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Hydrolytic Degradation of Desmedipham

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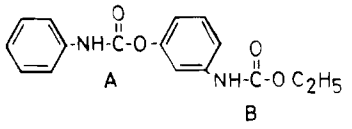
The alkaline hydrolysis of desmedipham into aniline and ethyl *N*-(3-hydroxyphenyl)carbamate was studied for hydroxide ion concentrations ranging from 10^{-6} to 3 N. The positive activation entropy and the fact that desmedipham fits well into a Brønsted plot log $k_{OH} = f(pK_a)$ obtained for the hydrolysis of alkyl and aryl *N*-phenylcarbamates with a slope value β of −1.15 supported an E1cB reaction scheme for desmedipham hydrolysis.

Phenmedipham and desmedipham are postemergence herbicides of the bis(carbamate) family with two carbamate functions, A and B (Trebst et al., 1968), and are sprayed on sugar beets to control certain broadleaf and grass weeds.



Desmedipham, ethyl [3-[[(phenylamino)carbonyl]oxy]phenyl]carbamate, a phenmedipham analogue, has been developed for the control of redroot pigweed (*Amaranthus retroflexus* L.), which is a problem weed in sugar beet crops and is resistant to phenmedipham (Schweizer and Weatherspoon, 1971; Laufersweiler and Gates, 1972; Sullivan and Fagala, 1977). In sugar beets (Knowles and Sonawane, 1972) and the rat (Sonowane and Knowles, 1971) the hydrolysis of desmedipham to ethyl *N*-(3-hydroxyphenyl)carbamate and subsequently to *m*-aminophenol is one of the main pathways of in vivo bis(carbamate) metabolism. In soils, desmedipham is also converted by microorganisms to ethyl *N*-(3-hydroxyphenyl)carbamate (Knowles and Benezet, 1981).

The only data in the literature concerning desmedipham stability in aqueous media are the values of the half-life measured at pH 7 ($t_{1/2} \simeq 14$ h) and pH 9 ($t_{1/2} \simeq 20$ min) at 26 °C (Röder et al., 1978).

In alkaline media, the hydrolytic breakdown of phenmedipham into methyl *N*-(3-hydroxyphenyl)carbamate and *m*-toluidine via *N*-(*m*-tolylcarbamic acid) follows an E1cB reaction scheme and involves the formation of *m*-tolyl isocyanate, which may lead to carbamylation reactions in biochemical systems (Bergon et al., 1985). To determine whether there is formation of phenyl isocyanate during the hydrolysis of desmedipham, we carried out a kinetic study of this reaction to identify its mechanism.

EXPERIMENTAL SECTION

Apparatus. A Unicam SP 1800 recording spectrophotometer fitted to an SP 1805 program controller and a thermostated multiple cell compartment or, for the more rapid reactions ($t_{1/2} < 10$ s), a Durrum D-110 stopped-flow spectrophotometer were used for all spectroscopic measurements. Optical density changes after mixing were recorded on a Gould storage oscilloscope (Model OS 4000).

The pH measurements were carried out on a Radiometer PHM 64 pH meter equipped with a Radiometer GK 2321 C electrode.

Synthesis of Desmedipham. Ethyl chloroformate (0.025 mol) was added dropwise at room temperature to 3-aminophenol (0.05 mol) dissolved in dry tetrahydrofuran (50 mL). The mixture was stirred for 2 h and the precipitated hydrochloride of 3-aminophenol was filtered off on cooling. The filtrate was evaporated to dryness to give ethyl *N*-(3-hydroxyphenyl)-carbamate, mp 94 °C (lit. mp 94–95 °C (Schering A.-G.)).

This carbamate was converted to desmedipham by reacting with phenyl isocyanate in dry benzene with a catalytic quantity of triethylamine and refluxing for 30 min; mp 120 °C (lit. mp 120 °C (Röder et al., 1978)).

pK_a Measurement. The ultraviolet spectra of the carbamate in aqueous media show an increase with the pH in the region 290–300 nm. In 1 N NaOH, the maximum observed at 295 nm is consistent with the formation of a phenolate ion (Scott, 1964). The pK_a was obtained from the intercept of the graph log $(D - D_{AH})/(D_{A^-} - D) = f(pH)$ where D_{A^-}, D_{AH}, and D are the optical densities of the phenolate ion in 0.05 N NaOH, of the nonionized carbamate in 1 N HCl, and of the mixture of the two species in buffer solutions ranging from pH 8.68 to 10.24.

The pK_a value of ethyl *N*-(3-hydroxyphenyl)carbamate is 9.77 (25 °C; μ 1.00, KCl).

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Kinetic Measurements. The changes in concentration of desmedipham were followed spectrophotometrically by recording the changes in optical density corresponding to the disappearance of the substrate (λ = 236 nm) or to the appearance of the substituted carbanilate anion and/or of the substituted phenol (λ = 290 nm). All reactions exhibited good first-order kinetics with respect to the substrate. The absorbance vs time plots gave the pseudo-first-order rate constants graphically using the experimental infinity value. The observed rate constants k_{obsd} were obtained by plotting log $(A_t - A_\infty)$ vs time, where A_∞ and A_t are the absorbance readings at infinity and at time t, respectively: log $(A_t - A_\infty)$ = (log $A_0 - k_{obsd}$)/2.303t.

In the stopped-flow determinations, with each buffer or hydroxide ion concentration, four to six reactions were carried out and the pseudo-first-order constant k_{obsd} was the mean value of several (usually five) separate kinetic runs.

Regression lines were obtained from a weighted least-squares program written for the Hewlett-Packard HP 97 computer.

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

Thermodynamic Parameter of Activation. When the logarithms of the observed pseudo-first-order rate constants k_{obsd} were plotted vs $1/T$, a straight line was observed, the slope of which, multiplied by $-2.303R$, gave the Arrhenius activation energy E_a. The entropy of activation $\Delta S^{\ddagger}$ was obtained from the equation log k_{obsd} = 0.43 log (k/h) + log T - $(E_a/2.3RT)$ + $(\Delta S^{\ddagger}/2.3R)$, where k and h are the Boltzmann and Planck constants, respectively, and R is the gas constant.

RESULTS AND DISCUSSION

Alkaline Hydrolysis of Desmedipham. Product Analysis of the Hydrolysis Reaction. An aliquot of desmedipham hydrolysis reaction in a buffer solution (borax 10^{-2} M) at pH 9.2 was analyzed by high-pressure liquid chromatography with a reversed phase in a methanol/water mixture.

The identification of aniline and ethyl *N*-(3-hydroxyphenyl)carbamate confirms that the A carbamate function is the more reactive of two.

Effect of pH. Desmedipham hydrolysis exhibited pseudo-first-order kinetics with respect to bis(carbamate) in aqueous media, and the rate constants were measured in various buffer solutions ranging from pH 8 to 11 and in sodium hydroxide solutions.

The ultraviolet spectra plotted as a function of time show two isosbestic points, indicating a 1:1 stoichiometry with no accumulation of intermediates. The plot of log k_{obsd} = f (pH) for the desmedipham hydrolysis reaction presents two distinct parts: a straight line of slope unity followed by a plateau (Figure 1). The general form of this curve is in agreement with the limit forms obtained for $a_H \gg K_a$ and $a_H \ll K_a$ of eq 1 and 2. These correspond to the E1cB and $B_{Ac}2$ mechanisms, respectively, both of which are possible hydrolysis pathways with N-monosubstituted carbamates (Williams and Douglas, 1975; Bergon et al., 1985).

$$k_{obsd} = k_1K_a/(K_a + a_H) \quad (1)$$

$$k_{obsd} = (k_2K_w/\gamma_{OH^-})/(K_a + a_H) \quad (2)$$

At the intersection of the two straight lines, the pH is equal to the pK_a of the ionizable proton on the nitrogen atom. This value is 12.9 for desmedipham, which is slightly more acidic than phenmedipham (pK_a = 13.3), which can be accounted for by the electron-donor effect of the methyl substituent of the latter.

In aqueous media the bimolecular rate constant k_{OH} = $k_{obsd}/[OH^-]$ (k_{OH} = 2.09 × 10^2 L mol^{-1} s^{-1}) shows a high reactivity matched only, in the carbamate herbicide family, by phenmedipham (k_{OH} = 1.06 × 10^2 L mol^{-1} s^{-1}; Bergon et al., 1985).

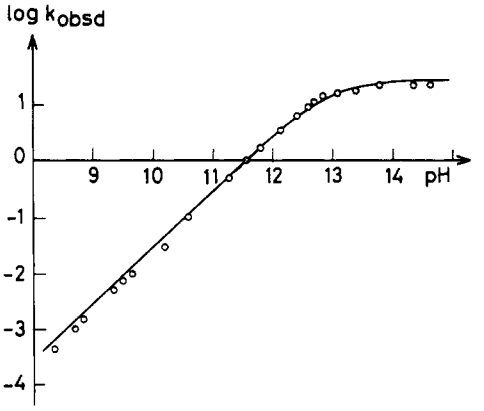


Figure 1. Plot of log k_{obsd} vs pH or h_- for the hydrolysis of desmedipham at 25 °C (μ = 1.00, KCl). The curve was drawn using eq 1 with the following values for the constants: k_1K_a = 2.88 × 10^{-12}, pK_a = 12.9.

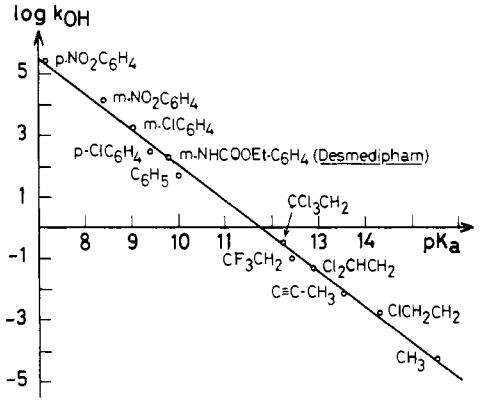


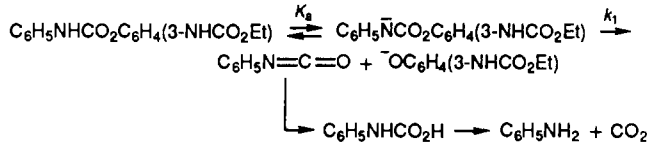
Figure 2. Brønsted plot of log k_{OH} vs pK_a of leaving group for the hydrolysis of aryl and alkyl *N*-phenylcarbamates at 25 °C (except for desmedipham, the k_{OH} values were determined by Williams).

Effect of the Temperature. In order to differentiate between the two mechanisms, the activation entropy is evaluated. Indeed, the two mechanisms present very different activation entropies; whereas the $B_{Ac}2$ mechanism shows a $\Delta S^{\ddagger}$ value of between -10 and -40 cal mol^{-1} K^{-1}, largely due to the addition of the hydroxyl ion (Bergon and Calmon, 1983), the E1cB mechanism involves a positive or a slightly negative value of activation entropy that can be attributed to the dissociation of the anionic species: $\Delta S^{\ddagger}$ = -5.8 cal mol^{-1} K^{-1} and +19 cal mol^{-1} K^{-1} for aldicarb and phenmedipham hydrolysis, respectively (Bank and Tyrrell, 1984; Bergon et al., 1985).

The activation entropy of the hydrolysis reaction of desmedipham, measured at temperatures ranging from 15 to 35 °C, is +16 cal mol^{-1} K^{-1}. The large positive value obtained indicates that an E1cB mechanism is involved.

Brønsted Relationship. The Brønsted relationship, which relates k_{OH} to the pK_a of the leaving group, also provides useful information as to the differentiation of the two reaction mechanisms (Hegarty and Frost, 1973; Bergon and Calmon, 1983; Bergon et al., 1985). The pK_a value of 9.77 for ethyl *N*-(3-hydroxyphenyl)-carbamate was measured as described previously. The point corresponding to desmedipham was introduced into the graph log k_{OH} = f(pK_a) of a precedent study on E1cB hydrolysis of substituted phenyl *N*-phenylcarbamates (Williams, 1973; Figure 2).

The slope, which is less than −1 ($\beta = -1.15$; $r = 0.998$, $s = 0.02$), is characteristic of a reaction mechanism involving elimination of the leaving group as the rate-limiting step. The fact that desmedipham fits into the correlation supports the argument that its hydrolysis follows an E1cB reaction mechanism:



In summary, alkaline hydrolysis of desmedipham, like that of phenmedipham, proceeds by an E1cB mechanism with formation of phenyl isocyanate. This breakdown product may lead to carbamylation reaction in regard to nucleophilic groups such as NH_2, OH, SH, and COOH encountered in biochemical systems during its metabolism in plants and animals.

Registry No. Desmedipham, 13684-56-5; ethyl chloroformate, 541-41-3; 3-aminophenol, 591-27-5; ethyl *N*-(3-hydroxyphenyl)carbamate, 7159-96-8; phenyl isocyanate, 103-71-9.

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