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Kinetics and Mechanism of the Nucleophilic Displacement Reactions of Chloroacetanilide Herbicides: Investigation of α-Substituent Effects

KATRICE A. LIPPA, SANDRA DEMEL, IRVIN H. LAU, AND A. LYNN ROBERTS*

Department of Geography and Environmental Engineering, 313 Ames Hall, Johns Hopkins University, 3400 N. Charles Street, Baltimore, Maryland 21218-2686

The ease with which α-chloroacetanilide herbicides undergo displacement reactions with strong nucleophiles, and their recalcitrance toward weak ones, is intimately related to their herbicidal properties and environmental chemistry. In this study, we investigate the kinetics and mechanisms of nucleophilic substitution reactions of propachlor and alachlor in aqueous solution. The role played by the α-amide group was examined by including several structurally related analogs of propachlor possessing modified α substituents. The overall second-order nature of the reaction, the negative $\Delta S^{\ddagger}$ values, the weak influence of ionic strength on reactivity, and structure−reactivity trends together support an intermolecular S_N2 mechanism rather than an intramolecular reaction for α-chloroacetanilides as well as the α-chlorothioacetanilide analog of propachlor. In contrast, the α-methylene analog exhibits kinetics and a salt effect consistent with anchimeric assistance by the aniline nitrogen. Electronic interactions with the α-anilide substituent, rather than neighboring group participation, can be inferred to govern the reactivity of α-chloroacetanilides toward nucleophiles.

KEYWORDS: Chloroacetanilides; chloroacetamides; nucleophilic aliphatic substitution; activation parameters; propachlor; alachlor; metolachlor; intramolecular substitution; anchimeric assistance; neighboring group participation; S_N2

INTRODUCTION

Recent work has shown that α-chloroacetanilide herbicides react readily with inorganic sulfur nucleophiles such as HS^-, S_n^{2-}, and $S_2O_3^{2-}$ (*1*, *2*). Earlier studies also documented their reactivity toward the thiolate group of glutathione (GSH) (*3*, *4*). Although the overall second-order kinetics and observed products are consistent with displacement of chlorine via an intermolecular S_N2 process, α-chloroacetanilides can display anomalously high reactivity: second-order rate constants for reactions of propachlor, alachlor, and metolachlor (**Figure 1**) with HS^- and S_n^{2-} are 3 orders of magnitude greater than are the corresponding rate constants for 1-chlorohexane (*5*).

The activation of α-chloroacetanilides toward strong sulfur nucleophiles confers a desirable selectivity that enables their use on tolerant crops, in which detoxification proceeds via chlorine displacement by GSH (*4*, *6*, *7*). It may also play a role in their herbicidal properties. Even though their primary mode of action remains indeterminate, some researchers have suggested the phytotoxicity of α-chloroacetanilides originates from the ability of chlorine to undergo displacement by sulfhydryl groups of enzymes, thereby inhibiting lipid, protein and flavonoid biosynthesis (*8*, *9*). This belief no doubt stemmed from early studies, which revealed that a halogen substituent was required for herbicidal activity (*10*).

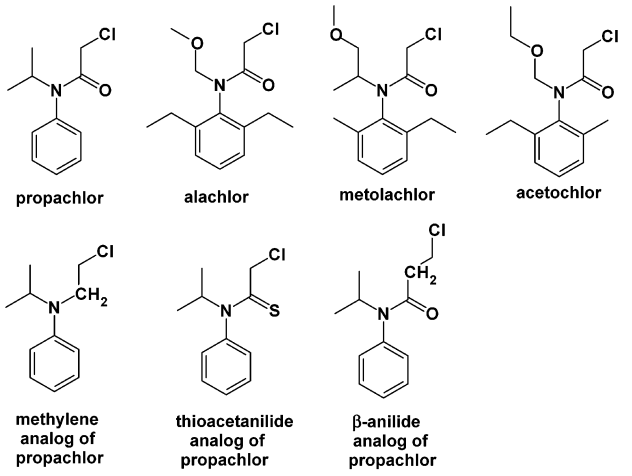

Figure 1. Structures of propachlor, alachlor, metolachlor, acetochlor, and structural analogs of propachlor in which the substituents α to the site of nucleophilic attack were selectively modified.

Another important aspect of the chemistry of α-chloroacetanilides relates to their carcinogenicity. Both alachlor and acetochlor are characterized by the U. S. Environmental Protection Agency as "likely" (class B2) human carcinogens

* To whom correspondence should be addressed. Tel.: (410) 516-4387. Fax: (410) 516-8996. E-mail: lroberts@jhu.edu.

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(*11*, *12*), while metolachlor is viewed as a class C ("possible") human carcinogen (*13*). Although many potential explanations exist for this carcinogenicity, the ability of α-chloroacetamides to serve as alkylating agents via reaction with nucleophiles has been invoked as one possibility (*14*).

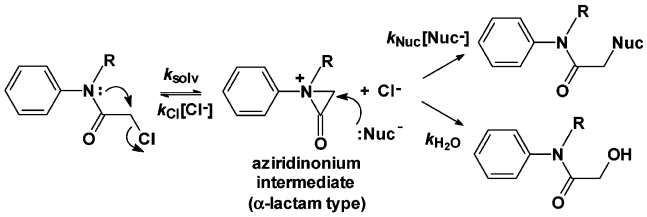
The degree of activation of chloroacetanilide herbicides toward nucleophiles also influences their environmental fate. Our work (*1*) has shown that half-lives anticipated for abiotic substitutions in natural sulfidic environments that might contain 3.4 mM HS^- and 0.33 mM S_n^{2-} (concentrations reported for the porewaters of the Great Salt Marsh in Delaware; ref 15) would be relatively brief, ranging from 10 min for propachlor to 5.5 h for metolachlor. The high reactivity of α-chloroacetanilides toward strong nucleophiles contrasts sharply with their inertness toward weaker ones such as H_2O. In this respect, chloroacetanilides actually appear deactivated toward reaction with weak nucleophiles; although chloroacetamides are more reactive than 1-chlorohexane toward strong sulfur nucleophiles, a reversal occurs such that chloroacetamides are less reactive toward H_2O than are simple alkyl chlorides. For example, the half-life for hydrolysis of acetochlor is substantially in excess of 6 years at pH 7 and 25 °C (*16*), significantly longer than the corresponding half-life for CH_3Cl hydrolysis of 1 year (*17*). If the same factor that activates chloroacetanilides toward strong nucleophiles also deactivates them toward weaker ones, then it is also closely linked to their persistence in oligotrophic environments such as groundwater.

At present, the factor(s) responsible for the degree of activation of the chlorine of α-chloroacetanilides toward nucleophilic displacement remain unclear. Activation could stem from electronic interactions of the α-anilide substituent with the S_N2 reaction center. Such electronic interactions have been invoked to account for the long recognized ability of α-carbonyl substituents to activate alkyl halides toward S_N2 reactions with strong nucleophiles (*18*−*20*), as well as the deactivating influence of α-carbonyl substituents in reactions with weaker nucleophiles such as amines (*21*). Some researchers have hypothesized that the α-carbonyl of chloroacetanilides is responsible for the electrophilicity of the carbon of the $-CH_2Cl$ group and hence the reactivity of α-chloroacetanilides toward "soft" nucleophiles such as GSH and other SH-containing moieties (*14*). The possibility of resonance with the nitrogen atom makes an α-amide (or anilide) substituent very different from an α-carbonyl substituent; what may be a valid explanation for the S_N2 reactivity of α-carbonyl derivatives may not adequately explain the behavior of α-chloroacetanilides.

Other explanations may account for the reactivity of chloroacetanilide herbicides. Anchimeric assistance provided by the ether oxygen has been previously invoked as one possible explanation for the alkylating ability of chloroacetanilides (*22*), and recent studies have demonstrated neighboring group participation of the ether oxygen of metolachlor under acidic conditions (*23*). If such intramolecular reactions were solely responsible for the apparent activation, those chloroacetanilides possessing an *N*-alkoxyalkyl side chain (such as alachlor and metolachlor) would be expected to be much more reactive than those with *N*-alkyl substituents (such as propachlor). The observation that propachlor is considerably more reactive toward HS^- or polysulfides than is either alachlor or metolachlor (*1*) forces us to seek alternative explanations.

Another possibility involves the displacement of chlorine via intramolecular attack by the anilide nitrogen to generate positively charged, three-membered, lactam-type intermediates (**Scheme 1**). Both α- and *β*-lactams are known to form through

Scheme 1



intramolecular cyclization of *N*-monosubstituted chloroamides in the presence of strong base (*24*−*27*). The question remains whether lactam-type intermediates possessing a quaternary nitrogen could form during substitution reactions of chloroacetamides. Such reactions could give rise to products similar to those of intermolecular S_N2 processes, differing only in whether the configuration at the carbon was retained (as anticipated if reaction proceeded as shown in **Scheme 1**) or inverted.

An important piece of evidence in weighing intramolecular versus intermolecular possibilities lies in the kinetics, specifically in the order of the reaction in the nucleophile concentration. An S_N2 reaction would be anticipated to exhibit kinetics that are first-order in nucleophile concentration. If formation of an aziridinonium intermediate is reversible, as shown in **Scheme 1**, then the application of the standard steady-state assumption leads to the following rate expression:

$$\text{rate} = \frac{-\text{d[R} - \text{Cl]}}{\text{dt}} = \frac{(k_{\text{Nuc}}[\text{Nuc}^-] + k_{\text{H}_2\text{O}})k_{\text{solv}}[\text{R} - \text{Cl}]}{k_{\text{Cl}}[\text{Cl}^-] + k_{\text{Nuc}}[\text{Nuc}^-] + k_{\text{H}_2\text{O}}}$$

$$= k_{\text{obs}}\,[\text{R} - \text{Cl}] \qquad (1)$$

Note that an identical expression can be derived for an S_N1 reaction proceeding via a carbocation intermediate. This expression will be zero-order in $[Nuc^-]$ if $k_{Nuc}[Nuc^-] + k_{H_2O} \gg k_{Cl}[Cl^-]$ (as is often the case). If, however, $k_{Cl}[Cl^-]$ is not negligible (e.g., in the presence of high concentrations of chloride salts), the rate of reaction will be depressed ("common ion effect") with kinetics intermediate between zero- and first-order in $[Nuc^-]$. Such kinetics might even be incorrectly inferred to reflect an intermolecular S_N2 mechanism. Additional evidence is therefore necessary in weighing the relative likelihood of intra- and intermolecular possibilities. Studies with varying concentrations of nonnucleophilic salts ("ionic strength effect") can prove helpful in this respect, as rates of intramolecular reactions that form charged intermediates (such as an S_N1 reaction or one involving anchimeric assistance such as shown in **Scheme 1**) would be expected to increase with ionic strength.

This study represents an experimental investigation of the influence of the α-anilide substituent on reactivity and reaction mechanism. Compounds whose reactions were examined included not only propachlor and alachlor, but also structural analogs of propachlor in which the α-substituent was selectively modified (**Figure 1**), thus altering key electronic and steric properties. Subtle changes in structure can lead to drastic changes in reactivity or mechanism. Studies of structural analogs can thus provide invaluable, albeit indirect, information regarding the mechanism(s) through which chloroacetamide herbicides react.

In the present study, emphasis was placed on experimental measurement of the kinetics and products of reaction of an array of nucleophiles with propachlor and alachlor, as well as with structural analogs of propachlor. Additional factors explored included ionic strength effects on reaction rates and determi-

nation of activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for reactions of HS^- with propachlor and its analogs. The experimental results were tested against current conceptual models of inter- and intramolecular reactions to assess the most likely mechanism for reaction of α-chloroacetanilides with nucleophilic species.

This work is part of our broader investigation (*28, 29*) of the influence of the α-anilide substituent on the reactivity of chloroacetanilide herbicides. Companion papers explore electronic interactions within the transition state of an intermolecular S_N2 reaction of chloroacetanilides and related compounds using density functional theory computational techniques (*28*) and test the applicability of Swain-Scott and Edwards models of S_N2 reactivity for chloroacetanilide herbicides and selected structural analogs (*29*). Other related work in our group pertains to the influence of the α-anilide substituent on the redox reactivity of chloroacetanilide herbicides (*30*).

MATERIALS AND METHODS

Reagents. All chemicals were used as received. Alachlor (99%) and propachlor (99%) were obtained from Chem Service; most other chemicals were purchased from Aldrich or Fluka. The propachlor analogs shown in **Figure 1**, as well as *N*-phenyl-*N*-isopropylacrylamide, were synthesized specifically for this and our related studies (*29*). A brief description of methods used to synthesize the propachlor analogs and *N*-phenyl-*N*-isopropylacrylamide is provided in Supporting Information; full details are provided in ref 5.

Solutions containing sulfur nucleophiles were prepared in deoxygenated pH buffer and were handled within an anaerobic chamber (95% N_2/5% H_2 atmosphere). Na_2S solutions were prepared with $Na_2S \cdot 9H_2O$, and polysulfide solutions via equilibration of HS^- with S_8(s) (*1*). Total hydrogen sulfide and total polysulfide concentrations were determined as previously described (*1*, *31*). Thiosulfate and thiophenolate solutions were standardized iodometrically. Solute speciation and ionic strength were calculated from measured solution pH and activity coefficients determined from the Davies approximation (*32*).

Experimental Systems. Reaction kinetics were generally determined under pseudo-first-order conditions, with added nucleophile concentrations ranging from 1.3 mM to 1.0 M. Parent compound decay, and wherever possible, product formation, were monitored by gas chromatography (GC). Reactions were initiated by spiking solutions with aliquots (50−500 μL) of methanol or tetrahydrofuran containing the appropriate organohalide, yielding initial R−Cl concentrations ranging from 20 to 50 μM. Reactors were vigorously mixed for 30 s and were incubated at the appropriate temperature (13.7−52.0 ± 0.1 °C). Aliquots (1 mL) were periodically extracted into *n*-hexane (1 mL), followed by GC or GC/MS analysis.

Gas Chromatographic Analysis. *n*-Hexane extracts were analyzed on a Carlo-Erba Mega 2 GC equipped with a nitrogen−phosphorus detector (NPD), a cold on-column injector, and a 30-m DB-5 J&W, 0.25-mm i.d. × 0.25-μm fused-silica capillary column. Selected *n*-hexane extracts were analyzed via a Thermo Finnigan Trace quadrupole GC/MS system to identify neutral (or methylated; ref 1) reaction products using an on-column injector and either a 30-m DB-5 J&W or 30-m DB-200 J&W, 0.25-mm i.d. × 0.25-μm fused-silica capillary column. MS modes included electron impact (EI) and positive chemical ionization (PCI) techniques. EI mass spectra were generated using an electron energy of 70 eV, monitoring for ions *m*/*z* 50−780 in full scan mode. A combination EI/PCI/NCI source was used for PCI, and methane (CH_4, 99.995%) was used as a reagent gas to produce an initial reagent ion ratio for the ions *m*/*z* 17^+, 29^+, and 41^+ of 1:1:0.25, respectively.

Product Quantitation. Three products (isopropylaniline, propachlor, and *N*-phenyl-*N*-isopropylacrylamide) could be quantified using reference materials that were commercially available or were synthesized for this study. Other hexane-extractable products were determined by assuming GC/NPD response factors identical to the parent compounds (or, for nitrogen-substituted products, proportional to the total number of nitrogen atoms), as detailed elsewhere (*5*). Products arising from reactions with HS^- and S_n^{2-} are described elsewhere (*1*).

Data Analysis. Pseudo-first-order or first-order rate constants (k_{obs} values) were obtained by regressing the natural log of the parent compound concentration versus time. Except for very slow experiments involving the β-anilide analog of propachlor, reactions were followed over 2 to 3 half-lives to verify first-order kinetics. In most cases, the parent compounds reacted quantitatively to a single product, and k_{obs} values increased in direct proportion to the concentration of the added nucleophile.

In a few cases, organohalides reacted via competing processes. Efforts were made in such situations to determine rate constants for the relevant reactions using the program *Scientist for Windows* (v. 2.01; MicroMath, Inc.). This software is capable of determining rate constants and associated parameters by fitting experimental data to numerically integrated solutions of systems of differential rate expressions. The differential rate expressions for two structural analogs of propachlor, along with the reaction schemes, are provided in Supporting Information.

Products of reactions of chloroacetamides with some nucleophiles (e.g., $S_2O_3^{2-}$, HS^-, and S_n^{2-}) were difficult to quantify owing to poor extractability or strongly tailing chromatographic peaks. In such cases, second-order rate constants were determined after first correcting k_{obs} values obtained in the presence of nucleophiles by subtracting k_{obs} values obtained in buffer control experiments conducted at the same temperature and pH. Rates of reactions in such buffer control experiments were generally negligible.

RESULTS AND DISCUSSION

Investigations of the nucleophilic substitution reactions of alachlor, propachlor and the propachlor analogs began by examining kinetics and products of reactions with nucleophiles of varying strengths. For reactions of alachlor and propachlor with HS^- and S_n^{2-}, such information was obtained from our prior work (*1*).

Alachlor Reactions with Nucleophiles. Example results for the reaction of alachlor with Br^- are provided in **Figure 2a**. This time course illustrates essentially 100% conversion of alachlor to the bromine-substituted product, as inferred by GC/NPD peak areas and mass spectral (EI) interpretation (**Figure 2b**). Hexane-extractable products observed for reactions of alachlor with other nucleophiles (i.e., OH^-, N_3^-, SCN^-, I^-, HS^-, PhS^-, S_n^{2-}; analyzed in the case of HS^- and S_n^{2-} after methylation) displayed EI mass spectra consistent with nucleophilic substitution of chlorine (*5*).

The good fit to a semilogarithmic plot for decay of the parent compound in **Figure 2a** is indicative of a first-order dependence on alachlor concentration. Similar results were obtained for reactions of alachlor with all other nucleophiles investigated. Linear regression analysis of log k_{obs} versus log [Br^-] yielded a slope equal to 1.11 (± 0.33). Note that reactions of propachlor, alachlor, and metolachlor with HS^- also exhibited first-order or near first-order dependence on [Nuc^-] (orders of 0.90 ± 0.12, 1.13 ± 0.27, and 0.87 ± 0.04, respectively) (*1*). Overall second-order kinetics have also been reported for the reaction of alachlor with thiosulfate (*2*). Moreover, the intercept of a linear plot of k_{obs} versus [Br^-] (**Figure 2c**) is not significantly different from zero (at the 95% confidence level), indicating that other nucleophiles present in solution (e.g., OH^-, NH_3, HPO_4^{2-}) do not react with alachlor at an appreciable rate under these conditions. This is consistent with the lack of discernible alachlor transformation in complementary buffer control experiments conducted at the same pH and over a comparable time interval.

A second-order rate constant (slope of k_{obs} versus [Br^-] plot) was computed by forcing the intercept through zero; this is equivalent to computing second-order rate constants by dividing each k_{obs} value by the relevant bromide concentration and averaging the results. Second-order rate constants (k_{Nuc} values)

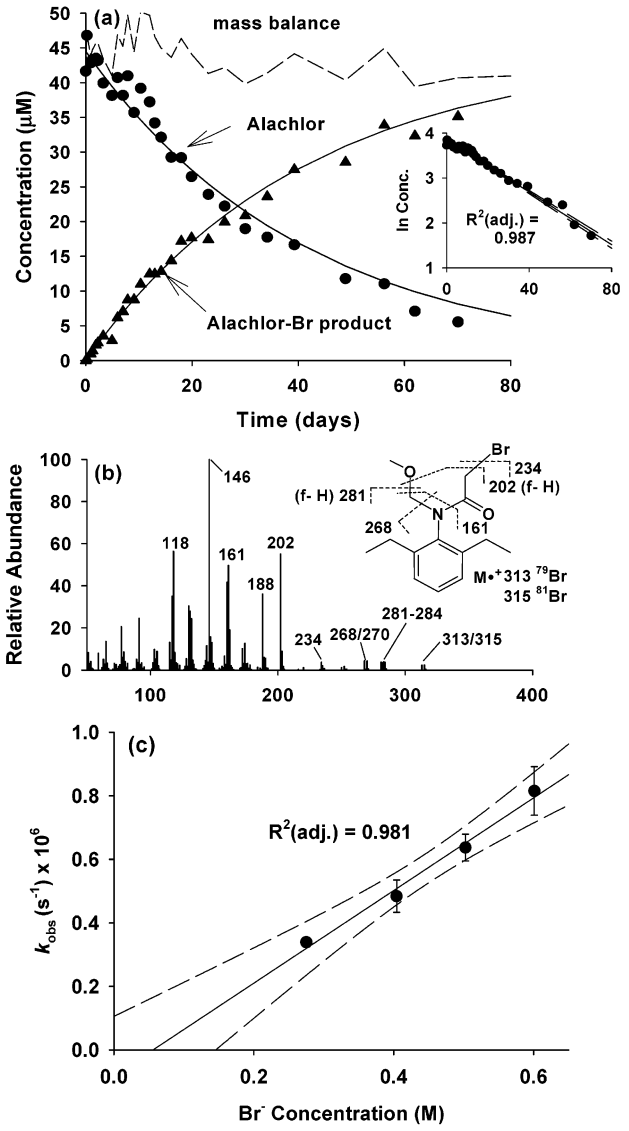


Figure 2. (**a**) Reaction of 25 μM alachlor (●) with 0.25 M Br^- at pH 7.0 (0.4 mM KH_2PO_4 buffer) indicating the formation of the bromine-substituted product (▲) at 25.0 °C. Note that the concentration of the bromine-substituted product was estimated from the GC–NPD response factor for alachlor. Solid lines represent model fits to the data assuming exponential decay of the parent compound to a single stable reaction product; dashed line represents the computed mass balance. Inset depicts the alachlor data plotted in semilogarithmic form. (**b**) Mass spectrum (EI) of bromine-substituted alachlor product. (**c**) Plot of pseudo-first-order rate constant k_{obs} (s^{-1}) vs Br^- concentration for the reaction of alachlor at pH 7.7 (5 mM $(NH_4)_2HPO_4$ buffer). These experiments were conducted at an ionic strength of 0.6 equiv/L (established with $NaClO_4$) and at 25.0 °C. Solid line represents linear regression of the data; dashed lines represent 95% confidence interval.

determined for reaction of alachlor (and related compounds) with a variety of nucleophiles are summarized in **Table 1**.

Propachlor Reactions with Nucleophiles. Results for propachlor are qualitatively similar in many respects to alachlor; k_{Nuc} values are summarized in **Table 1**. Overall, propachlor was 2- to 18-fold more reactive than alachlor was toward nucleophilic displacement. As with alachlor, no discernible transformation was observed in complementary buffer control experiments conducted at the same pH and time intervals. Hexane-extractable products were characterized by GC/MS (EI) analyses; mass spectra were consistent with the anticipated substitution products (*5*).

Propachlor differs from alachlor in that the former chloroacetanilide appears to react with hydroxide under strongly alkaline conditions via two different pathways (**Scheme 2**): (1) via displacement of chlorine to form the corresponding hydroxy-substituted product (not quantified in the present study) and (2) via base-catalyzed hydrolysis of the amide linkage. The latter reaction has been previously reported (*33*) to form *N*-isopropylaniline (iPA) (observed in the present study; **Figure 3**) and chloroacetate (not determined in this study). The high toxicity (*34*) of chloroacetate makes the amide cleavage reaction undesirable from an environmental perspective. The rate of propachlor reaction, as well as the rate of isopropylaniline formation, was faster at an NaOH concentration of 0.25 M than at 0.02 M (**Figure 3**).

The results for propachlor reaction with OH^- were modeled assuming parallel reactions

$$-\mathrm{d[propachlor]}/\mathrm{d}t = (k_{amide} + k_{OH^-})[OH^-] \cdot [\mathrm{propachlor}] = k_{obs}[\mathrm{propachlor}] \quad (2)$$

$$\mathrm{d[iPA]}/\mathrm{d}t = k_{amide}[OH^-][\mathrm{propachlor}] \quad (3)$$

$$\mathrm{d[hydroxypropachlor]}/\mathrm{d}t = k_{OH^-}[OH^-][\mathrm{propachlor}] \quad (4)$$

The concentration of hydroxypropachlor at each time point was assumed to be equal to the difference between the (model-fit) initial propachlor concentration and the sum of the measured propachlor and isopropylaniline concentrations, $[\mathrm{hydroxypropachor}]_t = [\mathrm{propachlor}]_o - ([\mathrm{propachlor}]_t + [\mathrm{isopropylaniline}]_t)$. Fitting the measured (or assumed) concentrations of propachlor, isopropylaniline, and hydroxypropachlor for each experiment to the integrated rate expressions corresponding to eqs 2−4 yields an average second-order amide hydrolysis rate constant (k_{amide}) of 1.0 (± 0.4) × 10^{-6} $M^{-1}s^{-1}$ and an average second-order rate constant leading to the substitution product (k_{OH^-}) of 2.61 (±0.09) × 10^{-5} M^{-1} s^{-1}.

Alachlor requires considerably harsher conditions to cleave the amide group (*33*), if indeed such a reaction is possible. This may reflect the hindered approach of OH^- to the amide carbonyl of alachlor, introduced by the bulky ethyl ring substituents (**Figure 1**), relative to the less sterically hindered propachlor.

Methylene Analog of Propachlor. The methylene analog of propachlor, unlike the other compounds investigated, hydrolyzed rapidly even at neutral pH. The hydrolysis rate was independent of pH over a wide range (6.5−11.8) in water or NaOH solutions with an ionic strength of 0.13 M (established with $NaClO_4$). Rate constants for parent compound disappearance (k_{obs} values) were 1.4−1.7 × 10^{-3} s^{-1}, more than 5 orders of magnitude greater than that reported (8.5 × 10^{-9} s^{-1}) for the S_N2 reaction of ethyl chloride with H_2O (*35*).

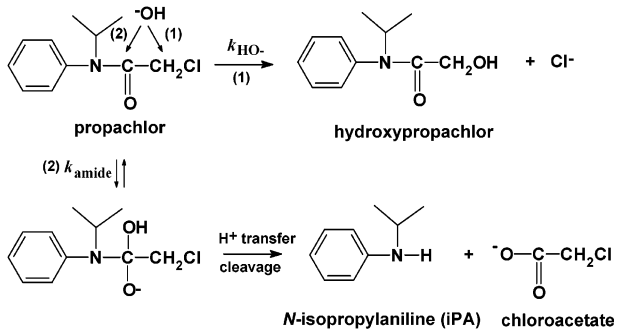
The reactions of the methylene analog were studied in the presence of high concentrations of nucleophiles (i.e., 0.3−1.0 M Br^-, I^-, $S_2O_3^{2-}$) in hopes of clarifying the mechanism. Such nucleophiles are known to be highly reactive in intermolecular S_N2 reactions of simple alkyl halides in aqueous solution (*36*). Example time courses for reactions of the methylene analog in NaBr and KI solutions are provided as **Figure 4**. Mass spectra of reaction products are provided elsewhere (*5*). Although halogen-substituted products were observed to form at rates that were dependent on both the concentration and the type of the added nucleophile (**Figure 4**), the overall first-order rate constants (k_{obs}) for these experiments (provided in **Table 2**)

Table 1. Second-Order Rate Constants Determined for the Nucleophilic Displacement Reactions of Alachlor and Propachlor and Propachlor Analogs at 25.0 °C[a]

nucleophile	alachlor k_{Nuc} ($M^{-1}s^{-1}$)	propachlor k_{Nuc} ($M^{-1}s^{-1}$)	thioacetanilide k_{Nuc} ($M^{-1}s^{-1}$)	β-anilide k_{Nuc} ($M^{-1}s^{-1}$)
Br^-	$9.73(\pm0.22)\times10^{-7}$	$2.97(\pm0.09)\times10^{-6}$	$7.52(\pm4.45)\times10^{-5}$ [b]	$1.96(\pm2.04)\times10^{-8}$
	$1.29(\pm0.11)\times10^{-6}$ [c]			
OH^-	$1.13(\pm0.10)\times10^{-5}$ [d,e]	$2.61(\pm0.09)\times10^{-5}$ [d,e]	$1.07(\pm0.05)\times10^{-2}$ [b,f]	
N_3^-	$1.63(\pm0.08)\times10^{-5}$			
SCN^-	$1.34(\pm0.04)\times10^{-5}$			
I^-	$3.28(\pm0.12)\times10^{-5}$ [e]	$1.19(\pm0.05)\times10^{-4}$ [e]	$1.35(\pm0.32)\times10^{-4}$ [b]	$2.63(\pm0.21)\times10^{-7}$
$S_2O_3^{2-}$	$1.86(\pm0.18)\times10^{-3}$ [g]	$4.18(\pm0.17)\times10^{-3}$	$9.24(\pm1.03)\times10^{-3}$	$1.12(\pm0.02)\times10^{-5}$
HS^-	$4.06(\pm0.20)\times10^{-2}$	$7.49(\pm0.70)\times10^{-2}$	$1.32(\pm0.05)\times10^{-1}$	$3.38(\pm0.15)\times10^{-5}$
	$1.50(\pm0.19)\times10^{-2}$ [h]	$5.03(\pm0.30)\times10^{-2}$ [h]		
PhS^-	$1.21(\pm0.04)\times10^{-1}$			
S_n^{2-}	$1.63(\pm0.06)\times10^{-1}$	2.90(±0.33)	$1.71(\pm0.57)\times10^{1}$	$2.95(\pm0.40)\times10^{-3}$ [e]

[a] Ionic strength of 0.25 equiv/L (except where noted). Nucleophilic displacement reaction products were identified by GC/MS (EI) analysis (with the exception of products of reaction with thiosulfate), in some cases following methylation with CH_3I, and are consistent with displacement of chloride by the nucleophile in question. [b] Ionic strength of 0.50 equiv/L. [c] Ionic strength of 0.60 equiv/L; determined from four experiments conducted at different bromide concentrations (**Figure 2c**). [d] Rate constant may contain a minor contribution from methoxide ion amounting to, at most, 1.5% of the concentration of hydroxide ion (see ref 5 for further discussion). [e] Average of two experiments. [f] Rate constant corresponds to that fraction of the overall pseudo-first-order rate constant inferred to reflect S_N2 reaction to hydroxy-substituted product; this product was not isolated (see text for details). [g] This is comparable to a rate constant of 1.80×10^{-3} M^{-1} s^{-1} measured at 20 °C by Gan et al. (*2*). [h] Ionic strength of 0.15 equiv/L; determined from experiments at four different HS^- concentrations from data reported in our prior work (*1*).

Scheme 2



varied at best only slightly, with values indistinguishable from k_{obs} determined in the absence of added nucleophiles.

The high reactivity of the methylene analog, as well as the insensitivity of k_{obs} values to solution conditions at constant ionic strength, suggested the possible involvement of nitrogen to form an aziridinium ion intermediate (**Scheme 3**). This intermediate can react with nucleophiles in solution to form either nucleophile-substituted products (as shown in **Figure 4**) or with the solvent to yield hydrolysis products (not quantified in the present investigation). For these experiments, $[Nuc^-]/[Cl^-] > 10^4$; it was therefore assumed that $k_{Cl}[Cl^-] \ll k_{Nuc}[Nuc^-] + k_{H_2O}$. The resulting differential expressions are

$$\frac{d[R-Cl]}{dt} = \frac{(k_{Nuc}[Nuc^-] + k_{H_2O})k_{solv}}{k_{Nuc}[Nuc^-] + k_{H_2O}}[R-Cl] = -k_{obs}[R-Cl] \quad (5)$$

$$\frac{d[R-Nuc]}{dt} = \frac{(k_{Nuc}[Nuc^-])k_{solv}}{k_{Nuc}[Nuc^-] + k_{H_2O}}[R-Cl] \quad (6)$$

$$\frac{d[R-OH]}{dt} = \frac{(k_{H_2O})k_{solv}}{k_{Nuc}[Nuc^-] + k_{H_2O}}[R-Cl] \quad (7)$$

As with propachlor, the concentration of the hydroxy-substituted product was assumed to equal the difference between $[R-Cl]_o$ and the sum of $[R-Cl]_t + [R-Nuc]_t$, and the data for each experiment were fit to the integrated rate expressions corresponding to eqs 5−7. The resulting rate constants (k_{Nuc}, k_{H_2O} and k_{solv}) for each experiment are provided in Supporting Information.

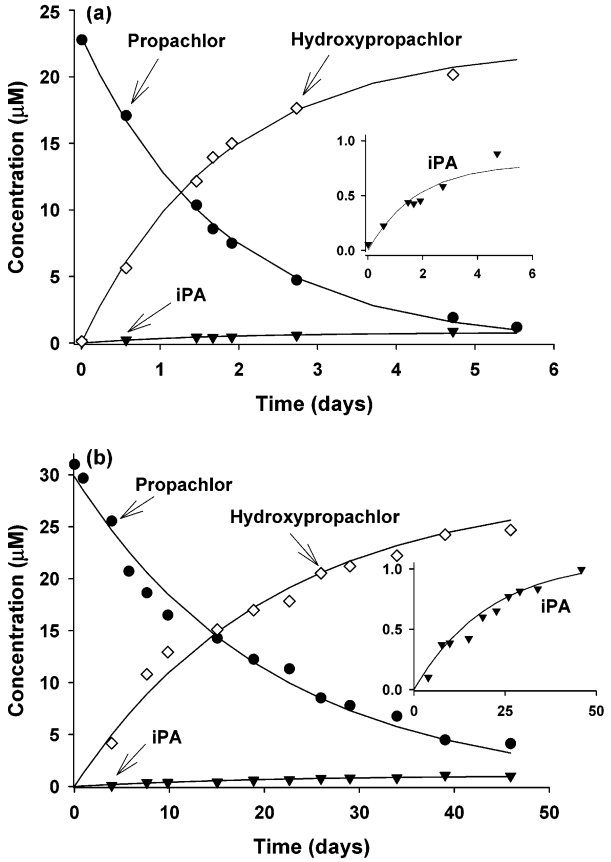


Figure 3. Reaction of propachlor (●) with (**a**) 0.25 M OH^- and (**b**) 0.020 M OH^- showing the formation of *N*-isopropylaniline (iPA; ▼) and the assumed concentration of the hydroxy-substituted product (◇) hydroxypropachlor (not quantified). Both experiments were conducted at an ionic strength of 0.25 equiv/L (established with NaCl) and at 25.0 °C. Insets provide an expansion of the data for iPA. Solid lines represent the model fits to the data assuming exponential decay of the parent compound via two parallel reactions, one assumed to form hydroxypropachlor and used to calculate k_{OH^-} and a second (k_{amide}) resulting in iPA.

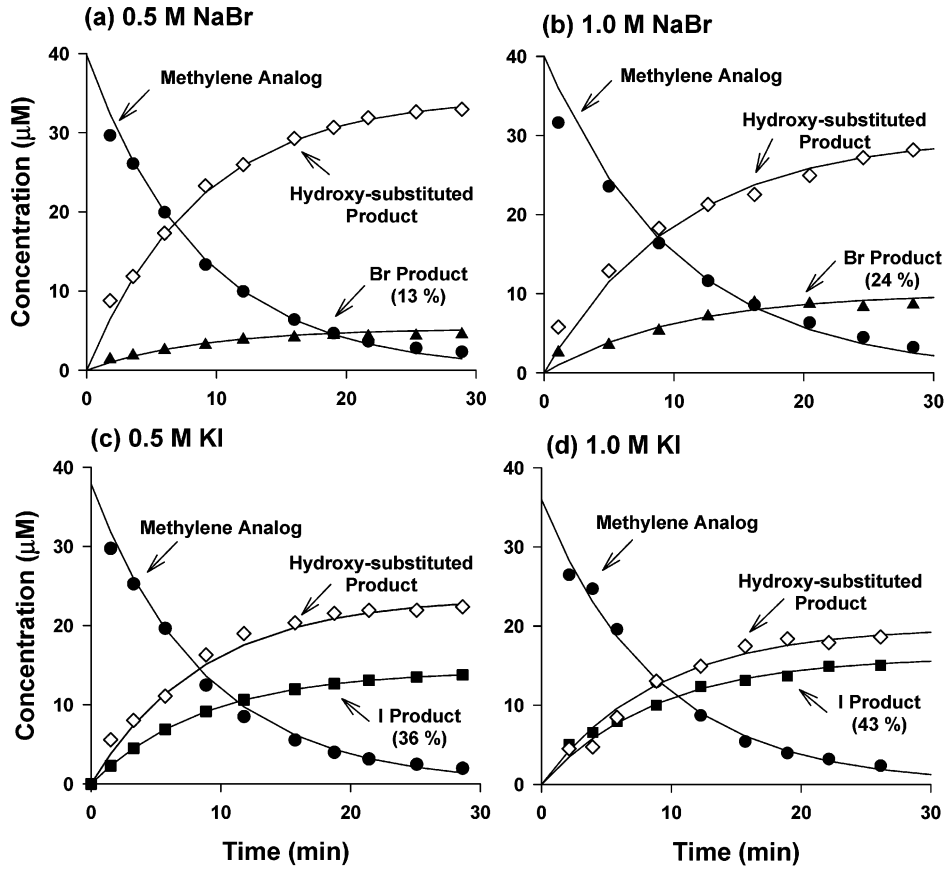


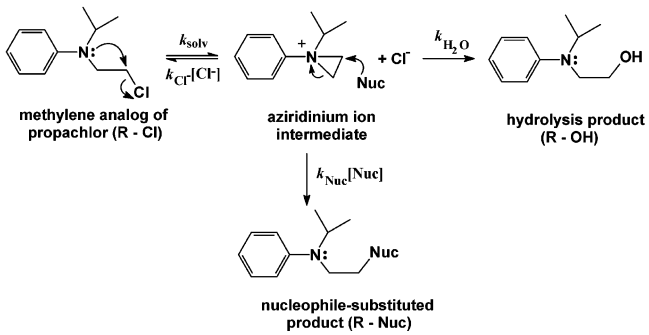
Figure 4. Reaction of 39 μM methylene analog of propachlor (●) in the presence of (**a**) 0.5 M NaBr, (**b**) 1.0 M NaBr, (**c**) 0.5 M KI, and (**d**) 1.0 M KI at pH 6.9 (0.4 mM KH_2PO_4 buffer) illustrating the formation of the bromine-substituted product (▲) or the iodine-substituted product (■) and the assumed concentration of the hydroxy-substituted product (◇), 2-hydroxy-*N*-isopropylaniline (not quantified). All experiments were conducted at an ionic strength of 1.00 equiv/L (established with $NaNO_3$) and at 25.0 °C. Solid lines represent model fits to the data (according to **Scheme 3**).

Table 2. First-Order Rate Constants (k_{obs}) for the Reaction of the Methylene Analog of Propachlor in the Presence of Various Nucleophiles at 25.0 °C[a]

nucleophile concn (M)	Br^- k_{obs} (s^{-1})[b]	I^- k_{obs} (s^{-1})[c]	$S_2O_3^{2-}$ k_{obs} (s^{-1})[c]
0.00	$2.1 (\pm 0.2) \times 10^{-3}$	$1.5 (\pm 0.1) \times 10^{-3}$	$1.5 (\pm 0.1) \times 10^{-3}$
0.06			$1.5 (\pm 0.1) \times 10^{-3}$
0.16			$1.6 (\pm 0.1) \times 10^{-3}$
0.25	$1.8 (\pm 0.2) \times 10^{-3}$		$1.6 (\pm 0.1) \times 10^{-3}$
0.33			$1.2 (\pm 0.1) \times 10^{-3}$
0.50	$1.6 (\pm 0.1) \times 10^{-3}$	$1.8 (\pm 0.2) \times 10^{-3}$	
	$1.7 (\pm 0.1) \times 10^{-3}$ [c]		
0.75	$1.4 (\pm 0.1) \times 10^{-3}$		
1.00	$1.3 (\pm 0.1) \times 10^{-3}$	$1.9 (\pm 0.2) \times 10^{-3}$	

[a] Uncertainty represents 95% confidence limits. [b] Ionic strength established at 1.00 equiv/L with $NaClO_4$, unless otherwise noted. [c] Ionic strength established at 1.00 equiv/L with $NaNO_3$.

Scheme 3



The model-fit values of k_{solv} are not significantly different from the first-order rate constants (k_{obs}) obtained from a linear regression of the concentration of the natural log of the concentration of the parent compound over time. Moreover, the computed values of k_{Nuc}(Nuc) in these experiments are 5−10% of k_{obs} for bromide, and 14−24% of k_{obs} for iodide, significantly less than the yields of the bromo- or iodo-substituted products (13−24% and 36−43%, respectively). These findings are consistent with a product-determining step that differs from the rate-determining step in the reaction.

The results for the methylene analog are similar in many respects to prior observations for aryl nitrogen mustard compounds (such as chlorambucil), commonly used as chemotherapeutic agents. These are well recognized to react via a mechanism involving intramolecular nucleophilic attack by the aniline nitrogen (*37*−*39*), although in some cases, reactions of nitrogen mustard compounds with strong nucleophiles can proceed via competing inter- and intramolecular processes (*40*). Even though we cannot rule out the possibility that reaction of the methylene analog of propachlor could occur to some extent via concurrent intramolecular and intermolecular processes, the evidence for a multistep reaction provided by the modeling results and the lack of a dependence of k_{obs} values on nucleophile concentration in these experiments argue that the halogen-substituted products form primarily through attack of halide ions on an aziridinium ion intermediate.

Ionic Strength Effects for Reactions of Alachlor and Methylene Analog of Propachlor. The influence of solution

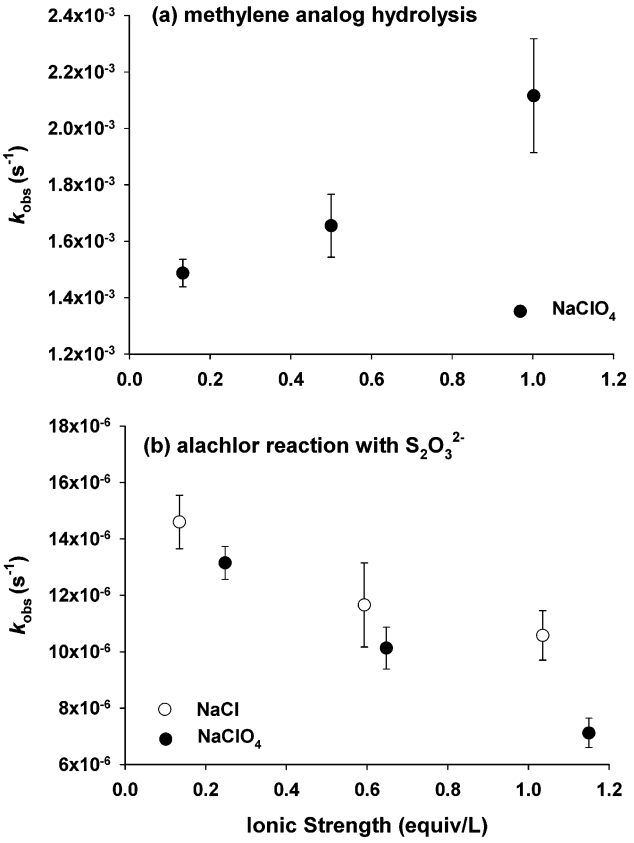


Figure 5. Effect of ionic strength (established by addition of $NaClO_4$ (●) or NaCl (○)) (**a**) on the hydrolysis rate constant of the methylene analog of propachlor at pH 6.9 and 25.0 °C and (**b**) on the pseudo-first-order rate constant obtained for the reaction of alachlor with 7.0 mM thiosulfate at pH 7.7 (10 mM $(NH_4)_2HPO_4$ buffer) and 25.0 °C.

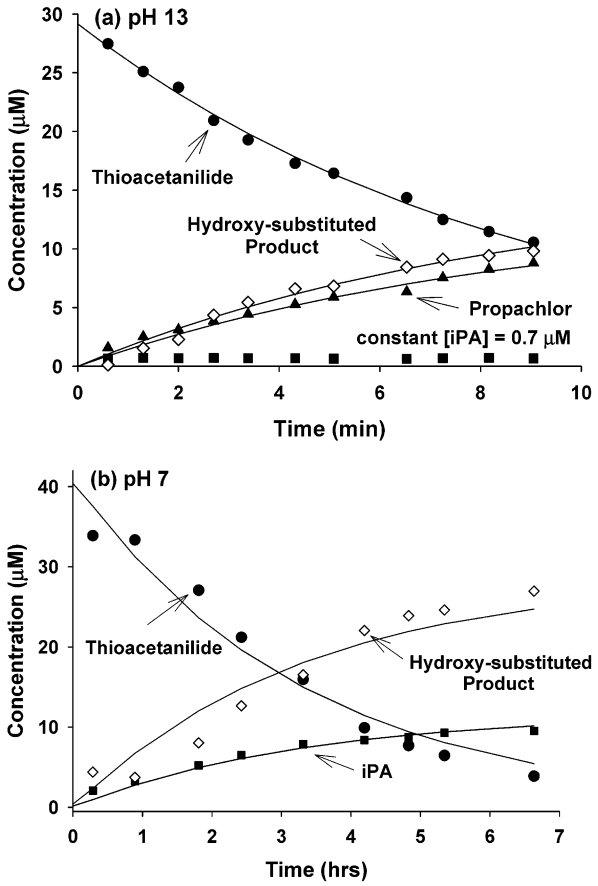


Figure 6. Reaction of the thioacetanilide analog of propachlor (●) (**a**) with 0.10 M OH^- illustrating the formation of propachlor (▲), the assumed concentration of the hydroxy-substituted product (◇) (not quantified), and constant background concentration of 0.7 μM *N*-isopropylaniline (iPA; ■) present in the reaction mixture and (**b**) at pH 6.9, illustrating the formation of iPA (■). Both experiments were conducted at an ionic strength of 0.5 equiv/L (established with NaCl) and at 25.0 °C. Solid lines represent the model fits to the experimental data (according to **Scheme S1** in Supporting Information).

ionic strength (or effective polarity) on reaction rates may provide evidence pertinent to the reaction mechanism. Reactions involving a transition state complex with increased charge development relative to the reactants should proceed more rapidly at high ionic strength. For example, rate constants of S_N1 reactions in which a neutral substrate forms a carbocation are typically accelerated by increasing ionic strength (*41*−*44*).

The dependence of the rate constant for the hydrolysis of the methylene analog of propachlor on solution ionic strength (adjusted with $NaClO_4$) is illustrated in **Figure 5a**. An increase in k_{obs} is observed with increasing ionic strength; this is consistent with a neighboring group participation mechanism in which the transition state complex leading to an ionic intermediate would exhibit greater charge development relative to the unreacted compound (*44*).

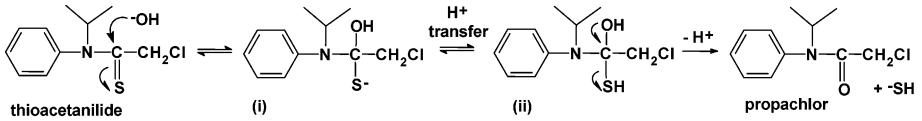
A markedly different dependence of k_{obs} on ionic strength (adjusted with NaCl or $NaClO_4$) is observed for the reaction of alachlor with thiosulfate (**Figure 5b**). The rate-depressing effect of increasing ionic strength is counter to expectations for intramolecular substitution involving an ionic intermediate (*44*). This decreasing trend in k_{obs} with increasing chloride content is not likely to reflect a common-ion effect ($k_{Cl}[Cl^-]$ in eq 1), because the data show that k_{obs} values in the presence of the nonnucleophilic ion ClO_4^- are, if anything, smaller than that with Cl^-.

Thioacetanilide Analog of Propachlor. The thioacetanilide analog of propachlor hydrolyzed more readily than propachlor in both basic and neutral aqueous solutions (**Figure 6**). Substantially greater reactivity was observed under basic conditions (**Figure 6a**), for which propachlor represented the major product quantitated. This reaction likely proceeds through a tetrahedral intermediate (i) resulting from a slow, rate-determining attack of OH^-, followed by proton transfer and collapse of the intermediate (ii) to yield propachlor (**Scheme 4**). No appreciable accumulation of *N*-isopropylaniline (iPA) was observed over the experimental time period at pH 13, suggesting that little or no cleavage of the tetrahedral intermediate occurred at the C−N bond. Note that the rate of propachlor reaction with OH^- is negligible over the duration of these experiments (see **Figure 3a**).

In the case of hydrolysis in neutral solution (**Figure 6b**), iPA was the major product isolated, although measured iPA concentrations were too low to account for the observed decay of the parent thioacetanilide. The remaining mass in the hydrolysis experiments was attributed to a hydroxy-substituted product that yields tailing peaks that are difficult to quantify. The data were modeled to determine the relevant second-order rate constants (**Table 1**) according to **Scheme S1** in Supporting Information.

If we assume that the neutral reaction is initiated by addition of H_2O to the thioamide carbon, a mechanism with initial steps similar to the base-promoted hydrolysis (**Scheme 4**) may be postulated, differing mainly in that a proton may also be transferred to the nitrogen atom of the tetrahedral intermediate. This would weaken the C−N bond, facilitating its cleavage to

Scheme 4



yield iPA and chlorothioacetic acid. Note that amides are generally not subject to facile neutral hydrolysis (*45*). This is not the case for thioamides, as illustrated by the significant difference between the reported hydrolysis half-lives for thioacetamide and acetamide (0.9 and 3950 years, respectively, at pH 7 and 25 °C; ref 46).

In computing second-order rate constants for reactions of the thioacetanilide analog of propachlor with HS^-, k_{obs} values obtained in the presence of HS^- were corrected by subtracting k_{obs} values obtained in buffer control experiments conducted at the same temperature and pH to account for competing hydrolysis. The difference was then divided by the HS^- concentration to yield k_{HS^-}. This assumes that any enhancement in the rate of reaction of the parent compound is attributable to reaction with HS^- ($k_{HS^-}[HS^-]$). This approach was also applied in computing k_{Nuc} values for reactions with thiosulfate ($S_2O_3^{2-}$) and polysulfides (S_n^{2-}). In the case of reactions with halide ions (Br^- and I^-), the relevant substitution products were readily extractable into *n*-hexane and were observed to accumulate as intermediates. Second-order rate constants were computed by simultaneously fitting the observed data for the unreacted thioacetanilide analog and the halogen-substituted products, and the assumed concentration of the hydroxy-substituted hydrolysis product, according to **Scheme S1** in Supporting Information. Further experimental details and mass spectral interpretations of the observed products are provided elsewhere (*5*).

***β*-Anilide Analog of Propachlor.** This analog proved considerably less reactive than propachlor or its thioacetanilide analog toward a similar array of nucleophiles (**Table 1**). In addition to forming substitution products, the *β*-anilide analog was subject to base-catalyzed dehydrochlorination to *N*-phenyl-*N*-isopropylacrylamide (see **Scheme S2** of Supporting Information). Similar accumulation of the dehydrochlorination product was observed in the presence of nucleophiles as in buffer control experiments conducted at the same pH and a comparable time interval, indicating this reaction is not subject to general base catalysis.

Measurable accumulation of substitution products occurred in the presence of Br^- and I^-; the data for parent compound and reaction products were modeled according to **Scheme S2** to obtain k_{Nuc} values shown in **Table 1**. Reactions with these nucleophiles were quite slow: after 55 h in the presence of 0.25 M I^- at pH 7, the concentrations of the dehydrochlorination product and the iodo-substituted product only represented 4 and 21%, respectively, of the initial *β*−anilide concentration. Undetected products represented less than 5% of the initial parent compound.

An example time course for the reaction of the *β*-anilide analog in an HS^- solution (pH 8.5) at 52.0 °C is provided in **Figure 7a**. The major product identified in the reaction of HS^- with the *β*-anilide analog (pH 8.5) was characterized via GC/MS analysis (**Figure 7b,d**) as the mercapto-*β*-anilide, consistent with displacement of chloride by HS^-. The dehydrochlorination product (**Figure 7b,c**) was formed at comparable rates in the presence of HS^- as in the buffer controls for each of the temperatures investigated. Because the mercapto-substituted product yielded tailing peaks that were difficult to quantify, k_{obs} values were corrected to account for competing elimination, as

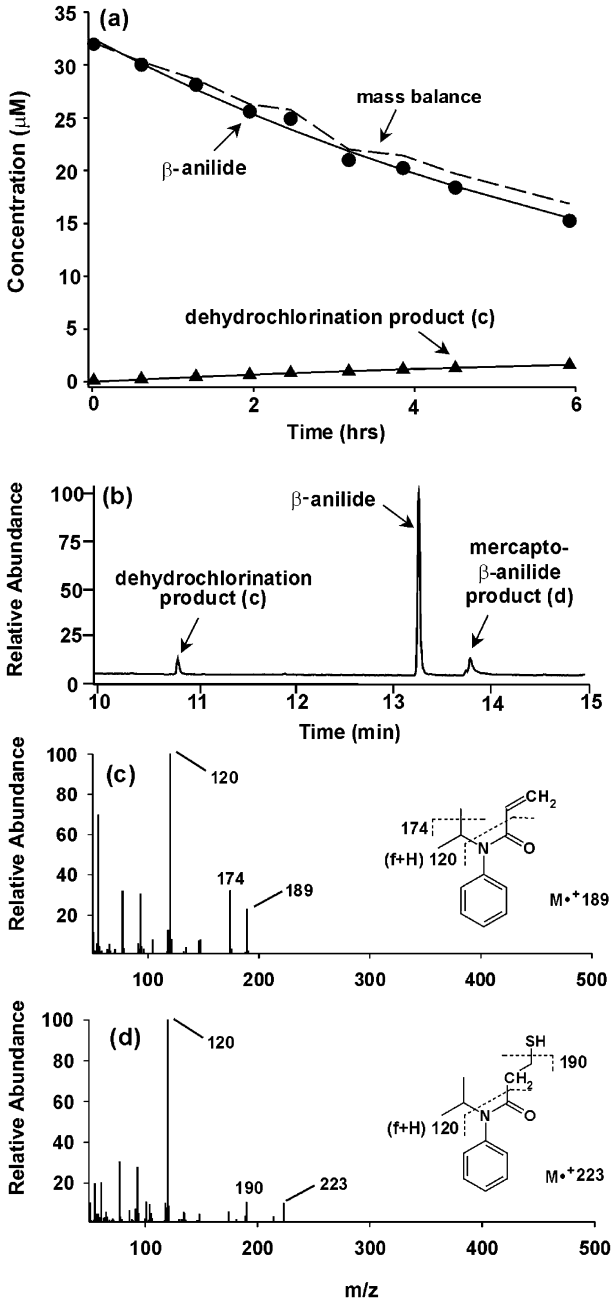


Figure 7. (**a**) Reaction of 31 *μ*M *β*-anilide analog of propachlor (●) with 47 mM HS^- at pH 8.5 (0.4 mM KH_2PO_4 buffer), illustrating formation of the dehydrochlorination product (▲) at an ionic strength of 0.15 equiv/L (established with NaCl) and at 52.0 °C. Solid lines represent model fits to the data according to **Scheme S2(a)** and dashed line represents observed mass balance. (**b**) Total ion chromatogram of hexane extract for reaction of HS^- with 31 *μ*M *β*-anilide analog of propachlor at pH 8.5 (0.4 mM KH_2PO_4 buffer). Also displayed are the mass spectra (EI) of the transformation products: (**c**) dehydrochlorination byproduct and (**d**) mercapto-*β*-anilide product.

previously described for the thioacetanilide analog. A similar approach was employed to compute the second-order rate constant for reaction of the *β*-anilide analog with $S_2O_3^{2-}$.

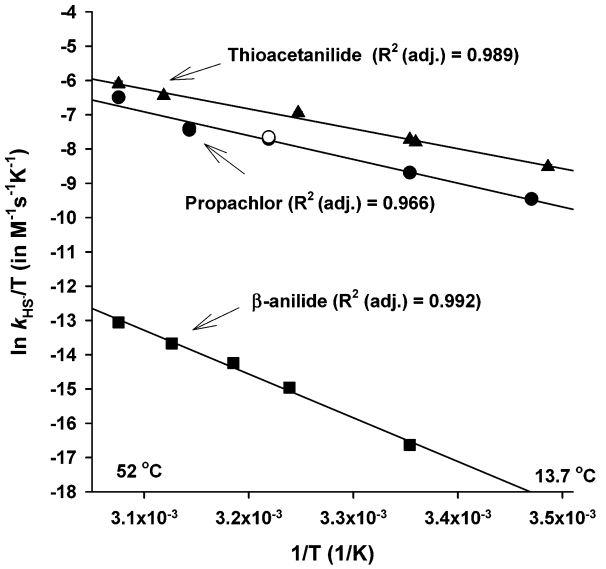


Figure 8. Eyring plots used for the determination of activation barriers ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for the reactions of HS^- with propachlor (●) and its thioacetanilide (▲) and β-anilide (■) analogs. Propachlor and thioacetanilide analog experiments were conducted at pH 9.0 (20 mM sodium tetraborate buffer), while β-anilide analog experiments were conducted at pH 8.5 (0.4 mM KH_2PO_4 buffer). The open symbol for propachlor (○) at 37.5 °C refers to an experiment at pH 6.7 (0.4 mM KH_2PO_4 buffer). All experiments were conducted at an ionic strength of 0.15 equiv/L (established with NaCl). Solid lines represent linear regressions to the data. Data for reaction of propachlor at 25.0 °C obtained from ref 1.

The β-anilide analog reacts more readily with S_n^{2-} than with HS^- (**Table 1**). Two experiments at different polysulfide concentrations (11 and 18 mM) yielded $k_{S_n^{2-}}$ estimates that were not significantly different, suggesting the reaction is roughly first-order in $[S_n^{2-}]$. Products possessing two and three sulfur atoms (following methylation), also consistent with an intermolecular S_N2 mechanism, were inferred by GC/MS (EI) analysis (*5*).

Activation Barriers ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for Reactions with Bisulfide. A 3 order of magnitude difference in k_{HS^-} was observed between propachlor and its much less reactive β-anilide analog (**Table 1**). The thioacetanilide analog proved to be approximately twice as reactive as propachlor toward HS^-. To explore whether such reactivity differences stem from steric or alternatively from electronic effects, the temperature dependence of k_{HS^-} was determined. Data for these three compounds were fit to a linearized version of the Eyring equation (*47*)

$$\ln(k_{HS^-}/T) = \ln(k_B/h) - \Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R \qquad (8)$$

where k_B is Boltzmann's constant, h is Planck's constant, R is the gas constant, T is temperature in Kelvin, and $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are the enthalpic and entropic contributions, respectively, to the overall activation barrier $\Delta G^{\ddagger}$. Results are shown in **Figure 8**. Activation parameters are provided in **Table 3**, along with our prior results for alachlor and metolachlor (*1*), as well as literature values for S_N2 reactions of several simple alkyl halides in aqueous solution (*48*−*51*).

The $\Delta H^{\ddagger}$ values for the three chloroacetanilides and the thioacetanilide analog of propachlor (**Table 3**) are somewhat lower than the range reported (76−100 kJ/mol; refs 52−54) for reactions of simple alkyl halides with anionic nucleophiles in polar protic solvents. $\Delta S^{\ddagger}$ values for the chloroacetanilides and the thioacetanilide analog fall within the range (−13 to −79 J/mol · K; refs 52−54) of values for S_N2 reactions of this charge type in polar protic solvents. Such negative values of $\Delta S^{\ddagger}$ are consistent with a highly ordered transition state (*47*).

Table 3. Experimentally Determined Activation Barriers[a] for Reactions of Propachlor, Alachlor, Metolachlor, and the Propachlor Analogs with HS^- [a]

reaction	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/mol · K)	$\Delta G^{\ddagger}$ (kJ/mol)	ref
propachlor + HS^-	57.7 ± 11.4	−76.3 ± 23.1	80.4 ± 13.3	this study, *1*
alachlor + HS^-	57.9 ± 11.9	−83.6 ± 28.3	82.8 ± 14.6	*1*
metolachlor + HS^-	63.8 ± 11.9	−80.7 ± 26.4	87.8 ± 14.2	*1*
thioacetanilide + HS^-	48.4 ± 6.2	−99.6 ± 21	78.0 ± 8.7	this study
β-anilide + HS^-	106 ± 15	20.8 ± 4.7	99.8 ± 15	this study
MeBr + Cl^-	100 ± 4.8	−16.0 ± 15	105 ± 6.6	*48*
MeCl + Br^-	96.1 ± 2.2	−43.8 ± 7.1	109 ± 3.1	*48*
MeCl + OH^-	96.1 ± 3.1	−20.6 ± 1.0	102 ± 3.1	*49*
EtCl + AcO^- [c]	93.3 ± 7.5	−60.0 ± 8.5	111 ± 7.9	*50*
MeF + I^-	93.1 ± 13	−79.4 ± 25	117 ± 15	*51*

[a] Uncertainty represents 95% confidence limits, unless otherwise noted. [b] Also shown are literature data obtained from Arrhenius parameters and calculated at 298.15 K pertaining to the S_N2 reactions of simple alkyl halides with charged nucleophiles in aqueous solution. [c] Uncertainty represents standard error of linear regression ($n = 3$ data points).

For the thioacetanilide analog of propachlor, $\Delta H^{\ddagger}$ appears smaller and $\Delta S^{\ddagger}$ somewhat more negative than for the three chloroacetanilides, although differences are not statistically significant at the 95% confidence level. The lower $\Delta H^{\ddagger}$ for the thioacetanilide analog is consistent with its greater reactivity and may result from a greater ability of the α-thioamide to accept electron density in the transition state (*28*).

A more dramatic difference is manifested by the β-anilide analog, for which $\Delta H^{\ddagger}$ is almost twice as large, and $\Delta S^{\ddagger}$ is significantly more positive than it is for propachlor. An increase in $\Delta H^{\ddagger}$ is anticipated if the β position of the anilide substituent renders this analog unable to effectively stabilize the electron density developing in the pentacoordinated carbon in the transition state.

The positive value of $\Delta S^{\ddagger}$ for the β-anilide analog contrasts sharply with the negative values anticipated for an intermolecular S_N2 reaction between a neutral molecule and an anionic nucleophile. This substantial decrease in the entropic barrier may indicate an intramolecular displacement process. Intramolecular displacement reactions, such as α-lactonization (*55*) and nucleophilic participation of the nitrogen in aryl nitrogen mustard compounds (*38*) typically exhibit small negative values of $\Delta S^{\ddagger}$ (−3.8 to −10.5 J/mol · K).

Mechanistic Inference Derived from Lactam and Lactone Chemistry. In considering the potential for chloroacetanilides (or the β-anilide analog) to react via anchimeric assistance by the anilide nitrogen (**Scheme 1**), it is instructive to consider the relative stability of the aziridinonium or azetidinonium ion intermediates that would be formed. Steric and electronic factors that control the formation and reactions of these intermediates may parallel those of their neutral α- and β-lactam and lactone analogs. An examination of reported cyclization rates for formation of α- and β-lactones from ω-bromocarboxylates in 99% aqueous DMSO at 50 °C (*55*) provides useful information. The four-membered β-lactone ring forms 1000 times more rapidly than its three-membered counterpart (*55*), reflecting the increased strain associated with incorporating an sp^2-hybridized carbon atom into a three-membered ring. The difference in reactivity is primarily manifested in $\Delta H^{\ddagger}$, which is greater for α-lactone than for β-lactone formation (92.0 vs 74.1 kJ/mol, respectively), with minor observed differences in $\Delta S^{\ddagger}$ (*55*).

Similar reactivity trends to those observed for α- and β-lactone formation would be anticipated for the intramolecular

reactions of propachlor and its β-anilide analog. The formation of an α-lactam-type intermediate (aziridinonium ion) from propachlor would require incorporation of the sp^2-hybridized carbon atom of the amide into a highly strained ring system, whereas this strain would be partially relieved in a β-lactam-type intermediate (azetidinonium ion) resulting from an intramolecular reaction of the β-anilide analog of propachlor. The β-anilide analog should, therefore, be much more reactive than propachlor if anchimeric assistance by the anilide nitrogen played an important role. Such a trend is supported by computational (gas phase) estimates of activation parameters for reactions that would lead to the relevant aziridinonium or azetidinonium ions (*5*); our estimates of $\Delta H^{\ddagger}$ are substantially greater (by 49.6 kJ/mol) for intramolecular reactions of propachlor than for its β-anilide analog.

That our experimental data show the α-chloroacetanilides to be much more reactive than the β-anilide analog could indicate that both propachlor and the β-anilide react via intermolecular S_N2 processes, or that propachlor reacts via an intermolecular S_N2 process while the β-anilide undergoes an intramolecular reaction. It argues against the possibility that both compounds react via intramolecular reactions, or that propachlor reacts via an intra- and the β-anilide reacts via intermolecular substitution. Although it is difficult to ascertain from the available evidence whether the β-anilide reacts via intra- or intermolecular displacement, an intermolecular S_N2 pathway for propachlor (and, by inference, for the other α-chloroacetanilides) seems most likely.

Relative Reactivity of Nucleophiles: Activation of Chloroacetanilides. Additional support of an S_N2 mechanism for α-chloroacetanilides is provided by the good adherence (R^2 (adj) > 0.81) of our data to the Edwards correlation (*56*), $\log k_{Nuc}/k_{H_2O} = \alpha E_n + \beta H$, where H represents the basicity and E_n the polarizability of each nucleophile. Application of this expression to the rate constants in **Table 1** yielded a negligible dependence on H and a strong dependence on E_n for all four compounds in question (*29*). The more prominent role of polarizability in dictating the relative reactivity of nucleophiles is characteristic of S_N2 reactions at sp^3-hybrized carbon (*57*). The relative order of k_{Nuc} values for reactions of these four compounds tended to parallel that previously reported for S_N2 reactions of methyl chloride (*48*, *49*).

In light of the negligible dependence on basicity, attempts were also made (*29*) to regress $\log k_{Nuc}$ against E_n via a single-parameter Edwards equation, $\log k_{Nuc} = \alpha E_n + \log k_{H_2O}$. Good fits ($R^2$ (adj) ≥ 0.94) were obtained for alachlor, propachlor, and the β-anilide analog (*29*). Interestingly, the resulting α values for alachlor and propachlor were significantly (at the 95% confidence level) greater than α for the S_N2 reaction of methyl chloride, and the computed values of the intercepts ($\log k_{H_2O}$) for alachlor and propachlor were significantly less than that for methyl chloride. This further corroborates what the differences between the relative reactivity of chloroacetanilides and *n*-alkyl chlorides toward HS^- compared to H_2O had previously suggested: The activation of chloroacetanilides toward reaction with strong nucleophiles appears closely linked to their deactivation toward weak ones.

In conclusion, kinetic results obtained for the reactions of a range of nucleophiles with chloroacetanilides provide evidence against intramolecular processes involving neighboring group participation. The first-order dependence of reaction rates for chloroacetanilides (and the β-anilide analog) on nucleophile concentration is consistent with an intermolecular S_N2 pathway. The k_{Nuc} values for reactions of the chloroacetanilides and the thioacetanilide and β-anilide analogs exhibit a pronounced dependence on E_n, as expected for an intermolecular S_N2 mechanism, and trends in k_{Nuc} values are similar to those for *n*-alkyl chlorides for which an S_N2 mechanism is well established. The very high reactivity of propachlor relative to the β-anilide analog is counter to the trend anticipated for intramolecular reactions and provides additional support for an intermolecular S_N2 mechanism, at least for propachlor.

The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values obtained for reactions of HS^- with the chloroacetanilide herbicides and the thioacetanilide analog are also consistent with an intermolecular S_N2 mechanism. The positive value of $\Delta S^{\ddagger}$ for the β-anilide analog might be interpreted to reflect an intramolecular substitution process. The close correspondence of k_{HS^-} and $k_{S_n^{2-}}$ for the β-anilide analog to the corresponding rate constants for 1-chlorohexane ($4.11 (\pm 1.01) \times 10^{-5}$ M^{-1} s^{-1} and $1.87 (\pm 0.31) \times 10^{-3}$ M^{-1} s^{-1}; ref 5), on the other hand, along with the strong dependence of k_{Nuc} on nucleophile strength, would tend to argue in favor of an intermolecular S_N2 process for the β-anilide.

The contrasting effects of ionic strength on the rate of hydrolysis of the methylene analog of propachlor and the rate of reaction of alachlor with thiosulfate are also consistent with the hypothesized mechanisms. Although ionic strength effects alone do not provide conclusive evidence of mechanism (*58*), the opposing effects encountered, in concert with other evidence, suggest that these two compounds react via different mechanisms.

Overall, the preponderance of the evidence presented herein strongly supports a conventional intermolecular S_N2 mechanism for the α−chloroacetanilide herbicides, alachlor and propachlor, as well as the thioacetanilide analog of propachlor. The activation of α-chloroacetanilides toward reaction with strong nucleophiles originates primarily through a decrease in $\Delta H^{\ddagger}$. This degree of activation, which plays such an important role in the environmental chemistry and utility of these herbicides, most likely reflects electronic interactions of the α-anilide substituent with the axis of displacement within the transition state, a topic explored in greater detail in a related study (*28*).

ABBREVIATIONS USED

GSH, glutathione; iPA, *N*-isopropylaniline.

Supporting Information Available: Schemes illustrating the system of reactions and the corresponding differential rate expressions for the thioacetanilide and β-anilide analogs of propachlor, a table presenting the model-fit rate constants for reaction of the methylene analog of propachlor with bromide and iodide, and a brief summary of methods used to synthesize the propachlor analogs and *N*-phenyl-*N*-isopropylacrylamide. This information is available free of charge via the Internet at http://pubs.acs.org.

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