JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Acid- and Base-Catalyzed Hydrolysis of Chloroacetamide Herbicides

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Despite the prevalence of chloroacetamides as herbicides, little is known about the rates or products of acid- or base-catalyzed hydrolysis of these compounds. Mechanisms of acid-catalyzed reactions may parallel those catalyzed by (hydr)oxide minerals, while base-catalyzed processes have as important counterparts reactions with environmental nucleophiles (such as reduced sulfur species). The current study systematically investigates how the structure of nine chloroacetamides affects their reactivity in 2 N NaOH, 2 N HCl, or 6 N HCl at 25 or 85 °C. Base-catalyzed hydrolysis proceeds either through an intermolecular S_N2 reaction to hydroxy-substituted derivatives or (in a few cases) through amide cleavage, while both amide and ether group cleavages are observed under acidic conditions. Our results reveal that subtle differences in chloroacetamide structure [notably the type of (alkoxy)alkyl substituent] can dramatically influence reactivity and reaction mechanism. Hydroxy-substituted, morpholinone, and secondary aniline derivatives were identified upon reaction for several years in deionized water at circumneutral pH.

KEYWORDS: Herbicide degradates; chloroacetanilides; acetochlor; alachlor; butachlor; dimethachlor; dimethenamid; pretilachlor; propachlor; metolachlor

INTRODUCTION

Chloroacetamides represent one of the most widely used classes of herbicides in the United States (*1*). Within this broad class, the popularity of some compounds, such as alachlor, has waned in recent years, while the use of others, such as acetochlor and dimethenamid, is increasing. Although such changes have been shown to be reflected in the relative concentrations of parent herbicides in environmental samples (*2*), little information exists pertaining to the influence of variations in chloroacetamide structure on reactivity and, hence, environmental persistence. At present, we are unable to anticipate how the structure of the parent chloroacetamide compound will affect the different types of products that will result from transformations of these herbicides in the environment.

Perhaps the most fundamental environmental reaction is hydrolysis. Although chloroacetamides can readily undergo photolysis and biotransformation (*3*), there are environments where these processes are negligible and slower reactions may predominate. Ex situ degradation studies in the presence of aquifer materials have reported disappearance half-lives of 1−5 years for these compounds (*4*, *5*). Under such conditions, hydrolysis may represent an important process in controlling chloroacetamide fate in the environment. Despite years of research on the environmental fate of these herbicides, information pertaining to the rates of chloroacetamide hydrolysis under environmentally relevant conditions (**Table 1**) is still scarce in the peer-reviewed literature (*6*−*15*). Published half-lives (1−7 years) are generally substantially greater than the duration of most investigations (*6*, *7*). Products of hydrolysis reactions have been identified for the *N*-alkoxymethyl-substituted chloroacetamides butachlor (*8*, *11*) and propisochlor (*9*); both *N*-dealkylation and chlorine substitution products have been reported (**Table 1**). Additional studies not included in **Table 1** have examined other reactions under more strongly acidic conditions. These include ones in which the alkoxymethyl substituent is cleaved, as observed for alachlor in 5 N HCl/acetone at 46 °C (*16*), and a unique intramolecular ether hydrolysis reaction, as reported for metolachlor at elevated temperatures and HCl concentrations (*17*, *18*).

Studies of both acid- and base-catalyzed hydrolysis of chloroacetamides may provide valuable information regarding other environmental reactions that involve similar mechanisms. Metal ions—either in solution or present as components of (hydr)oxide mineral surfaces—may be able to facilitate hydrolysis by acting as Lewis acids, coordinating the oxygen of either the amide (*19*) or the *N*-alkoxyalkyl group (if present). Indeed, enhanced hydrolysis of tertiary amides has been observed previously in the presence of copper, cobalt, and zinc ions (*20*, *21*). In addition, an improved understanding of the base-catalyzed reactions of chloroacetamides could provide insights into environmental and metabolically relevant interactions between these herbicides and various nucleophiles, such as reduced sulfur species (*14*, *22*, *23*).

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10.1021/jf0530704 CCC: $33.50
Published on Web 06/07/2006

Table 1. Literature Data Pertaining to Chloroacetamide Hydrolysis

herbicide	T (°C)	pH	rate constant ($days^{-1}$)	$t_{1/2}$ (days)	time (days)[a]	products observed	ref
propachlor	25	5	2.2×10^{-3}	320	160		*6*
		7	1.2×10^{-3}	600	160		
		9	7.8×10^{-4}	890	160		
acetochlor	25	4	5×10^{-4}	1400	130		*7*
		7, 10	3×10^{-4}	2300	130		
butachlor	25	4	1.1×10^{-3}	630	130	hydroxybutachlor	*7, 8*
		7, 10	6×10^{-4}	1200	130		
propisochlor	70	2	1.6×10^{-2}	4.4	NA[e]	*N*-dealkylation product	*9*
		11	4.1×10^{-2}	1.6	NA[e]	hydroxypropisochlor	
dimethachlor	70	7	3.6×10^{-1}	19	NA[e]		*10*
pretilachlor	70	7	4.3×10^{-1}	17	NA[e]		*10*
butachlor	*b*	1–10	no degradation observed		103	*N*-dealkylation product at pH 1 (trace)	*11*
metolachlor	20	4, 7, 9	<5% degradation		100		*12*
alachlor	*b*	5	3.6×10^{-2}	19	140		*13*
		7	3.5×10^{-2}	20	140		
		8	3.2×10^{-2}	22	140		
metolachlor, acetochlor, propachlor, and alachlor	20	H_2O[c]	<0.01	>100	NA[e]		*14*
propachlor	*d*	1–3	0.147 ($M^{-1}\ h^{-1}$)		NA[e]		*15*

[a] Duration over which the reaction was monitored. [b] Room temperature (23–27 °C). [c] Deionized water. [d] Extrapolated to room temperature from high-temperature experiments. [e] Information not provided in original source.

Knowledge regarding the products of hydrolysis reactions, as well as their toxicity relative to that of their parent compounds, is needed in order to assess the effects of chloroacetamide usage on human health and the environment. As a result of concerns regarding the toxicity of chloroacetamides, the U.S. EPA has established drinking water standards for alachlor (*24*). Regulations for metolachlor in drinking water are reportedly under consideration (*25*). Some hydrolysis products, such as the chloroacetamide formed from the *N*-dealkylation of alachlor and butachlor, have been found to be mutagenic and may bind to DNA (*26*). Indeed, the primary aniline degradates of alachlor and metolachlor are both teratogenic, and in the case of metolachlor, the degradate has been reported to be less cytotoxic but more teratogenic than the parent (*27*). In some cases, however, hydroxy-substituted products have been found to be either not mutagenic (*26*), less mutagenic (*15*), or less phytotoxic (*28*) than their respective parents. In part because of such toxicity concerns, the U.S. EPA has included acetanilide pesticide degradation products, as well as additional chloroacetamide herbicides, on the second Contaminant Candidate List of substances that may be regulated in the future (*29*).

In this research, we systematically evaluated the hydrolysis of chloroacetamide herbicides under both acidic (2 N HCl) and basic (2 N NaOH) conditions at 25 °C, in addition to conducting a more limited range of experiments in 6 N HCl at 85 °C. Experiments in sterile deionized water were also carried out over the course of 2−3 years to ascertain whether products encountered at circumneutral pH were the same as those measured under more extreme conditions. While the departure from environmentally relevant conditions in most of the experiments lessens the direct applicability of our results, it allows us to compare the reactivity of a suite of chloroacetamide herbicides (**Figure 1**) both quantitatively and qualitatively on an experimentally accessible time scale. The results further allow us to explore the effect of structural modifications on reaction pathways and hydrolytic reactivity (and, by extension, reaction with metal ions and environmental nucleophiles); this information furnishes a more complete understanding of the behavior of chloroacetamide herbicides in environmental systems.

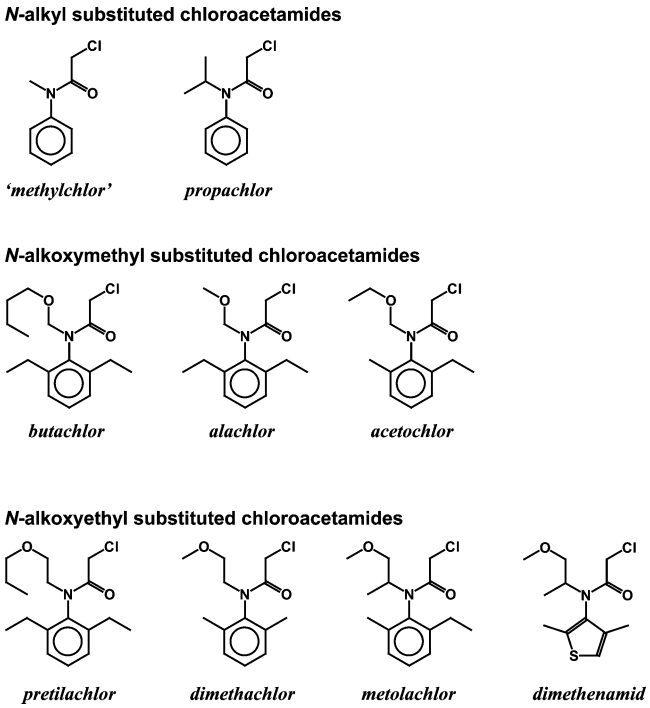


Figure 1. Structures of chloroacetamides examined in this study. All except for 2-chloro-*N*-methylacetanilide, herein referred to as methylchlor, are commercial herbicides.

MATERIALS AND METHODS

Chemicals. Acetochlor [2-chloro-2′-ethyl-6′-methyl-*N*-(ethoxymethyl)acetanilide; 99%], alachlor [2-chloro-2′,6′-diethyl-*N*-(methoxymethyl)acetanilide; 99%], butachlor [2-chloro-2′,6′-diethyl-*N*-(butoxymethyl)acetanilide; 99%], metolachlor [2-chloro-2′-ethyl-6′-methyl-*N*-(1-methyl-2-methoxyethyl)acetanilide; 99%], propachlor [2-chloro-*N*-isopropylacetanilide; 99.5%], and 2-ethyl-6-methyl-*N*-(1-hydroxypropan-2-yl)aniline (an amino alcohol degradate of metolachlor, 99%) were obtained from Chem Service (West Chester, PA). Dimethachlor [2-chloro-2′,6′-dimethyl-*N*-(methoxyethyl)acetanilide; 99.8%], dimethenamid [2-chloro-*N*-(1-methyl-2-methoxyethyl)-*N*-(2,4-dimethyl-thien-3-yl)acetamide; 99.9%], pretilachlor [2-chloro-2′,6′-diethyl-*N*-(propoxyethyl)acetanilide; 98.3%], 2-chloro-*N*-phenyl-*N*-methyl-acetamide, *N*-isopropylaniline (99%), *N*-methylaniline (99.5%), 2-ethyl-6-methyl-

aniline (99%), and 2-nitro-*m*-xylene (99%) were obtained from Sigma-Aldrich (Milwaukee, WI). HCl (2.0 and 6.0 N) and NaOH (2.0 N) were obtained from Fisher Scientific.

Several potential hydrolysis products were synthesized during the course of this and related studies. These include the metolachlor derivatives 2-chloro-*N*-(2-ethyl-6-methyl)-*N*-(1-hydroxypropan-2-yl)-acetamide; 4-(2-ethyl-6-methylphenyl)-5-methyl-3-morpholinone; 2-chloro-*N*-(2-ethyl-6-methylphenyl)acetamide (also a potential acetochlor degradate); and 2-chloro-*N*-(2,6-diethylphenyl)acetamide, a potential degradate of butachlor, alachlor, and pretilachlor. Synthesis of these compounds is described by Hladik et al. (*30*). Two other hydrolysis products synthesized for this study are the metolachlor degradation product 2-ethyl-6-methyl-*N*-isopropylideneaniline and the propachlor derivative 2-hydroxy-*N*-phenyl-*N*-isopropyl-acetamide. Methods used to synthesize these compounds are provided in the Supporting Information, along with mass and ^{1}H NMR spectral data.

^{18}O-labeled water (95%) was obtained from Isotec, Inc. (Miamisburg, OH). ^{18}O-labeled solutions were generated by passing a stream of purified N_2 gas through concentrated aqueous HCl (~12 N) and $H_2{}^{18}O$ (to form 2.3 N HCl, as estimated by titration) or by diluting this solution with concentrated aqueous HCl (to form 6.0 N HCl). The maximum extent of ^{18}O label incorporation into the reaction products in the 2.3 and 6.0 N HCl solutions (~75 and ~35%, respectively) corresponded closely to the gravimetric estimates of ^{18}O content in the two solutions.

Experimental Systems. Reactions were carried out in amber glass bottles maintained in the dark in a water bath with an accuracy of ±0.25 °C and a temperature stability of ±0.05 °C. Aliquots (1.00 mL) of reaction solution were periodically removed and extracted with 1.00 mL of *n*-hexane containing nitroxylene as an internal standard. For acid-catalyzed reactions of 2-chloro-*N*-phenyl-*N*-methyl-acetamide (methylchlor), propachlor, alachlor, and metolachlor and for base-catalyzed reactions of methylchlor and propachlor, products were synthesized or commercially purchased to allow for quantification; all other chloroacetamide reaction products were identified by their electron ionization (EI) mass spectra. Extraction efficiencies of parent compounds were between 71 and 103%, while those of products for which authentic reference materials were available ranged between 79 and 101%.

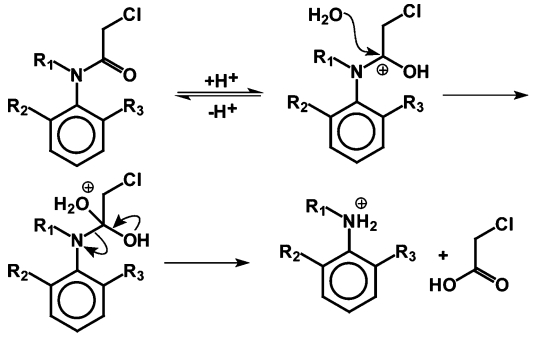
Reactions in 2 N HCl or 2 N NaOH were conducted at a temperature of 25.0 °C. Chloroacetamides were introduced in these experiments by adding 0.50 mL of a saturated aqueous solution of the compound in question, resulting in a final concentration of 1.96 N HCl or NaOH. Aqueous spikes were used to avoid side reactions with a carrier solvent; preliminary experiments in NaOH solutions revealed substitution by methoxide when a methanolic spike was used and formation of unidentified (and unanticipated) products when an acetone spike was used. For some samples from the reactions in 2 N HCl, 1.00 mL aliquots were neutralized by adding 0.172 g of $NaHCO_3$ prior to extraction, to facilitate product identification and quantification.

For reactions in 6 N HCl at 85 °C, smaller (0.10 mL) spikes were used, to minimize perturbations of reactor temperature. Methanol was used as a carrier in such cases to attain the desired initial concentrations. Preliminary experiments showed no effect on rates or product distribution from the presence of the methanol. Samples were removed through an exterior valve attached to a Teflon needle inside the bottle. The reaction was quenched by cooling the sample vials in water. For some samples, 1.00 mL aliquots were neutralized by adding 0.515 g of $NaHCO_3$ prior to extraction. The rationale for this neutralization procedure is provided below.

Long-term experiments were carried out in unbuffered deionized, UV- and filter-sterilized (0.2 μm) water (pH between 5 and 6) equilibrated for several days with solid or liquid chloroacetamide. The supernatant solution was removed and transferred to bottles that had been baked in a muffle furnace (400 °C) prior to use; caps were not sterilized. The solutions were tightly sealed and stored in the dark, and the temperature was not controlled. Sterility ($<10^4$ cells/mL, the same as distilled, deionized, filtered, and UV-irradiated water) was confirmed at the end of the reaction using the acridine orange method (*31*).

Gas Chromatography (GC) and GC/Mass Spectrometry (MS) Analyses. The hexane extracts were analyzed using a Thermo Finnigan Trace quadrupole GC/MS system equipped with an on-column injector and a 30 m J&W DB-5 or Restek Rtx-5, 0.25 mm i.d. × 0.25 μm fused silica capillary column or a Carlo-Erba Mega 2 GC equipped with an on-column injector, a flameless nitrogen phosphorus detector, and a 30 m DB-5 J&W, 0.25 mm i.d. × 0.25 μm fused silica capillary column. The EI mass spectra were generated using an electron energy of 70 eV; data were acquired in full scan mode (*m*/*z* 65−550).

Scheme 1



Data Analysis. Rate constants were calculated by regressing the natural logarithm of the parent chloroacetamide concentration against time, using at least seven data points for each kinetic run. Statistical analyses showed $R^2 > 0.990$ in all cases, with $R^2 > 0.998$ for the majority of the experiments. No trends in the residuals were evident that might be indicative of deviation from pseudo-first-order reaction. In cases where products were quantified, the software package Scientist (Micromath) was used to model parent compound disappearance and product appearance simultaneously, by either assuming exponential decay to a single product or concurrent transformation of one parent compound to two stable products, as appropriate.

RESULTS AND DISCUSSION

Reactions in 2 N HCl at 25 °C. The chloroacetamides shown in **Figure 1** can be divided into three groups based on whether they contain an *N*-alkyl, *N*-alkoxymethyl, or an *N*-alkoxyethyl substituent. Each group reacted by very different pathways under acidic conditions. The two compounds possessing *N*-alkyl substituents, propachlor and 2-chloro-*N*-phenyl-*N*-methyl-acetamide (hereafter referred to as methylchlor for convenience), reacted solely through a well-recognized (*32*) A_{AC2} (acid-catalyzed acyl cleavage, bimolecular) amide hydrolysis mechanism (**Scheme 1**) in 1.96 N HCl at 25 °C, as inferred from product yields (**Figure 2a**). Rate constants for these reactions are shown in **Table 2**.

The three compounds possessing *N*-alkoxymethyl substituents reacted at roughly similar rates (**Table 2**), presumably through an initial ether hydrolysis step (**Scheme 2**) to form the *N*-dealkylation products (mass spectra are shown as **Figure S1** in the Supporting Information). An example time course, showing the disappearance of alachlor and the appearance of its *N*-dealkylation product, is provided in **Figure 2b**. *N*-Dealkylation appeared to be followed by very slow hydrolysis of the amide linkage, as suggested by the observation of small amounts of primary anilines (identified by GC/MS) in neutralized reaction solutions after several months. Dealkylation of alachlor and butachlor to 2-chloro-*N*-(2,6-diethylphenyl)acetamide has been observed previously (*9*, *11*, *16*), but a mechanism does not appear to have been proposed for chloroacetamides. Our hypothesized mechanism (**Scheme 2**) involves an initial protonation of the ether oxygen, followed by the formation of a Schiff base intermediate (center, **Scheme 2**). The Schiff base would rapidly hydrolyze to form the observed secondary aniline. Such a mechanism was first proposed in 1932 for the transformation of dialkylaminomethyl ethers in aqueous acidic solution at room temperature (*33*). A similar mechanism has been

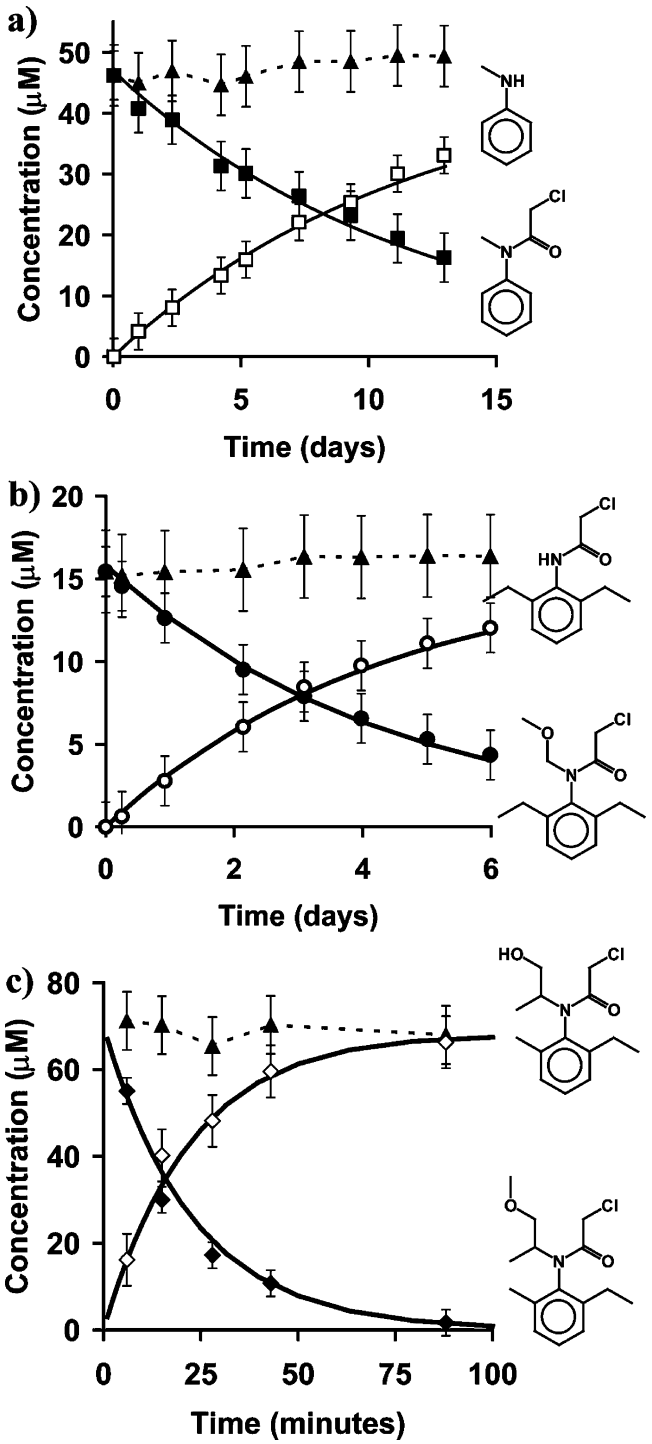


Figure 2. Example time courses for acid hydrolysis: (**a**) methylchlor (■) in 2 N HCl at 25 °C, (**b**) alachlor (●) in 2 N HCl at 25 °C, and (**c**) metolachlor (◆) in 6 N HCl at 85 °C. Dashed lines and triangles (▲) represent mass balances on parent compounds and products shown, solid lines represent model fits assuming pseudo-first-order transformation to a single stable product, and error bars represent 95% confidence intervals.

proposed for the loss of an *N*-methoxymethyl group from a tertiary aniline in basic methanol (*34*), the main difference being in the degree of protonation of the ether oxygen and, hence, the leaving group.

The remaining chloroacetamides, possessing an *N*-alkoxyethyl moiety, were substantially more recalcitrant toward reaction in acidic solution. Reactions of these compounds primarily appeared, at least initially, to involve conversion of the ether side chain to the corresponding alcohol. Rate constants for reaction in 1.96 N HCl at 25 °C (**Table 2**) were estimated from the rates of appearance of the products and disappearance of the parent compounds over a period of 297 days. As the shortest half-life estimate from these experiments was greater than 200 days, these conditions were clearly not suitable for obtaining precise rate measurements.

Reaction of Metolachlor in 6 N HCl at 85 °C. The mechanism of the acid hydrolysis of metolachlor was studied in greater detail under more highly acidic conditions and at a higher temperature. **Figure 2c** shows the results from a series of short-term experiments for this compound. Under these conditions, a complex set of reactions (**Scheme 3**) beginning with an intramolecular attack by the ether oxygen on the amide (**Scheme 4**) appears to have occurred. [**Schemes 3** and **4** are based on our work and that of Arcelli et al. (*17, 35*−*39*) with metolachlor and related compounds.] **Figure 3** shows the time courses (on a logarithmic scale) for the disappearance of metolachlor and the appearance of its degradates over a period of 2 weeks. Our results are consistent with the previous studies, with one exception: Arcelli et al. (*17*) suggested, in the case of metolachlor, that **3** and **4** are formed from **1** through two parallel reactions involving the ether oxygen, one involving nucleophilic acyl addition at the carbonyl to form **3**, and the second involving intramolecular S_N2 cyclization to form **4**. Our results, however (**Figure 3**), indicate that substantial amounts of **4** do not appear until most of the metolachlor (**1**) has reacted. This observation suggests that **4** only forms indirectly via **2** and **3**, implying that dual assistance by the ether oxygen does not occur. Arcelli et al. had observed both **3** and **4** following neutralization of the acidic solution by NaOH. Our methods, in contrast, use $NaHCO_3$ for neutralization. We were able to reproduce their results by neutralizing with NaOH and, therefore, suspect that imperfect mixing and the generation of substantial amounts of heat during neutralization with NaOH resulted in the rapid production of **4**—thereby obscuring the transient appearance of **2** and **3**—during the experiments conducted by Arcelli et al. For this reason, only $NaHCO_3$ was used for neutralization in this work. During neutralization with $NaHCO_3$, **2** was consistently found to be transformed (with yields of more than 98% on the basis of peak areas) into **3**, which was initially absent. Therefore, the alcohol **3** can be used as a surrogate for **2** in **Figure 3**.

Labeling experiments were used to further explore the formation of the morpholinone derivative (**4**) by tracking the origin of the oxygen atoms in the positions corresponding to the ether (oxygen A, **Scheme 3**) and amide (oxygen B) groups in metolachlor. Oxygen B in compound **3** (and by inference **2**) acquired 70% ^{18}O after reaction in ^{18}O-labeled 2.3 N HCl solution for 1 h at 75 °C. The unreacted metolachlor did not acquire a label on either of its oxygens. When the extract with labeled compound **3** was subsequently added to unlabeled 6.0 N HCl and the hexane was evaporated, the label on oxygen B was lost after incubating the solution for 1 h at 85 °C. This confirms that oxygen B in compound **3** is labile under acidic conditions (*35*).

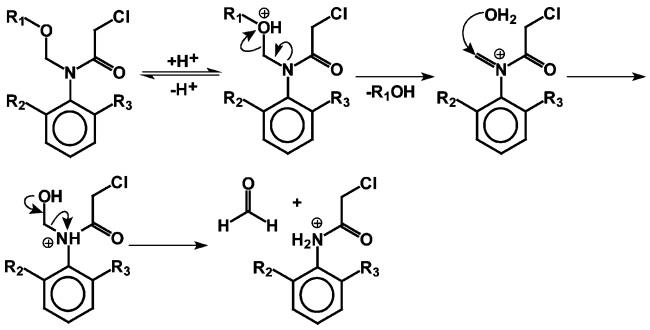
Longer term labeling experiments showed that oxygen A in compounds **2** and **3** acquired up to 34% ^{18}O after reaction in ^{18}O-labeled 6.0 N HCl solution for 2 days at 85 °C. When the extract with labeled compounds **2** and **3** was subsequently added to unlabeled 6.0 N HCl and the hexane was evaporated, 30% of the label on oxygen A was removed after incubating the solution for 1 h at 85 °C. This indicates that, surprisingly, oxygen A is also relatively labile, although not as labile as oxygen B. The morpholinone **4** also showed full labeling of

Table 2. Observed Pseudo-First-Order Rate Constants for Chloroacetamide Hydrolysis[a]

	k_{obs} (s^{-1})			
chloroacetamide	1.96 N HCl, 25 °C	6.0 N HCl, 85 °C	1.96 N NaOH, 25 °C amide hydrolysis[b]	1.96 N NaOH, 25 °C S_N2[b]
***N*-alkyl substituted**				
methylchlor	$8.44\ (\pm0.56) \times 10^{-7}$		$1.44\ (\pm0.04) \times 10^{-2}$	
propachlor	$1.09\ (\pm0.09) \times 10^{-7}$		$2.51\ (\pm0.67) \times 10^{-6}$	$9.39\ (\pm0.38) \times 10^{-5}$
***N*-alkoxymethyl substituted**				
alachlor	$2.45\ (\pm0.06) \times 10^{-6}$			$2.95\ (\pm0.17) \times 10^{-5}$
acetochlor	$2.72\ (\pm0.18) \times 10^{-6}$			$3.06\ (\pm0.09) \times 10^{-5}$
butachhlor	$1.93\ (\pm0.07) \times 10^{-6}$			$3.04\ (\pm0.32) \times 10^{-5}$
***N*-alkoxyethyl substituted**				
pretilachlor	2×10^{-10}–4×10^{-10}[c]	$6.22\ (\pm0.23) \times 10^{-5}$		$2.22\ (\pm0.10) \times 10^{-5}$
dimethachlor	NA[d]	$3.77\ (\pm0.30) \times 10^{-5}$		$1.79\ (\pm0.02) \times 10^{-5}$
dimethenamid	5×10^{-9}–4×10^{-8}[c]	$3.39\ (\pm0.29) \times 10^{-4}$		$6.77\ (\pm0.35) \times 10^{-6}$
metolachlor	9×10^{-9}–2×10^{-8}[c]	$7.25\ (\pm0.26) \times 10^{-4}$		$3.83\ (\pm0.12) \times 10^{-6}$

[a] Stated uncertainties represent 95% confidence limits except as noted; rate constants may represent more than one mechanism and should not be extrapolated. [b] Mechanism assigned based on observed products. [c] Reflects range of estimates, not confidence limits. [d] NA, not available; as results under these conditions were not promising for the other N-alkoxyethyl-substituted chloroacetamides, the relevant experiments with dimethachlor were not performed.

Scheme 2



oxygen A, supporting its formation from the intermediate **3** rather than via nucleophilic attack by the ether oxygen. (Had the latter been the case, **4** would not have been expected to acquire any of the ^{18}O label during this experiment, given that ^{18}O was not observed to be incorporated into metolachlor itself). As was observed for metolachlor (**1**), no significant change in the label was observed following incubation of labeled **4** in unlabeled solution.

The morpholinone derivative was not the only compound produced from the reaction of metolachlor in 6 N HCl at 85 °C. **Figure 3** shows that the major product at the end of 2 weeks (~24000 min) was the amino alcohol (**5**), which we infer is formed via hydrolysis of an aminoester {chloromethyl-2-[*N*-(2-ethyl-6-methylphenyl)amino]propyl-carboxylate}, as reported for analogous compounds (*35*, *36*). **Figure S2** in the Supporting Information expands the pathways depicted in **Scheme 3**. The amino alcohol (**5**) reacts via a series of intermediates, of which the Schiff base (2-ethyl-6-methyl-*N*-isopropylidene aniline, **7**, **Figure S2**) was observed in trace amounts, to form the primary aniline 2-ethyl-6-methylaniline (**6**, **Figure 3**). Dehydration of the amino alcohol (**5**) might then be expected to form an enamine intermediate. The enamine would be in equilibrium with the imine (Schiff base, **7**), an equilibrium that is thought to strongly favor the imine form (*40*). The Schiff base can easily hydrolyze to form 2-ethyl-6-methylaniline (**6**), a reaction that was observed in separate experiments with 2-ethyl-6-methyl-*N*-isopropylidene aniline as the starting material. We speculate that the Schiff base (**7**), as well as the resulting primary aniline (**6**), could also be formed earlier in the reaction sequence by elimination of chloroacetic acid from the aminoester {chloromethyl-2-[*N*-(2-ethyl-6-methylphenyl)amino]propylcarboxylate} or amide hydrolysis of 2-chloro-*N*-(2-ethyl-6-methylphenyl)-acetamide (**8**, **Figures 3** and **S2**). At high temperatures and under strongly acidic conditions, therefore, metolachlor can be transformed into its primary aniline degradate (**6**), albeit slowly.

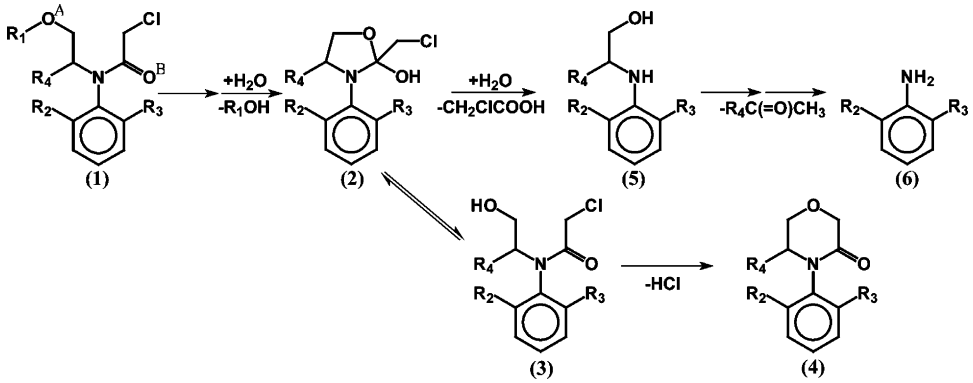
Hydrolysis of Pretilachlor, Dimethachlor, and Dimethenamid in 6 N HCl at 85 °C. More limited studies were carried out to examine the acid hydrolysis of the other *N*-alkoxyethyl-substituted chloroacetamides at elevated temperature in 6 N HCl. The resulting rate constants are shown in **Table 2**. For pretilachlor and dimethachlor, the end products were the primary anilines and the morpholinone derivatives. Mass spectra of the observed products are shown in **Figures S3**−**S8** of the Supporting Information. The thienyl-based herbicide dimethenamid reacted differently under acidic conditions, forming what appeared to be several unidentified polymers (as determined by GC/MS). These products would be consistent with prior observations of the polymerization of thiophene at high temperatures and highly acidic conditions (*41*).

Substituent Effects on Reactions of Chloroacetamides in Acid Solution. Among the chloroacetamides studied, substituents affect reactions in acidic solution in multiple ways. For example, relatively rapid reaction occurs under acidic conditions if an *N*-alkoxymethyl substituent is present, while reactivity under comparable conditions is somewhat depressed for *N*-alkyl-substituted chloroacetamides and is greatly depressed for *N*-alkoxyethyl-substituted chloroacetamides (**Table 2**).

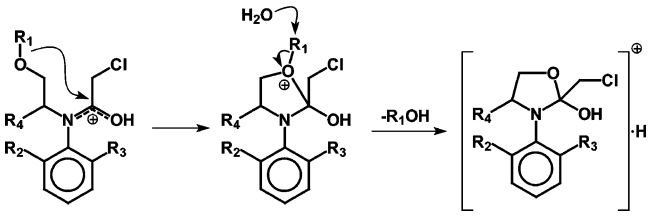
Within a particular group of chloroacetamides, minor variations in reactivity can often be attributed to steric effects. For example, the slower reactivity of propachlor relative to methylchlor (**Table 2**) can be rationalized on this basis. A comparison of their structures (**Figure 1**) suggests that increasing the steric hindrance of the *N*-alkyl substituent slows the rate of attack by H_2O during the A_{AC2} reaction (**Scheme 1**).

Subtle structural differences within a group can result in substantial differences in reactivity. For example, even among the alkoxyethyl-substituted chloroacetamides, the data in **Table 2** reveal reactivity differences of more than an order of magnitude. The lower reactivity of pretilachlor as compared to metolachlor or dimethenamid could reflect greater steric hindrance in the initial attack by the ether oxygen at the carbonyl (**Scheme 3**) that the bulkier propyl substituent would provide relative to the methyl substituent in the other two compounds. However, this effect alone does not explain why dimethachlor—with less steric hindrance than pretilachlor—reacts more slowly still. Influences other than steric effects also appear to be responsible for the fact that metolachlor (which, as compared

Scheme 3



Scheme 4[a]



[a] Adapted from ref *17*. The structure on the right has a delocalized positive charge with a proton in an unknown location.

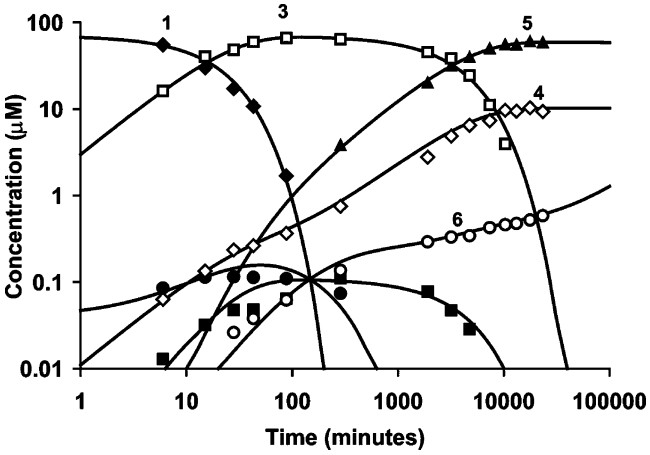


Figure 3. Reaction time course for metolachlor in 6 N HCl at 85 °C, analyzed upon neutralization with $NaHCO_3$ and extraction into hexane. Note the log scale on both axes. Concentrations of intermediates were estimated from mass response on GC/MS analysis of hexane extracts; model fits were performed assuming pseudo-first-order conditions for reactions shown in **Scheme 3** and **Figure S2**. Key: 1**,** metolachlor (◆); 3, formed from 2 during neutralization (□); 4, morpholinone derivative (◇); aminoester, chloromethyl-2-[*N*-(2-ethyl-6-methylphenyl)amino]propylcarboxylate (■); 5, amino alcohol (▲); 6, 2-ethyl-6-methylaniline (○); 2-chloro-*N*-(2-ethyl-6-methylphenyl)acetamide—present as an impurity in metolachlor initially but also formed during reaction (●). Concentrations of the aminoester were estimated based on the mass response of other chloroacetamide derivatives, as no authentic standard was available.

to dimethachlor, has methyl groups replacing two hydrogen atoms) reacts in 6.0 N HCl nearly 20 times faster than dimethachlor.

Substituents affect not only reactivity and the initial products formed in acid solution but also the final products. *N*-Dealkylation was not observed for the alkyl-substituted compounds propachlor and methylchlor even after several months. In contrast, the formation of primary anilines was observed for six of the seven *N*-alkoxyalkyl-substituted chloroacetamides (the exception being dimethenamid). *N*-Dealkylation followed by slow amide hydrolysis was observed for the *N*-alkoxymethyl-substituted chloroacetamides, while a complex sequence of reactions (**Figure S2**) led to the primary anilines for those chloroacetamides possessing *N*-alkoxyethyl substituents.

The different chloroacetamides evinced interesting differences in the rates of reaction at their common chloroacetamide functional group under acidic conditions. At 25 °C, the hydrolysis of the amide linkage was observed to occur on a time scale of days for methylchlor, weeks for propachlor, and months to years for the *N*-dealkylation products of alachlor and butachlor [2-chloro-*N*-(2,6-diethylphenyl)acetamide] and acetochlor [2-chloro-*N*-(2-ethyl-6-methylphenyl)acetamide], while the reaction was too slow to measure for metolachlor (at 25 °C). Contrasts in steric hindrance provide at least a partial explanation for these observations. Thus, while the bulkier *N*-isopropyl group may have slowed the hydrolysis reaction more for propachlor than did the *N*-methyl group of methylchlor (a pattern also observed under basic conditions, as described in the next section), even greater steric hindrance by the ortho substituents on the aromatic ring of the product of alachlor *N*-dealkylation [2-chloro-*N*-(2,6-diethylphenyl)acetamide] may contribute to the observation that the latter compound does not react appreciably under the same conditions (as shown by the relatively consistent mass balance in **Figure 2b**).

Electronic effects may also be responsible for some of these observed relations between structure and reactivity. Methylchlor and propachlor also have an alkyl substituent on the amide nitrogen in place of the hydrogen of 2-chloro-*N*-(2,6-diethylphenyl)acetamide, and this could also play a role in the reactivity of the amide group. Biechler and Taft (*42*), for example, have found that 2,2,2-trifluoro-*N*-methyl-*N*-phenylacetamide underwent amide hydrolysis faster than 2,2,2-trifluoro-*N*-phenyl-acetamide under basic conditions. They suggested that the rate-enhancing effect of an *N*-methyl group might stem from its inhibition of amide resonance, which would also occur under our acidic conditions. This effect could help explain the faster rates of amide hydrolysis observed for methylchlor and propachlor, relative to 2-chloro-*N*-(2,6-diethylphenyl)acetamide and 2-chloro-*N*-(2-ethyl-6-methylphenyl)-acetamide. Unfortunately, we lack data for the acid hydrolysis of the amide linkage of 2-chloro-*N*-acetamide, which might help in clarifying whether steric hindrance to attack of the amide group introduced by ortho substituents on the ring or resonance inhibition by the *N*-alkyl substituent better accounts for the reactivity trends that we observed.

Reactions in Basic Solution. Two types of reaction were observed in 1.96 N NaOH at 25 °C: nucleophilic substitution of chloride by OH^- and base-catalyzed amide hydrolysis. A

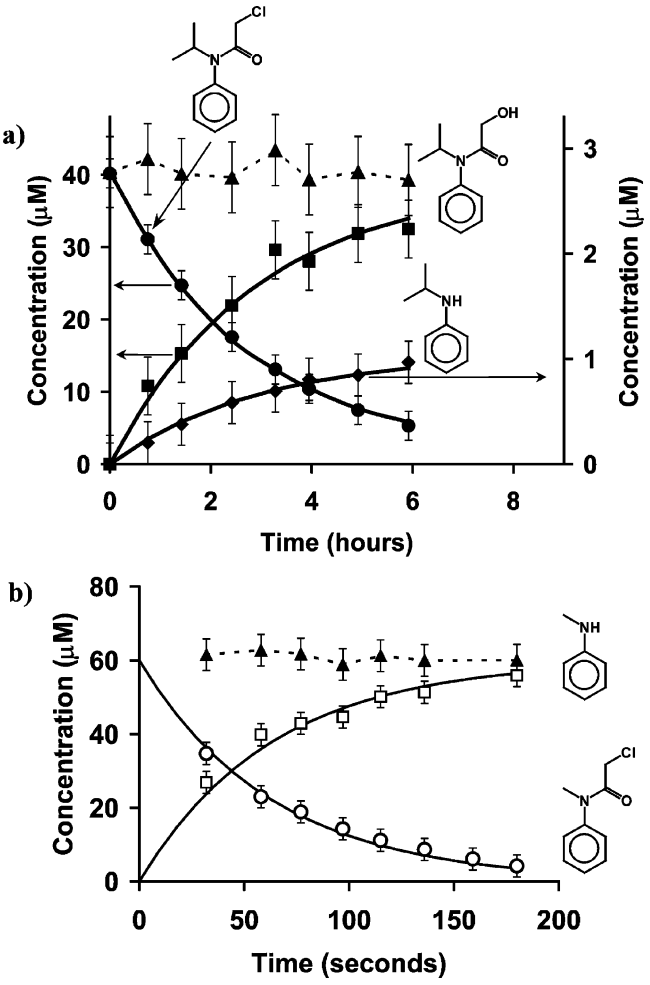


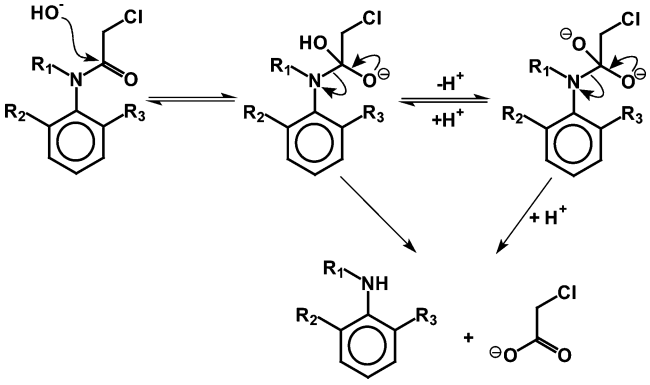
Figure 4. Example time courses for reaction in 2 N NaOH at 25 °C for (**a**) propachlor (●) and (**b**) methylchlor (○). Note that the secondary *y*-axis for the reaction with propachlor is for isopropylaniline (◆) only. Dashed lines and triangles (▲) represent mass balances on parent compounds and products shown, solid lines represent model fits assuming pseudo-first-order transformation to one (methylchlor) or two (propachlor) stable products, and error bars represent 95% confidence intervals.

time course for propachlor (**Figure 4a**) shows the appearance of the products of both reactions, hydroxypropachlor (2-hydroxy-*N*-isopropylacetanilide) and *N*-isopropylaniline. Propachlor was the only chloroacetamide for which both reactions appeared to take place concurrently. Pseudo-first-order rate constants for these reactions are given in **Table 2**. Longer term experiments showed that the hydrolysis of the amide group of hydroxypropachlor is sufficiently slow as to be negligible over the time frame shown in **Figure 4a**.

Methylchlor reacted via amide hydrolysis to form *N*-methylaniline so rapidly (with a half-life of less than 50 s) that no substitution product was observed (**Figure 4b**). The rate constant (**Table 2**) for this reaction was nearly 4 orders of magnitude greater than the corresponding amide hydrolysis rate constant for propachlor. As suggested earlier for the acidic reactions, this effect appears to reflect (at least in part) the greater tendency of the isopropyl group to block access to the reaction site at the amide carbon, relative to a methyl group in the same location.

The alkaline hydrolysis of amides has been postulated to involve two preequilibrium steps as shown (**Scheme 5**), resulting in two reactive intermediates and two rate constants. For the first reaction, whose rate is first-order with respect to hydroxide

Scheme 5[a]



[a] Modified from ref *42*.

(B_{AC2}; base-catalyzed acyl cleavage, bimolecular), the amide group is attacked by a hydroxide ion to form an ionic intermediate that subsequently cleaves to form the products shown in **Scheme 5**. In the second reaction, whose rate is second-order in hydroxide ion concentration (*42*), the ionic intermediate formed in the first reaction loses a proton prior to formation of the products. Biechler and Taft used data for the reaction of methylchlor at hydroxide concentrations varying from 0.0557 to 0.557 M to calculate the two relevant rate constants (*42*). Applying their results (8.8×10^{-4} M^{-1} s^{-1} and 1.8×10^{-3} M^{-2} s^{-1}, respectively) to our system results in a predicted pseudo-first-order rate constant of 8.8×10^{-3} s^{-1}, which is within a factor of two of our measured value of 1.4×10^{-2} s^{-1}. The predicted value is dominated by the process that is second-order with respect to hydroxide, which makes up 80% of the overall rate constant. Although Biechler and Taft claimed that ionic strength had little effect on reaction rate (*42*), these rate constants are only strictly applicable to an ionic strength of 0.557.

Aside from methylchlor, the other chloroacetamides reacted primarily, if not exclusively, via nucleophilic substitution under basic conditions, with rate constants that varied over nearly 2 orders of magnitude (**Table 2**). Time courses for selected chloroacetamides are shown in semilogarithmic form in **Figure 5**, and the mass spectra of the hydroxy-substituted products are shown in **Figure S9** of the Supporting Information. For the alkoxyalkyl-substituted chloroacetamides, small amounts of amide hydrolysis products were only observed long after the substitution reactions were complete.

Relative S_N2 reactivity trends for the reactions of different chloroacetamides with a variety of nucleophiles in aqueous solution tend to be largely independent of the identity of the nucleophile (**Table 3**). For example, the relative reactivities of chloroacetamides toward hydroxide generally parallel those observed in the reactions of these compounds with sulfur nucleophiles (*14*, *22*, *23*), with the order of reactivity being propachlor > alachlor > metolachlor. Differences in reactivity among the different compounds were found to be smaller for reactions with glutathione than for reactions with smaller nucleophiles, perhaps because the latter are less likely to encounter adverse steric interactions. Although these reactivity trends are based on a limited set of data, their consistency across different nucleophiles indicates that each chloroacetamide may have an inherent susceptibility to nucleophilic substitution that remains relatively independent of nucleophile identity.

The rate of chlorine displacement from a chloroacetamide may be related to the distribution of the molecule between its cis and trans forms at equilibrium (**Scheme 6**). The trans

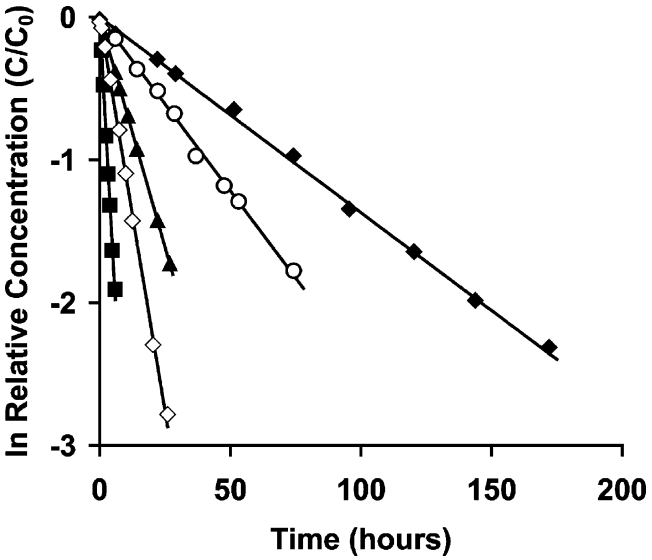


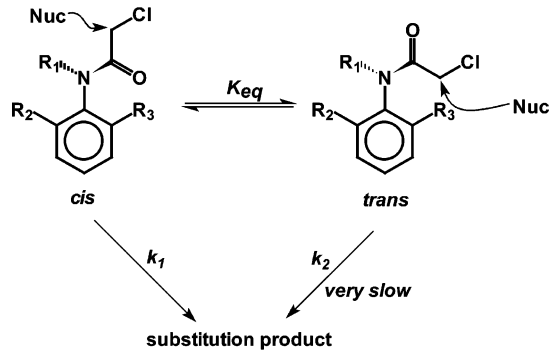
Figure 5. Selected time courses for reactions of chloroacetamides in 2 N NaOH at 25 °C, including metolachlor (◆), dimethenamid (○), dimethachlor (▲), acetochlor (◇), and propachlor (■). As described in the text, propachlor reacts under these conditions via concurrent substitution and amide hydrolysis, while only substitution products were observed for the other chloroacetamide herbicides. Solid lines represent linear regressions to the data shown.

Table 3. Relative Reactivity for Substitution Reactions of Chloroacetamides[a]

	nucleophile and ref				
chloroacetamide	OH^- *b*	HS^- (*22*)	S_n^{2-} (*22*)	$S_2O_3^{2-}$ (*14*)	glutathione[c] (*23*)
propachlor	25	20	36	15	2.9
acetochlor	8.0			5.2	1.7
butachlor	7.9				0.9
alachlor	7.7	6.0	2.0	7.1	1.9
pretilachlor	5.8				2.0
dimethachlor	4.7				1.4
dimethenamid	1.8				
metolachlor	1	1	1	1	1

[a] Normalized to the rate constant for metolachlor for each nucleophile. [b] This study. [c] Estimate of relative reactivity based on extent of reaction after 3 h in the absence of glutathione transferase.

Scheme 6

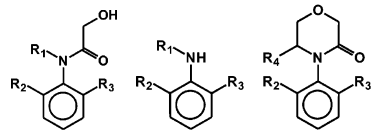


conformation is much less reactive toward substitution at the chlorine because of hindrance to backside attack imposed by the aromatic ring. Haloacetamides with the carbonyl group trans to the aromatic ring have been shown to be 250−40000 times less reactive toward nucleophilic substitution than the cis conformer (*43*, *44*), even though the trans isomer is the predominant configuration (*43*, *45*). Previous work has shown that the cis to trans interconversion rate is on the order of seconds for alachlor and acetochlor (*46*) and thus on a time scale that is much shorter than the rate of hydroxide substitution. In such a case, the Winstein−Holness equation (*47*) can provide an expression for the observed rate constant (k_{obs}):

$$k_{obs} = k_1 \cdot x_{cis} + k_2 \cdot x_{trans} \quad (1)$$

where x_{cis} and x_{trans} are the mole fractions of the chloroacetamide molecule that are present in the cis and trans conformations, respectively. If the contribution of the trans conformation to substitution reactivity is assumed to be negligible ($k_2 \cong 0$) and the reactivities of different chloroacetamides in the cis conformation are approximately the same (similar k_1 values), then the overall reaction rates of chloroacetamides would vary directly with the proportion of the molecules that are present in the cis form (x_{cis}). Research has shown that the cis:trans ratios, which are likely to be at least somewhat dependent on the solvent, vary slightly for alachlor, acetochlor, and metolachlor in various organic solvents, ranging from <1 to 8% cis (*46*). Variations in the cis:trans ratio might, therefore, be sufficient to account for the observed 8-fold variation in the observed rates of nucleophilic substitution reactions with hydroxide.

Table 4. Estimated Amount of Hydrolysis Products Observed after Incubation in Distilled, Deionized H_2O[a]



chloroacetamide	length of incubation (days)	substitution product (%)	amide hydrolysis product (%)	morpholinone product (%)
N-alkyl substituted				
methylchlor	521	1	1	
propachlor	759	14	trace	
N-alkoxymethyl substituted				
alachlor	600	4		
acetochlor	600	3		
butachlor	600	0.1		
N-alkoxyethyl substituted				
pretilachlor	600	1		6
dimethachlor	521	2		0.1
dimethenamid	600	0.2		0.1
metolachlor	1052	1		8

[a] Reactors were stored in the dark; the pH was not controlled but was measured at the end of the experiment and found to be ~5.5. Amounts given are percents of total observed mass estimated from total ion chromatogram (TIC) peak areas, assuming mass response for the product similar to the parent (this approach generally results in a significant underestimation of concentrations for hydroxy-substituted chloroacetamides). The balance of the mass is the parent. In a few cases, values are corrected for impurities (<1%) observed in initial samples after 3 days of incubation. Rate constants should not be extrapolated from data in this table.

Reactions under Environmentally Relevant Conditions. It is difficult to extrapolate the observed rate constants in **Table 2** to an environmentally relevant pH because the relative contributions of the reactions that are first-order and second-order with respect to OH^-, discussed above, are not known for all of the chloroacetamides. Moreover, reaction with the neutral species (H_2O) might dominate the overall transformation rate at neutral pH. The nonideal conditions of high ionic strength solutions also affect the rate constants. For instance, we found

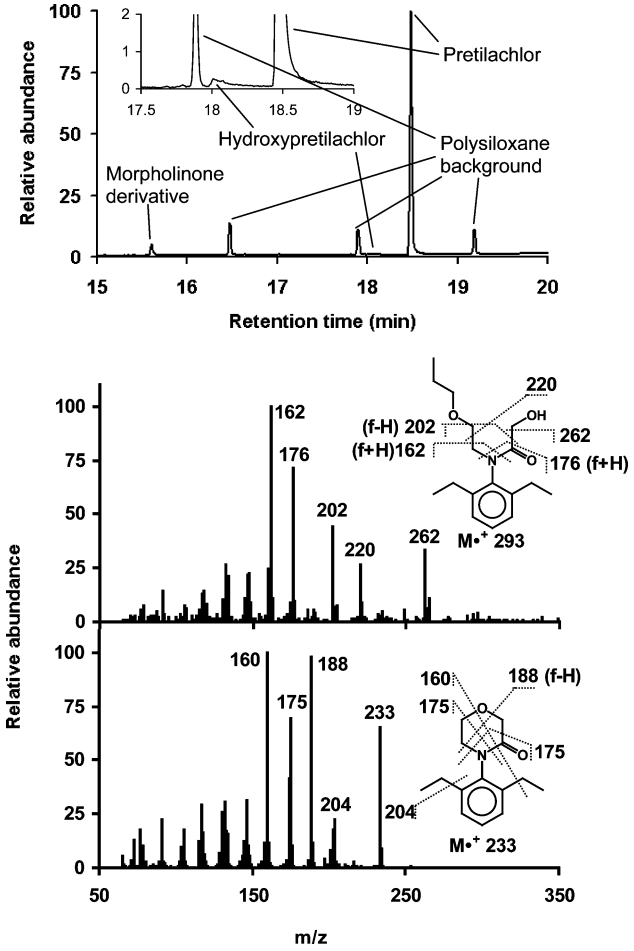


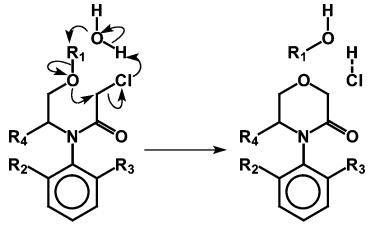
Figure 6. Total ion chromatogram of hexane extract of aqueous solution of pretilachlor after 600 days of incubation in deionized water at pH ~5.5. The EI mass spectra of the two degradates identified (hydroxypretilachlor and the morpholinone derivative) are shown; all other peaks are present in solvent blanks. The insert in the chromatogram shows an expanded version for retention times between 17.5 and 19 min.

that the reaction of propachlor in 1 N NaOH was nearly 30% slower when the ionic strength was doubled (using $NaClO_4$).

Additional experiments were therefore carried out for a period of 2−3 years in deionized water at a pH between 5 and 6 (measured at the end of reaction). Three samples (including an initial sample) were taken, and the hexane extracts were examined to monitor the appearance of nonionized hydrolysis products. The results from the analysis of the final sample for each compound are shown in **Table 4**. For seven of the nine chloroacetamides, the hydroxy-substituted product was observed to accumulate in significant quantities (≥1% by the final measurement). For the *N*-alkyl-substituted chloroacetamides, the amide hydrolysis product was also observed. Finally, for the *N*-alkoxyethyl-substituted chloroacetamides, morpholinone derivatives were also observed. In the case of the metolachlor derivative, this was confirmed by comparison with an authentic standard. No *N*-dealkylation products were observed for any chloroacetamide.

As an illustration of the compounds produced by these reactions, **Figure 6** shows a total ion chromatogram for pretilachlor, as well as the mass spectra for the two products observed. The values in **Table 4** represent rough estimates of product concentrations based on the areas of relatively small, often tailing peaks of compounds for which reference materials could not always be obtained. As a result, these estimates have

Scheme 7



a high degree of uncertainty and thus should not be used to calculate rate constants.

Although the rate constants in **Table 2** cannot be used to predict environmental persistence at neutral pH, extrapolations can still provide a useful perspective. Using metolachlor as an example, we computed an upper limit estimate for the second-order rate constant for an S_N2 reaction, assuming solely first-order kinetics with respect to OH^-. On the basis of the rate constant in **Table 2**, for the reaction with hydroxide, we estimate that only 0.00006% of the parent would react to form hydroxymetolachlor at pH 5.5 after 3 years at room temperature (approximately 25 °C). This corresponds to a half-life for metolachlor on the order of 3 million years for this pathway. Likewise, estimates of the amount of metolachlor undergoing transformation via the acid-catalyzed pathway are approximately 0.0001−0.0002%; the proportion of the parent compound that reacts to form the morpholinone product by this route would be even smaller. **Table 4** clearly shows much larger amounts of product formation than these calculations suggest. The products observed during this set of experiments are therefore likely to be the result of neutral reactions. The formation of the hydroxy-substituted and amide hydrolysis products can be easily explained by reaction with H_2O as a nucleophile. The formation of the morpholinone derivatives would be a more surprising result, but one possible concerted mechanism for these reactions is depicted in **Scheme 7**.

The unexpected presence of the morpholinone products in the long-term near-neutral pH experiments highlights the importance of a systematic evaluation of the reactivity of chloroacetamides, even under reaction conditions that are substantially different from those encountered in the hydrologic system. The high-temperature, high-concentration acid- and base-catalyzed hydrolysis studies formed several products that were also detected for chloroacetamide hydrolysis under environmentally relevant conditions. These observed products are rarely considered in investigations of the occurrence of chloroacetamide degradates in the environment. The results presented here suggest that these degradates may form in substantial quantities, especially under conditions of low biological activity and long hydraulic residence times—conditions that are commonly encountered in groundwater.

ACKNOWLEDGMENT

We are grateful to Michelle Hladik and Jonie Hsiao for assistance with synthesis and NMR and Tanya Oxenberg for assistance with the acridine orange method.

Supporting Information Available: Procedures used to synthesize two chloroacetamide degradates and data pertaining to their mass and ^{1}NMR spectra. Mass spectra of hydrolysis products observed in this study as well as a scheme outlining proposed pathways in acid hydrolysis of *N*-alkoxyethyl-substituted chloroacetamides. This material is available free of charge via the Internet at http://pubs.acs.org.

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Received for review December 8, 2005. Revised manuscript received April 4, 2006. Accepted April 5, 2006. This material is based upon work supported under a National Science Foundation Research Fellowship, an American Water Works Association Abel Wolman Fellowship, and an Academic Rewards for College Scientists (ARCS) Fellowship awarded to D.L.C. Additional support for this research was provided by the National Science Foundation (NSF, #CHE-0089168) as part of the Collaborative Research Activities in Environmental Molecular Science (CRAEMS) project in Environmental Redox-Mediated Dehalogenation Chemistry at Johns Hopkins University. Early stages were funded by an NSF Young Investigator Award (Grant BES-9457260) to A.L.R. Additional support for K.D.T. was provided by a Provost's Undergraduate Research Award and by a Woodrow Wilson undergraduate fellowship.

JF0530704