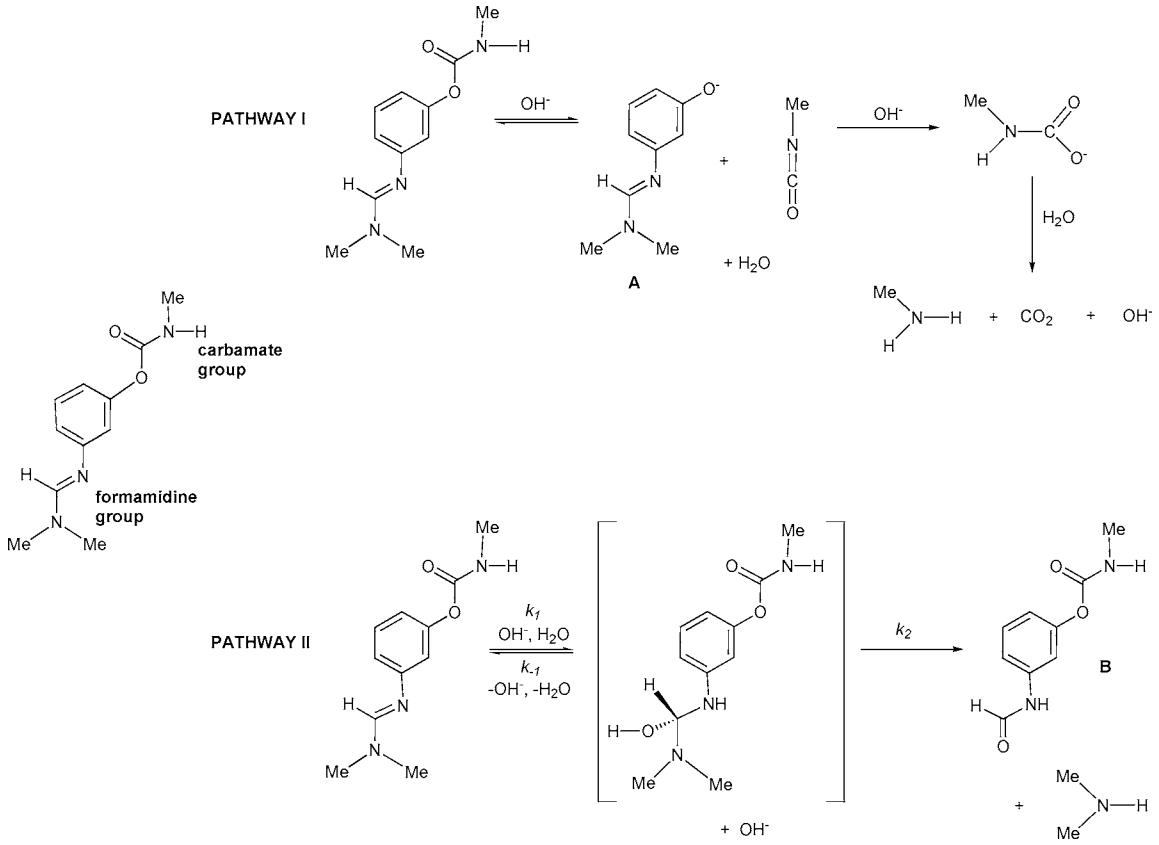
Scheme 1. Two Pathways for Hydrolysis of Formetanate under Basic Conditions



Kinetics Experiments. ^{1}H spectroscopy and ^{13}C NMR spectroscopy were conducted on a 400 MHz Bruker Avance instrument or on a 200 MHz Gemini 200 MHz instrument. Ultraviolet−visible spectroscopy was conducted on a Cary 100 UV−vis spectrophotometer and on a Jasco Inc. V-530 spectrophotometer. Freshly prepared aqueous solutions of formetanate hydrochloride were used for each experiment. ^{1}H NMR spectroscopy was used to determine the fate of formetanate hydrochloride by monitoring solutions of formetanate hydrochloride in D_2O at pH 2.6, 7, and 11 over a period of 2 weeks.

The rate of base-promoted degradation was measured by obtaining ^{1}H NMR spectroscopy every 30 min over at least 3 half-lives. Formetanate concentration was determined by monitoring the disappearance of the amidine methyl signal at 2.85 ppm relative to tetramethylammonium bromide internal standard. This experiment was performed with formetanate concentrations of 0.13, 0.10, 0.07, and 0.03 M at 20 °C, each with a 10-fold excess of base.

Formetanate degradation at lower concentrations was followed by UV−vis spectroscopy by monitoring the decay of the maximum absorption peak at 267 nm every 30 min for at least 6 h. Initial rates were used to compare rates of reaction due to the interference of reactant (λ_{max} 267 nm) and product (λ_{max} 230 nm) maxima. Initial rates were obtained from tangents to the decay plots over the first 150 min of reaction. This experiment was performed with formetanate solutions with concentrations of 1.0×10^{-5}, 2.0×10^{-5}, 4.0×10^{-5}, and 8.0×10^{-5} M at 20 °C. Each solution contained a 10-fold excess of base. Time course measurements were also obtained on a 4.0×10^{-5} M solution at $T = 33$ °C and pH 7.6. This sample was treated with $Na_2HPO_4/NaHPO_4$ buffer instead of sodium hydroxide solution and immersed in a 33 °C water bath over the entire course of the reaction. Aliquots of this solution were removed periodically for spectroscopic analysis.

RESULTS AND DISCUSSION

Our immediate goals were to determine the relative stability of the two functional groups, to identify the products of decomposition, and to pinpoint the prevalent pathway of degradation. Both carbamate and formamidine groups are known to undergo alkaline hydrolysis, and this decomposition in formetanate hydrochloride may occur at either or both of the sites (**Scheme 1**).

Base-promoted hydrolysis at the carbamate group (pathway I) proceeds via proton abstraction by hydroxide to yield *m*-[(dimethylamino)methylene]amino phenoxide (compound **A**) and methyl isocyanate. The methyl isocyanate intermediate undergoes further reaction with hydroxide and an intramolecular rearrangement to yield carbon dioxide and methylamine (*29*, *30*).

Base-catalyzed hydrolysis of the formamidine group (pathway II) may mimic hydrolysis of formamidinium compounds and proceed via nucleophlic addition of hydroxide to the formamidine carbon to generate a tetrahedral intermediate (*28*, *31*−*33*). This transient species rearranges to yield dimethylamine and *m*-formamidophenylmethylcarbamate (compound **B**). Apart from the difference in the site of reactivity, these two pathways contrast the behavior of hydroxide as a nucleophile and a base (pathway I) and as a nucleophile only (pathway II). Additionally, pathway I requires stoichiometric quantities of base, whereas pathway II is catalytic in hydroxide. Importantly, pathway I yields methylamine, whereas pathway II produces dimethylamine.

The pH stability range of formetanate hydrochloride was determined by monitoring aqueous solutions of the pesticide by ^{1}H NMR spectroscopy at various pH levels at 20 °C. Under acidic and neutral conditions, the compound exists as the formetanate hydrochloride salt and is converted to the conjugate base formetanate under basic conditions. The pesticide showed negligible decomposition after several weeks under acidic conditions (pH 2.6), marginal decomposition after several days at pH 7, and substantial decomposition in hours under basic

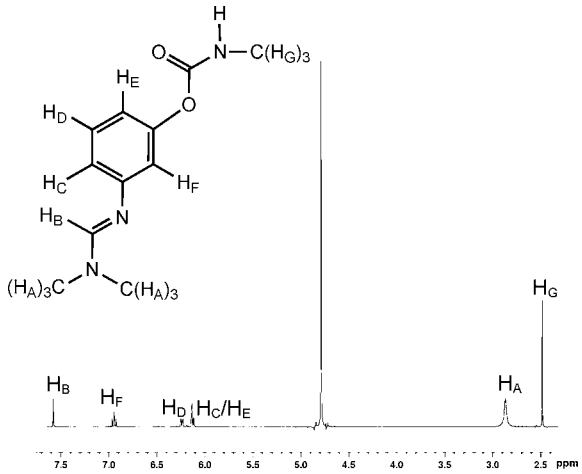


Figure 1. ^{1}H NMR spectrum of formetanate in D_2O (δ 4.79). The carbamate protons (H_G) are located at 2.50 ppm.

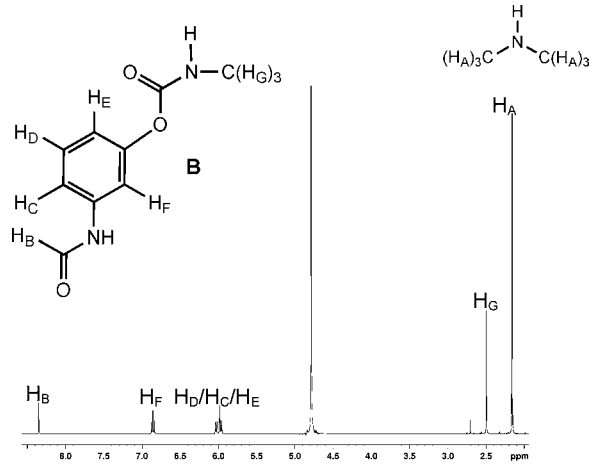


Figure 2. ^{1}H NMR spectrum of *m*-formamidophenylmethylcarbamate (**B**) in D_2O (δ 4.79) generated from decomposition of formetanate in hydroxide. The carbamate signal (H_G) at 2.50 ppm is identical to that in formetanate. The peak at 2.15 ppm (H_A) is liberated dimethylamine.

conditions (pH 11). Therefore, basic conditions facilitated the most rapid degradation.

Product identification was conducted by monitoring aqueous solutions of formetanate in D_2O by ^{1}H NMR spectroscopy for 6 h at 20 °C in hydroxide base. The initial spectrum ($t = 0$ h) is shown in **Figure 1**, and the final spectrum ($t = 6$ h) is shown in **Figure 2**. After this time, the peak corresponding to the formamidine hydrogen atom (H_B in **Figure 1**) at 7.55 ppm had almost completely disappeared, and a new signal was observed downfield at δ 8.33 (H_B in **Figure 2**). The broad amidine methyl peaks at δ 2.85 (H_A in **Figure 1**) also disappeared, and a new peak was observed upfield at 2.15 ppm (H_A in **Figure 2**). Interestingly, the carbamate methyl region remained unaltered with the peak at δ 2.50 being present in both spectra (H_G in **Figures 1** and **2**).

The change in the formamidine region and the unchanged carbamate peaks suggest that base-catalyzed reaction occurs at the formamidine site and *not* at the carbamate group. Addition of external dimethylamine to the NMR tube resulted in an increase in the intensity of the signal at 2.15 ppm, indicating that dimethylamine and not methylamine was formed. Importantly, no carbon dioxide enrichment was observed by ^{13}C NMR spectroscopy, confirming that formetanate hydrolysis via pathway I to form the methyl isocyanate intermediate was not occurring.

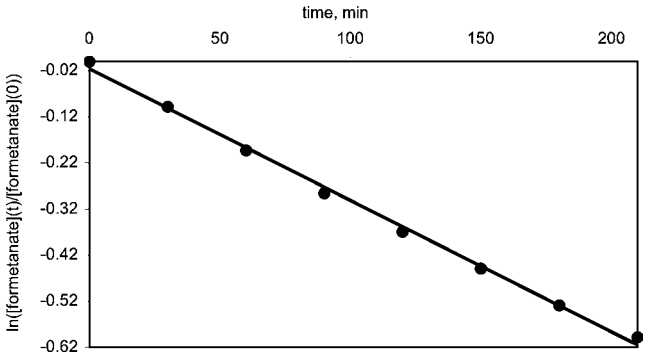


Figure 3. Linear first-order plot for the disappearance of 0.13 M aqueous solution of formetanate at 20 °C in excess base; $k_{obs} = 2.9 \times 10^{-3}$ min^{-1}, $t_{1/2} = 3.9$ h.

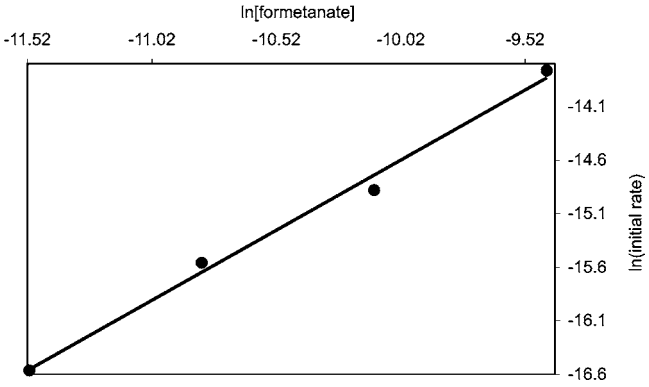


Figure 4. Plot of ln(initial rate) of formetanate disappearance versus ln [formetanate] for formetanate concentrations of 1.0×10^{-5}, 2.0×10^{-5}, 4.0×10^{-5}, and 8.0×10^{-5} M at 20 °C; initial rate $= k_{obs}$ (formetanate)^n, $n = 1.31$.

These results are consistent with the formation of compound **B** and dimethylamine via pathway II and indicate that formetanate's formamidine group is more labile than its carbamate group under basic conditions. Importantly, although compound **B** was generated from formetanate over a period of 6 h, it remained stable in base for at least 2 days. Therefore, pathway II represents a probable mechanism for hydrolysis of formetanate hydrochloride under our reaction conditions. The longevity of the pesticide was determined by measuring the rate of decomposition via pathway II.

The tetrahedral intermediate invoked in the proposed mechanism was not observed in our experiments, implying that this species is short-lived. It is therefore reasonable that $k_2 \gg k_{-1}$ and that the rate law for the reaction is

$$\text{rate} = k_1[OH^-][H_2O][\text{formetanate}] \quad (1)$$

By maintaining steady-state concentrations of hydroxide and water through the use of excess hydroxide and water as the solvent, respectively, the rate law simplifies to

$$\text{rate} = k_{obs}[\text{formetanate}] \quad (2)$$

Thus, pseudo-first-order kinetics measurements were performed by monitoring the disappearance of formetanate alone. Reaction rates were measured by monitoring the disappearance of the formamidine methyl signal (H_A). The rate of this decomposition showed first-order dependence on the concentration of formet-

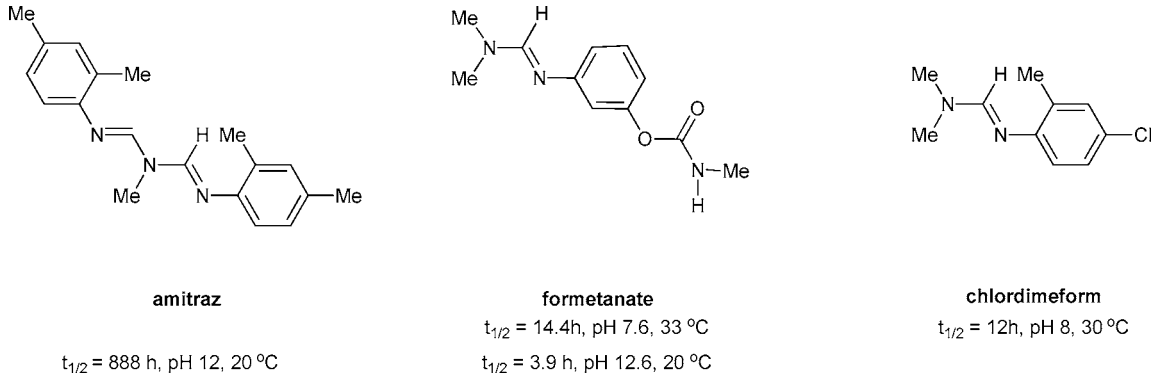


Figure 5. Structures of formamidine pesticides showing the identical formamidine group in formetanate and chlordimeform and consequent similarity in half-lives. Structurally distinct amitraz has a much longer half-life than formetanate.

anate as determined by a linear first-order plot (**Figure 3**). The observed rate constant, k_{obs}, was determined as 2.9×10^{-3} min^{-1}, and the half-life for decomposition was 3.9 h at 20 °C.

An important aspect of this study was the investigation of the pesticide's fate under predetermined field conditions. To this end, formetanate hydrochloride was studied under conditions determined by our group in the Guayas River basin in Ecuador (*34*). This location was selected for fieldwork for several reasons. First, the region, one of the world's most important banana-growing areas, is intensively and extensively cultivated and pesticide use is widespread (*35*, *36*). Second, surface water is abundant in the area due to the numerous tributaries and streams that flow into the Guayas delta. Third, high equatorial temperatures mean that pesticide degradation may occur more rapidly than in temperate zones.

UV−vis spectroscopy was utilized to measure rates of hydrolysis of dilute formetanate solutions at concentrations detected in the environment for carbamate pesticides (*37*). The UV spectra of the initial and final solutions showed that formetanate displayed λ_{max} at 267 nm and the final product, compound **B**, had λ_{max} at 230 nm. These two peaks have some overlap and make accurate monitoring of reactions over the entire time course difficult. Thus, initial rates of decomposition were measured instead.

Initial rates of formetanate disappearance were measured at 1.0×10^{-5}, 2.0×10^{-5}, 4.0×10^{-5}, and 8.0×10^{-5} M at 20 °C. These values were selected because they lie within the range of concentrations for carbamate pesticides determined via groundwater sampling (*38*). The slope of the ln(initial rate) versus ln([formetanate]) plot (**Figure 4**) provided the order of the reaction with respect to formetanate as 1.31. Thus, in dilute solutions, first-order dependence on formetanate concentration is still observed.

The average temperature and pH of water in the Guayas River basin were determined to be 33 °C and 7.6, respectively. Under these conditions, the decay of a 4.0×10^{-5} M formetanate solution displayed first-order kinetics. The observed rate constant for hydrolysis at pH 7.6 and 33 °C was 8.0×10^{-4} min^{-1}, and the half-life for decomposition was 14.4 h. These data suggest that it is likely that formetanate hydrochloride would be relatively short-lived in surface water in the Guayas River basin and converted to the carbamate degradant **B**.

The rate of formetanate hydrochloride hydrolysis can be compared to that of other formamidine pesticides (**Figure 5**). The half-life of formetanate degradation ($t_{1/2}$ = 14.4 h, pH 7.6, 33 °C) is close to that of the insecticide chlordimeform ($t_{1/2}$ = 12 h, pH 8, 30 °C) (*39*). This similarity is expected because the two compounds have identical formamidine groups. Furthermore, the proposed formamidine hydrolysis mirrors that known

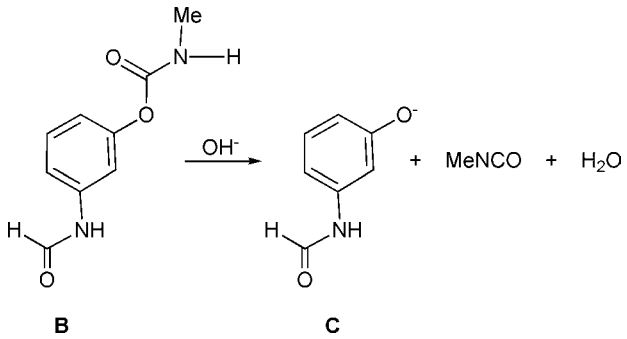


Figure 6. Base-promoted hydrolysis of degradation product **B**.

for chlordimeform. It also follows that structurally distinct formamidines should hydrolyze at different rates. For example, the formamidine insecticide amitraz (*40*), which differs structurally from formetanate, hydrolyzes much more slowly ($t_{1/2}$ = 888 h, pH 12, 20 °C) than formetanate ($t_{1/2}$ = 3.9 h, pH 12.6, 20 °C).

The resistance of base-catalyzed degradation at the carbamate site of formetanate, even at high pH values, is noteworthy. Retention of the carbamate group, under these conditions, implies that degradation products bearing this group may exhibit activity long after the parent compound decays.

Theoretical studies by Wolfe et al. have shown *N*-methyl carbamates that yield phenoxides with pK_a values of 10 or greater have hydrolysis half-lives of 6 months or greater at pH 8 and 25 °C (*10*). Thus, hydrolytic decay of the carbamate group under basic conditions largely depends on the basicity of the phenoxide leaving group. In the case of compound **B**, base-promoted carbamate hydrolysis should yield the phenoxide product **C** (**Figure 6**). This phenoxide leaving group is expected to have a pK_a value close to 9.39, (*41*), indicating that the half-life of compound **B** is likely to be in the region of 6 months or more at pH 8 and 25 °C. The phenoxide's pK_a value provides a rationale for the lack of reaction at the carbamate group in formetanate and further evidence that pathway I is indeed disfavored.

The likely longevity of compound **B**, with its hydrolysis-resistant, acetylcholinesterase-inhibiting carbamate group, raises questions about its prolonged pesticide activity. The mode of action of carbamate pesticides involves the binding of the carbamate group, $-CO-NR-CH_3$, to the serine-hydroxyl group in the active site of acetylcholinesterase. The reversibility of this binding is disfavored if R= methyl and if an electron-withdrawing substituent is located in the meta-position relative to the carbamate (*42*, *43*). Compound **B** fulfills both of these criteria. The carbamate group contains a methyl group, and the

electron-withdrawing formamido group is located meta to the carbamate. This property is suggestive of less reversible binding of compound **B** at the enzyme active site and may prolong its pesticide action at the cellular level.

Thus, we predict that in the aquatic environments that we examined, formetanate hydrochloride is likely to degrade first at the formamidine group to yield compound **B**, which bears a potentially active and long-lived carbamate group. The persistence of this carbamate moiety raises concern over the need for remediation of surface water contaminated with formetanate hydrochloride. Currently, agricultural runoff laced with formetanate hydrochloride can be decontaminated via heterogeneous photocatalytic degradation with titanium oxide catalysts (*44*). The efficiency of this and other methods can be greatly enhanced by specifically targeting known byproducts such as *m*-formamidophenylmethylcarbamate, **B**.

Future studies will involve examination of the relative activity of formetanate and compound **B**. Because electrophilic carbamates disfavor reversible binding in the active site of acetylcholinesterase (*42*, *43*), it is likely that compound **B** binds less reversibly than the parent compound. This is because the formamide group in compound **B** with its iminium cationic resonance contributor would withdraw electrons more than formetanate's formamidine group, which has an anionic amido resonance contributor. In addition, further mechanistic investigations are planned under a broader range of aquatic conditions, as is expansion of the scope of the study to include other pesticides used in tropical agriculture.

ABBREVIATIONS USED

NMR spectroscopy, nuclear magnetic resonance spectroscopy; UV−vis spectroscopy, ultraviolet−visible spectroscopy; k_{obs}, observed rate constant.

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