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Isocyanate Formation in the Decomposition of Phenmedipham in Aqueous Media

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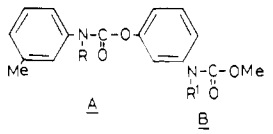
The alkaline hydrolysis of phenmedipham and one of its N-methylated derivatives, 3-[[(methoxycarbonyl)methyl]amino]phenyl *N*-(3-methylphenyl)carbamate, into *m*-hydroxyphenols and *m*-toluidine via *m*-tolylcarbamic acid was studied for hydroxide ion concentrations ranging from 10^{-6} to 6 N. The pH–rate profiles correspond to the rate laws of the ElcB or $B_{Ac}2$ reaction mechanisms that can be involved in the hydrolysis of carbamates. The positive activation entropy, the Brønsted β value of −1.21 for the hydrolysis of a series of aryl and alkyl *N*-(3-methylphenyl)carbamates, and the Hammett ρ value of 0.74 for the hydrolysis of a series of 3-[(methoxycarbonyl)amino]phenyl *N*-(substituted phenyl)carbamates are in favor of the involvement of a ElcB reaction scheme for phenmedipham hydrolysis. The importance of the formation of *m*-tolyl isocyanate during phenmedipham decomposition is underlined as this intermediate, although only transient, may lead to carbamylation reactions of enzymatic systems during the metabolism of the herbicide in plants or animals.

Phenmedipham, or 3-[(methoxycarbonyl)amino]phenyl *N*-(3-methylphenyl)carbamate **1**, is a herbicide of the bis(carbamate) family (Trebst et al., 1968) used for postemergence weed control in beet crops and strawberry plants (Arndt and Kötter, 1968).



R=R¹=H Phenmedipham
R=Me R¹=H Biscarbamate 2
R=H R¹=Me Biscarbamate 3

In acid soils, the herbicide decomposes into *m*-toluidine and methyl *N*-(3-hydroxyphenyl)carbamate with a half-life of ca. 28–55 days (Kossmann, 1970). In basic soils, Sonawane and Knowles (1971a) noted that methyl *N*-(3-hydroxyphenyl)carbamate subsequently decomposes into *m*-aminophenol.

In plants (Von Kassebeer, 1971) and the rat (Sonawane and Knowles, 1971b) the hydrolysis of the carbamate A function is one of the main pathways of in vivo bis(carbamate) metabolism.

The only data in the literature concerning phenmedipham stability in aqueous media are the values of the half-life measured at pH 7 ($t_{1/2} \simeq 5$ h) and pH 9 ($t_{1/2} \simeq 10$ min) at 30 °C (Martin and Worthing, 1974).

Previous studies on the stability of carbamates in alkaline media demonstrated a difference in the reactivity between N-monosubstituted and N,N-disubstituted compounds (Dittert and Higuchi, 1963). The latter compounds do not have a mobile proton in the carbonyl α position and are hydrolyzed via a $B_{Ac}2$ mechanism. The hydrolysis of the N-monosubstituted derivatives, however, may proceed via two reaction schemes: a bimolecular $B_{Ac}2$ pathway and a monomolecular ElcB pathway involving the formation of isocyanate (Hegarty and Frost, 1973; Williams, 1972) (Figure 1). Hence the hydrolysis of carbaryl (Vontor et al., 1972) and the O-(methylcarbamoyl) oximes (Mrlina and Calmon, 1980) involves the formation of methyl isocyanate whereas that of propham, chlorpropham, and swep follows a $B_{Ac}2$ reaction scheme (Bergon and Calmon, 1983).

During the hydrolysis of phenmedipham, any isocyanates that may be formed cannot be directly demonstrated because of their high reactivity in aqueous media (Williams and Ibrahim, 1981). We therefore carried out a kinetic study of this reaction in order to determine its mechanism (Ben Hamida et al., 1981, 1982).

As phenmedipham is characterized by the presence of two carbamate functions, two monoanions **4** and **5** may form in alkaline media (Figure 2). In order therefore to determine the ionization site of the phenmedipham molecule we examined, on the one hand, the effect of the substitution of the aromatic nucleus on the acidity of a series of methyl carbanilates including bis(carbamate) **2**, and on the other hand, the hydrolysis reaction kinetics of 3-[[(methoxycarbonyl)methyl]amino]phenyl *N*-3(methylphenyl)carbamate **3**, the N-methylated derivative on the phenmedipham B function.

Finally, in order to look for Hammett and Brønsted relationships of the type $\log k_{OH} = f(\sigma \text{ or } pK_a)$ with ρ and β values that characterize the hydrolysis mechanism of a carbamate function (Sartoré et al., 1977), we synthesized two families of carbanilates with a chemical structure analogous to that of phenmedipham: the 3-[(methoxycarbonyl)amino]phenyl carbanilates and 3-methylcarbanilic acid esters.

EXPERIMENTAL SECTION

Apparatus. A Unicam SP 1800 recording spectrophotometer fitted with a SP 1805 program controller and a thermostated multiple cell compartment or, for the more

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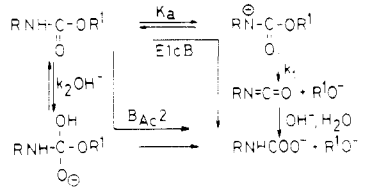

Figure 1. Mechanisms of alkaline hydrolysis of carbamates.

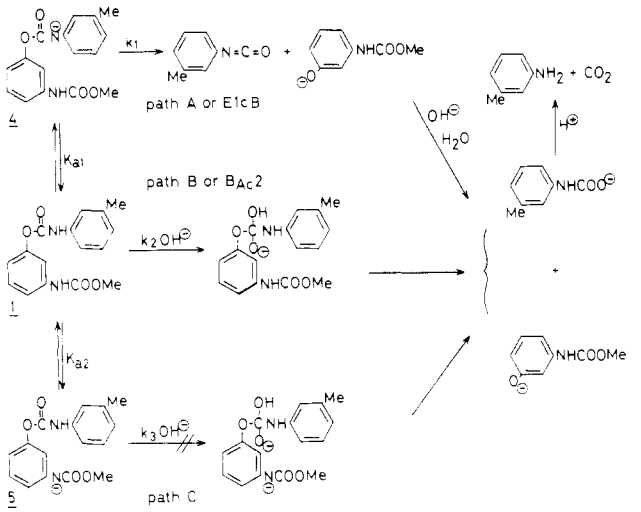

Figure 2. Mechanisms of alkaline hydrolysis of phenmedipham.

rapid reaction ($t_{1/2}$ < 10 s), a Durrum D-110 stopped-flow spectrophotometer were used for all spectroscopics measurements. Optical density changes after mixing were recorded on a Gould storage oscilloscope (Model OS 4000).

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

Synthesis of Carbamates. 3-[(Methoxycarbonyl)amino]phenyl *N*-(Substituted Phenyl)carbamates. They were prepared by a two-step process. At room temperature, methyl chloroformate (0.025 mol) was added dropwise to 3-aminophenol (0.05 mol) dissolved in dry tetrahydrofuran (50 mL). The mixture was stirred for 2 h and the precipitate, hydrochloride of 3-aminophenol, was filtered off on cooling. The filtrate was evaporated to dryness to give methyl *N*-(3-hydroxyphenyl)carbamate [mp 95 °C; (lit. mp 94–96 °C, Wilson and Hill, 1968)].

This carbamate was converted to bis(carbamate) by reacting with substituted phenyl isocyanate in dry benzene with a catalytic quantity of triethylamine and refluxing for 30 min.

The physical characteristics of the bis(carbamates) are listed in Table I.

***N*-(3-Methylphenyl)carbamic Acid Esters.** *m*-Tolyl isocyanate (0.05 mol) was reacted for 0.5 h with the corresponding alcohol or phenol (0.05 mol) in anhydrous benzene (40 mL) in the presence of catalytic amounts of triethylamine. The physical characteristics of these esters are listed in Table II.

Methyl Carbanilates. A substituted phenyl isocyanate (0.05 mol) was reacted with methyl alcohol (0.05 mol) in anhydrous benzene (40 mL) in the presence of triethylamine (2 mL) used as a catalyst. The reaction mixture was refluxed for 0.5 h. The physical characteristics of the derivatives thus prepared are listed in Table III.

The structure of all these carbamates was corroborated by the detailed analysis of their NMR spectra.

3-[(Methoxycarbonyl)amino]phenyl *N*-methyl-*N*-(3-methylphenyl)carbamate (**2**) and 3-[[(methoxycarbonyl)-methyl]amino]phenyl *N*-(3-methylphenyl)carbamate (**3**) were gifts from Schering A.-G. (Berlin).

Table I. Physicochemical Characteristics of 3-[(Methoxycarbonyl)amino]phenyl *N*-(Substituted Phenyl)Carbamates $XC_6H_4NHCO_2C_6H_4(3\text{-}NHCO_2Me)$

X	mp, °C[a]	lit. mp, °C
p-Me	167	162–163[b]
m-Me	145	143–144[b]
H	154	152[b]
p-Cl	178	178[b]
m-CF_3	159	157–158[c]
m,p-Cl_2	185–188	188–190[b]

		elemental analysis					
		calcd			found		
X	mp, °C[a]	C	H	N	C	H	N
p-NO_2	167	54.38	3.95	12.68	54.36	3.88	12.62

[a] Recrystallized from hexane–chloroform (3:1, v/v). [b] Schering A.-G. (1967). [c] Badische Anilin; Soda-Fabrik, A.-G. (1969).

Table II. Physicochemical Characteristics of Alkyl and Substituted Phenyl *N*-(3-Methylphenyl)carbamates $3\text{-}MeC_6H_4NHCO_2R$

		elemental analyses					
		calcd			found		
R	mp or bp, °C[a]	C	H	N	C	H	N
p-$NO_2C_6H_4$	129	61.76	4.44	10.29	62.26	4.44	10.19
p-AcC_6H_4	117	71.36	5.61	5.20	71.44	5.63	5.21
m-AcC_6H_4	114	71.36	5.61	5.20	71.60	5.57	5.18
p-ClC_6H_4	109	64.25	4.62	5.35	63.83	4.54	5.16
m-ClC_6H_4	100	64.25	4.62	5.35	64.24	4.61	5.39
C_6H_5	91	73.99	5.77	6.16	74.41	5.79	6.10
p-$MeOC_6H_4$	101	70.02	5.88	5.44	70.21	5.90	5.40
CF_3CH_2	33	51.51	4.32	6.00	52.09	4.24	6.01
$CH_3OCH_2CH_2$	186–188[b]	63.14	7.23	6.69	63.05	7.52	6.69
CH_3	70[c]						

[a] Recrystallized from hexane–chloroform (3:1, v/v). [b] At 10 mmHg. [c] Literature mp 67.5–69 °C, Shulman and Griepentrog (1962).

Table III. Physicochemical Characteristics of Methyl Carbanilates $XC_6H_4NHCO_2Me$

X	mp, °C[a]	C
p-MeO	89	90[b]
p-Me	97	98.5–99.5[c]
H	44–45	47[d]
p-Cl	112–115	112–114[e]
m-Cl	82–83	83–84[f]
m,p-Cl_2	114	112–114[g]
m-NO_2	148–149	150[b]

		elemental analysis					
		calcd			found		
X	mp, °C[a]	C	H	N	C	H	N
m-CF_3	83	49.32	3.68	6.39	49.52	3.63	6.41

[a] Recrystallized from hexane–chloroform (3:1, v/v). [b] Attaway et al. (1962). [c] Shulman and Griepentrog (1962). [d] Hentschel (1885). [e] Kricheldorf and Leppert (1976). [f] Newcomer et al. (1958). [g] Melnikov (1971).

pKa Measurements. Methyl *N*-(3-Hydroxyphenyl]carbamate. Hydroxyl Group Ionization. The ultraviolet spectra of the carbamate in aqueous media show an increase in absorption 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 $\log [(D - D_{AH})/(D_{A^-} - D)] = f(\text{pH})$ 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

for pH ranging from 8.86 to 10.47.

The pK_a value of methyl *N*-(3-hydroxyphenyl)carbamate is 9.64 (25 °C, μ = 1, KCl).

NH Group Ionization. The ultraviolet spectra of the phenoxide ion of methyl *N*-(3-hydroxyphenyl)carbamate were recorded at 25 °C for various sodium hydroxide concentrations (0.05–6.0 M) corresponding to definite values of the basicity function h_- (Hammett, 1940; Coussemant et al., 1969). As the dianionic form of the carbamate could not be reached, the data obtained from spectroscopic measurements were treated by the method developed by Maroni and Calmon (1964): $1/(D_{obsd} - D_{AH})$ was plotted against h_- at various wavelengths; D_{AH} and D_{obsd} are the optical densities of the monionized carbamate (phenolate ion) in 0.05 N NaOH and of the mixture of monoanion and dianion carbamate at a definite hydroxide ion concentration, respectively.

The pK_a value relative to the NH group in the methyl *N*-(3-hydroxyphenyl)carbamate at 25 °C is 15.60.

Methyl Carbanilates. The pK_a values for these compounds were obtained by the method used for propham, chlorpropham, and swep (Bergon and Calmon, 1983).

Kinetics Measurements. 3-[(Methoxycarbonyl)amino]phenyl *N*-(Substituted Phenyl)carbamates, Substituted Phenyl *N*-(3-Methylphenyl)carbamates. Phenmedipham and *N*-Methyl Derivative. The changes in concentration were followed spectrophotometrically by recording at appropriate wavelengths the changes in optical density corresponding to the disappearance of the substrate or to the appearance of the substituted carbanilate anion and/or of the substituted phenol. 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 by using the experimental infinity value. The observed rate constants k_{obsd} were obtained by plotting log $(A_t - A_\infty)$ vs. time, where A_t and A_∞ are the absorbance readings at time t and at the completion of reaction, respectively: log $(A_t - A_\infty)$ = log $A_o - (k_{obsd}/2.303)t$.

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. Apparent second-order rate constants k_{OH} are the mean values calculated from $k_{obsd}/[OH^-]$ for four different hydroxide ion concentrations.

As some 3-[(methoxycarbonyl)amino]phenyl *N*-(substituted phenyl)carbamates are water insoluble, the rate constants for the hydrolysis of this series were measured in a 3:1 v/v water–dioxane mixture.

Alkyl *N*-(3-Methylphenyl)carbamates. In weakly alkaline media (pH < 11), the UV spectra of alkyl carbanilates exhibit an intense absorption peak around 235 nm (ϵ ca. 15 000). In alkaline media (0.005 N < $[OH^-]$ < 1.0 N), the difference in absorbance between esters and carbanilic acids is very small and the reaction progress cannot be followed by recording directly the changes in optical density. The following procedure was then used: at suitable time intervals, a sample (2 mL) of an alkaline carbanilate solution was acidified with concentrated hydrochloric acid (1 mL) to yield anilinium ions after the instant decarboxylation of the carbanilic acid (Caplow, 1968; Johnson and Morrison, 1972). The changes in optical density of the acidified samples vs. time up to 95% of the total reaction were measured at 235 nm where only the carbanilate ester exhibits an absorption.

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

Table IV. pK_a Values of Methyl Carbanilates $XC_6H_4NHCO_2Me$ at 25 °C and σ Values

X	σ^a	pK_a	corr coeff, r	SD, s
m-O^-	−0.70[b]	15.60	0.998	0.18
p-MeO	−0.268	14.94	0.999	0.03
p-Me	−0.17	14.90	0.999	0.02
H	0	14.77	0.998	0.05
p-Cl	0.227	14.35	0.998	0.03
m-Cl	0.373	14.20	0.999	0.02
m-CF_3	0.43	14.07	0.999	0.02
m,*p*-Cl_2	0.525[b]	13.86	0.999	0.03
m-NO_2	0.710	13.56	0.999	0.01
2		14.29	0.999	0.02

[a] Usual σ Hammett values (Hammett, 1970). [b] σ values from Jaffe (1953).

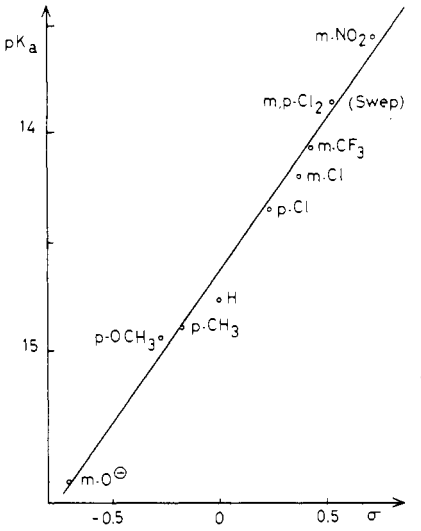

Figure 3. Hammett plot of log K_a vs. σ for the ionization of methyl carbanilates at 25 °C.

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

RESULTS AND DISCUSSION

I. Ionization of a Series of Methyl Carbanilates: Hammett Relationship. The effect of the substitutents carried by the *N*-phenyl group on the ionization of a series of methyl carbanilates (Table IV) including swep (X = 3,5-Cl_2) and methyl *N*-(3-hydroxyphenyl)carbamate (X = 3-OH), a product of phenmedipham hydrolysis, fits the Hammett equation $pK_a = -1.40\sigma + 14.64$ (r = 0.933, s = 0.06)(Figure 3). Bis(carbamate) **2** does not appear in this relationship as the value of the σ parameter for the substituent 3-(3-$MeC_6H_4NMeC(=O)O$) is not known. The value of 14.3 obtained for the pK_a of **2** is between the values measured for the methyl 3-chloro- and 4-chlorocarbanilates. This group therefore has an electron-withdrawing effect and the corresponding values of σ is between 0.2 and 0.4.

We were not able to measure the ionization constants of phenmedipham and bis(carbamate) **3** with the usual spectrophotometric methods as these compounds are

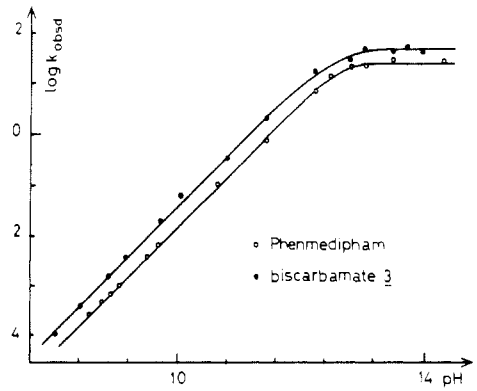

Figure 4. Plot of log k_{obsd} vs. pH or h_- for the hydrolysis of phenmedipham and bis(carbamate) **3** at 25 °C.

highly unstable in alkaline media (with a half-life of ca. 20 ms in 1 N sodium hydroxide). These constants were determined from the rate law deduced from the study of their hydrolysis reaction kinetics according to a method called "kinetic method".

II. Alkaline Hydrolysis of Phenmedipham and Bis(carbamate) 3. Product Analysis of the Hydrolysis Reaction. The ultraviolet spectrum of the products of phenmedipham hydrolysis at 25 °C in a carbonate buffer solution of pH 9.66 was the same as that of a mixture, at the same concentration of 5×10^{-5} M of *m*-toluidine and methyl *N*-(3-hydroxyphenyl)carbamate. The characterization of these two compounds was also confirmed from a high performance liquid chromatogram of an aliquot of the phenmedipham hydrolysis reaction in a solution of pH 9.45 with a carbamate concentration of 5×10^{-5} M.

These results show that the carbamate A function is the most reactive. This is because the 3-[(methoxycarbonyl)amino]phenolate ion ($pK_a = 9.64$) is a better leaving group than the methylate ion ($pK_a = 15.09$, Murto, 1964). Under the same experimental conditions, bis(carbamate) **3** is hydrolyzed into *m*-toluidine and methyl *N*-(3-hydroxyphenyl)-*N*-methylcarbamate.

Effect of pH. Under the experimental conditions used with an initial phenmedipham concentration of 5×10^{-5} M in buffer solutions with a pH ranging from 8 to 11 or sodium hydroxyde, the hydrolysis reaction carried out at 25 °C exhibited first-order kinetics with respect to bis(carbamate). The presence of two isosbestic points (λ 224 and 266 nm) on the ultraviolet spectra plotted as a function of time reflects the occurrence of a simple 1:1 stoichiometry and shows that there is no accumulation of intermediates. The plot of log $k_{obsd} = f(pH)$ for the phenmedipham hydrolysis reaction has two distinct parts: a straight line of slope unity followed by a plateau (Figure 4). The trend of this curve is in agreement with the limit forms obtained for $a_H \gg K_{a1}$ and $a_H \ll K_{a1}$ of the following equations:

$$k_{obsd} = \frac{k_1 K_{a1}}{K_{a1} + a_H} \quad (1)$$

$$k_{obsd} = \frac{k_2 K_w / \gamma_{OH^-}}{K_{a1} + a_H} \quad (2)$$

These correspond to the ElcB and $B_{Ac}2$ mechanisms of the A and B pathways which can be followed by phenmedipham (Figure 2).

The A pathway involves the formation of isocyanate, which was identified during the assay of phenmedipham in highly alkaline media (Haumesser et al., 1981).

The rate law corresponding to pathways B and C involving the reactivity of **1** and the anion **5** takes the form

$$k_{obsd} = \frac{k_2 K_w / \gamma_{OH^-} + k_3 K_{a2}[OH^-]}{K_{a2} + a_H}$$

which is of second order with respect to the hydroxide ion and therefore in disagreement with the experimental rate law.

A nonreactive anion **5** may be formed as the rate law corresponding to this reaction scheme, pathways A and B, of the form

$$k_{obsd} = \frac{k_1 K_{a1}}{a_H + K'_a} + \frac{k_2 K_w / \gamma_{OH^-}}{a_H + K'_a}$$

with $K'_a = K_{a1} + K_{a2}$ is consistent with the experimental rate law. This hypothesis may nevertheless easily be rejected as it is highly unlikely that the attack of the hydroxide ion on the nonionized carbamate A function of the anion **5** is not involved.

The formation of a dianion has not been considered as the second dissociation constant of phenmedipham must be very low (Haumesser et al., 1977).

In aqueous media, the reactivity of bis(carbamate) **3** measured by the bimolecular rate constant $k_{OH} = k_{obsd}/[OH^-]$ ($k_{OH_{25°C}} = 2.90 \times 10^2$ L mol^{-1} s^{-1}) is very close to that of phenmedipham ($k_{OH_{25°C}} = 1.06 \times 10^2$ L mol^{-1} s^{-1}). The log $k_{obsd} = f(pH)$ plot for the hydrolysis reaction of **3** is analogous to that of the herbicide. The intersecting point of the two straight lines of the graph corresponds to a pH value equal to that of the pK_a of the only ionizable proton carried by the nitrogen atom of the carbamate A function (Figure 4). The pK_a of **3** measured by the kinetic method is 13.2.

The value of 13.3 obtained for the pK_a of phenmedipham with the kinetic method under the same conditions corresponds therefore to the pK_a of the NH group of the carbamate A function and not to the pK_a of the NH group of the carbamate B function which should be about 14.3 as has been observed for the compound **2**. Phenmedipham is therefore a weak acid and volumetric assays with strong bases may be carried out to control its purity in formulations (Haumesser et al., 1977, 1981, 1982).

Overall, these results which give a pK_a of 13.3 for the carbamate A function and a first-order rate constant with respect to the hydroxyl ion show that pathway C is not involved in phenmedipham hydrolysis.

Effect of the Temperature. The mathematical expressions of the rate eq 1 and 2 corresponding to the ElcB and $B_{Ac}2$ mechanisms of pathways A and B are equivalent and cannot be used to distinguish between these reaction schemes. However, the values of the entropy of activation for each of these two mechanisms should be very different (Schaleger and Long, 1963).

The entropy of activation of the phenmedipham hydrolysis reaction determined from the rate constants measured at several temperatures in a 0.01 M borax buffer solution (pH 8.96 at 25 °C, $\mu = 1$ with KCl) is +19 cal deg^{-1} mol^{-1} (Ben Hamida et al., 1983). The bimolecular rate constant $k_{OH} = k_{obsd}/[OH^-]$ are given by $k_1 K_{a1} \gamma_{OH^-}/K_w$ for the ElcB mechanism and k_2 for the $B_{Ac}2$ mechanism over the pH range where $a_H \gg K_{a1}$.

The large positive value of $\Delta S^{\ddagger}$ makes it possible to reject the $B_{Ac}2$ mechanism for which an entropy value of between −10 and −40 cal deg^{-1} mol^{-1} is expected as has been observed for the slow addition of the hydroxide ion on the carbonyl group of a carboxylic ester (Kirby, 1973) or a N,N-disubstituted carbamate (Christenson, 1964).

On the other hand, for the ElcB mechanism, the breakdown reaction, with constant k_1, should have a positive entropy, and the ionization of carbamate (K_a) and

Table V. Entropy of Activation Values for the Hydrolysis via an ElcB Pathway of Various Carbamates

carbamate	$\Delta S^{\ddagger}$, cal deg^{-1} mol^{-1}
$C_6H_5NHCOOC_6H_5$[a]	+5
$C_6H_5NHCOSC_6H_5$[b]	+21.1
$C_6H_5NHCSOC_6H_5$[c]	+10.8
$CH_3CONHCOOC_6H_5$[d]	+15.5
phenmedipham[e]	+19

[a] Christenson (1964). [b] Branstad et al. (1973). [c] Sartoré et al. (1977). [d] Bergon and Calmon (1976). [e] Our results.

Table VI. Bimolecular Rate Constants k_{OH} for the Hydrolysis of Aryl and Alkyl *N*-(3-Methylphenyl)carbamates at 25 °C and pK_a Values of the Leaving Group ROH

R	k_{OH}, L mol^{-1} s^{-1}	pK_a (ROH)	corr coeff, r	SD, s
p-$NO_2C_6H_4$	11.71×10^4	7.15[a]	0.999	0.07
p-AcC_6H_4	8.42×10^3	8.05[a]	0.999	0.11
m-ClC_6H_4	7.58×10^2	9.02[a]	0.999	0.14
m-AcC_6H_4	4.49×10^2	9.19[a]	0.999	0.02
p-ClC_6H_4	1.18×10^2	9.38[a]	0.994	0.08
m-$CH_3CO_2NHC_6H_4$	1.06×10^2	9.64[b]	0.999	0.01
C_6H_5	1.99×10^1	10.0[a]	0.998	0.06
p-$CH_3OC_6H_4$	5.26	10.50[a]	0.999	0.06
CF_3CH_2	9.89×10^{-3}	12.37[c]	0.999	0.09
$CH_3OCH_2CH_2$	4.39×10^{-5}	14.82[c]	0.999	0.03
CH_3	5.08×10^{-5}	15.09[d]	0.999	0.05

[a] Barlin and Perrin (1966). [b] Determined spectrophotometrically in this study. [c] Ballinger and Long (1960). [d] Murto (1964).

water (K_w) negative entropies of the same order of magnitude so that the k_1K_{al}/K_w term may have a positive value in agreement with the experimental data. This result may be compared with the positive values of activation entropy obtained for ElcB hydrolyses of carbamates (Table V).

III. Effects of the Substituents on the Alkaline Hydrolysis of Phenmedipham Derivatives. Alkyl and Aryl *N*-(3-Methylphenyl)carbamates: Brønsted Relationship. The Brønsted relationship which relates the logarithm of the bimolecular rate constant k_{OH} to the pK_a of the leaving group is a very good criterion for distinguishing between the ElcB and $B_{Ac}2$ reaction mechanisms (Williams, 1973; Bergon and Calmon, 1976, 1983; Sartoré et al., 1977). In order to confirm the hypothesis of a ElcB mechanism for phenmedipham hydrolysis, we looked for a Brønsted relationship for the hydrolysis of a series of aryl and alkyl *N*-(3-methylphenyl)carbamates.

For all these compounds the rate increases in linear fashion with the concentration of hydroxide ions in agreement with the limit forms of eq 1 and 2.

The straight line of the equation log k_{OH} = −1.21 pK_a + 13.65 (r = 0.996, s = 0.03) plotted in Figure 5 was obtained from the values of the bimolecular rate constants k_{OH} given in Table VI.

Whatever the nature of the ester group, all the carbamates studied are situated on the same straight line with slope −1.21. This β value of less than −1 is in agreement with a ElcB hydrolysis scheme like that which has been observed for the hydrolysis of various carbonyl derivatives where the elimination of RO^- from the conjugate base of the substrate is the rate-determining step, and, in particular, for the aryl and 2,2,2-trichloroethyl 3,4-dichlorocarbanilates (Bergon and Calmon, 1983). On the other hand, a $B_{Ac}2$ reaction scheme should give a β value of greater than −0.5 as for the aliphatic *N*-acetylcarbamates (β = −0.23; Bergon and Calmon, 1976), O-aryl *N*-methyl-*N*-phenylthiocarbamates (β = −0.47, Sartoré et al., 1977), and the methyl (swep), ethyl, and methoxyethyl 3,4-dichlorocarbanilates (β = −0.31, Bergon and Calmon, 1983).

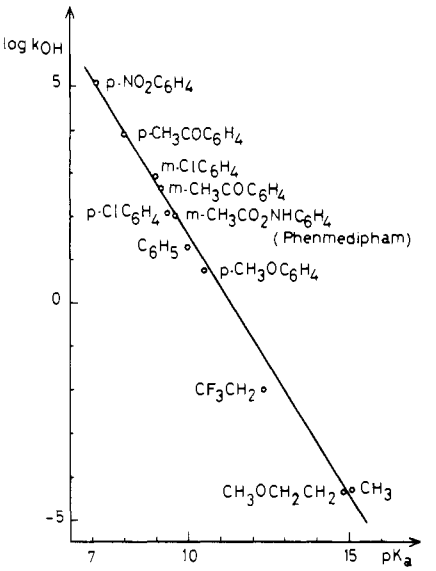

Figure 5. Brønsted plot of log k_{OH} vs. pK_a of leaving group for the hydrolysis of alkyl and aryl *N*-(3-methylphenyl)carbamates at 25 °C. [The datum points are surrounded by circles whose radius is equal to the standard deviation of log k_{OH} (± 0.01 log unit).]

It should be noted that a Hammett relationship log k_{OH} = 2.83σ^- + 1.52 (r = 0.993, s = 0.13) is demonstrated from the aromatic esters alone. In order to introduce phenmedipham into this correlation, the σ value of 0.13 for X = 3-NHCOOMe was determined from the equation pK_a = 9.92 − 2.23σ (Barlin and Perrin, 1966) and from the pK_a value of 9.64 measured at 25 °C for methyl *N*-(3-hydroxyphenyl)carbamate.

This high ρ value (ρ = 2.83) obtained for the aryl *N*-(3-methylphenyl)carbamates is comparable to those reported in the literature for carbamates hydrolyzed via a ElcB pathway (Williams and Douglas, 1975). In particularly, this relationship is obtained by using the σ^- parameter for substitutents withdrawing electrons by a mesomeric effect such as the p-NO_2 and p-Ac groups, resulting in a very marked phenolate ion character in the transition state, and is in favor of a ElcB pathway (Williams, 1972).

3-[(Methoxycarbonyl)amino]phenyl *N*-(Substituted Phenyl)carbamates: Hammett Relationship. We have attempted to complement the preceding criteria obtained from the activation entropy and the Brønsted straight line by looking for a Hammett relationship for the hydrolysis of a series of 3-[(methoxycarbonyl)amino]phenyl *N*-(substituted phenyl)carbamates. This is because the value of the parameter ρ, the slope of the straight line log $k_{OH} = f(\sigma)$, is characteristic of the mechanism involved in the hydrolysis of *N*-phenyl substituents of *N*-phenylcarbamates: it is greater or equal to 1 for a $B_{Ac}2$ scheme (Bergon and Calmon, 1983) and less than 1 for a ElcB mechanism (Hegarty and Frost, 1973).

The values of the pseudo-first-order rate constant k_{obsd} for each carbamate measured at four different pH values, increase in proportion with the hydroxide ion concentration. The bimolecular rate constants of the 3-[(methoxycarbonyl)amino]phenyl *N*-(substituted phenyl)carbamates listed in Table VII were determined from the expression:

$$k_{OH} = \frac{k_{obsd}}{[OH^-]} = \frac{k_{obsd}\,\gamma_{OH^-}a_H}{K_w}$$

in which the K_w and γ_{OH^-} terms are equal to 1.00×10^{-15} (Harned and Fallon, 1939) and 0.31 (Bergon and Calmon, 1983), respectively, for a 3:1, v/v, water–dioxane mixture

Table VII. Bimolecular Rate Constants k_{OH} for the Hydrolysis of 3-[(Methoxycarbonyl)amino]phenyl *N*-(Substituted Phenyl)carbamates at 25 °C in 3:1 v/v Water–Dioxane

X	$10^{-2}k_{OH}$, L mol^{-1} s^{-1}	corr coeff, r	SD, s
p-NO_2	4.46	0.999	0.04
m,p-Cl_2	3.05	0.999	0.05
m-CF_3	2.14	0.998	0.09
p-Cl	1.63	0.999	0.03
H	1.28	0.998	0.04
m-CH_3	0.95	0.998	0.03
p-CH_3	0.88	0.998	0.03

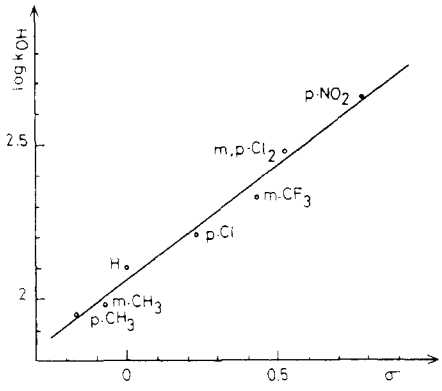

Figure 6. Hammett plot of log k_{OH} vs. σ for the hydrolysis of 3-[(methoxycarbonyl)amino]phenyl *N*-(substituted phenyl)carbamates at 25 °C.

at 25 °C. They are correlated by the Hammett equation log k_{OH} = 0.74σ + 2.06 (r = 0.991, s = 0.04) (Figure 6).

The decrease in the rate of hydrolysis of phenmedipham in the water–dioxane mixtures is of the same order of magnitude as that observed for phenyl carbanilate (ElcB scheme) or swep ($B_{Ac}2$ scheme) under the same experimental conditions. It should therefore be pointed out that the reaction mechanism is not affected by solvent effects (Hegarty and Frost, 1973).

The value of 0.74, which is less than 1 and close to that observed for the ElcB hydrolysis of phenyl *N*-(substituted phenyl)carbamates (ρ = 0.64), is in good agreement with the unimolecular mechanism proposed for phenmedipham.

It may be noted that the substituent p-NO_2 fits well on the Hammett straight line in Figure 6 when the value of 0.778, used for phenyl *N*-(*p*-nitrophenyl)carbamate which is hydrolyzed via a ElcB pathway (Hegarty and Frost, 1973), is taken for $\sigma(p\text{-}NO_2)$, whereas for a $B_{Ac}2$ scheme a σ value of between σ and σ^- (σ–(p-NO_2) = 1.27) is required, as for methyl *N*-(*p*-nitrophenyl)carbamate (Bergon and Calmon, 1981).

CONCLUSIONS

The bimolecular rate constant determined for the alkaline hydrolysis of phenmedipham at 25 °C is 1.06 × 10^2 L mol^{-1} s^{-1}. At temperatures and pH values close to those encountered in natural environments (6 < pH < 9, Stumm and Morgan, 1970) the half-life of bis(carbamate) at pH 7 is approximately 20 h. It is therefore much less stable than the other carbamate herbicides such as propham and chlorpropham which have half-lives of the order of 10^7 days under the same conditions (Bergon and Calmon, 1983).

In alkaline media, the hydrolytic breakdown of phenmedipham into methyl *N*-(3-hydroxyphenyl)carbamate and *m*-toluidine via *N*-(*m*-tolyl)carbamic acid follows a ElcB reaction scheme and involves the formation of *m*-tolyl isocyanate. Under alkaline conditions at which the hydroxyl group is ionized (pH ≥ pK_a + 2), methyl *N*-(3-hydroxyphenyl)carbamate subsequently hydrolyzes into methanol and *m*-aminophenol following a unimolecular pathway analogous to phenmedipham though it is 5 × 10^6 times less reactive than the herbicide (Ben Hamida et al., 1983).

Alkyl or aryl isocyanates give rise to carbamylation reactions in regard to nucleophilic groups such as NH_2, OH, SH, COOH, and imidazole encountered in chemical systems (Brown and Wold, 1973 a) or in macromolecules (Lown and Chauhan, 1981). Such carbamylation reactions have been observed during the incubation, under physiological conditions of amino acids, peptides, or proteins with cyclohexyl isocyanate which is either added directly to the reaction medium, or formed in situ by breakdown of an antineoplastic nitrosourea (CCNU) (Wheeler et al., 1975).

This chemical reactivity confers on isocyanates an inhibitory activity against enzymes which have a nucleophilic group such as the OH of serine or SH of cysteine in their active site. This is the case notably for chymotrypsin and elastase (Brown and Wold, 1973a,b), guinea pig liver transglutaminases (Gross et al., 1975), and yeast alcohol dehydrogenase (Twu and Wold, 1973).

There are many reports in the literature of the activity of isocyanates formed by the decomposition of drugs and pesticides such as the nitrosoureas and benomyl. For example, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) was found to inactivate chymotrypsin only after it had broken down to form cyclohexyl isocyanate (Babson et al., 1977) and several nitrosoureas (BCNU, CCNU, Me CCNU, *trans*-4-OH CCNU), with isocyanate degradation products, have been shown to inhibit the polymerization of purified brain tubulin in a dose-dependent manner (Brodie et al., 1980). If appreciable amounts of isocyanate were not formed because of intramolecular carbamylation (chlorozotocin and *cis*-2-OH CCNU) this polymerization was not inhibited.

Moreover, 2-chloroethyl isocyanate and cyclohexyl isocyanate, breakdown products of BCNU and CCNU, have been shown to inhibit DNA synthesis (Wheeler and Bowdon, 1968) and the former markedly inhibited the repair of single-strand breaks (Kann et al., 1974) by acting specifically at the ligase step (Fornace et al., 1978).

Benomyl in solution is spontaneously converted into methyl 2-benzimidazolecarbamate (MBC), the major fungicidal compound, and butyl isocyanate (Chiba and Doornbos, 1974; Calmon and Sayag, 1976) which is an irreversible inhibitor of cholinesterase (Krupka, 1974). Recently, Köller et al. (1982) have shown that cutinase purified from *Fusarium solari* f. sp. pisi was effectively inhibited by benomyl. This irreversible inhibition has been attributed to the reaction of butyl isocyanate with the active serine of the enzyme.

Overall, these results show the high reactivity and specificity of isocyanates for enzymatic systems. In consequence, the *m*-tolyl isocyanate, breakdown product of phenmedipham, may lead to carbamylation reactions in biochemical systems during its metabolism in plants and animals.

Note Added in Proof. After this manuscript was submitted for publication, the irreversible and selective inactivation of serine proteases (PPE and HLE) by some amino acid derived azolides, that are actually isocyanate precursors, was reported: Groutas, W. C.; et al. *J. Med. Chem.* **1985**, *28*, 204.

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Registry No. 1, 13684-63-4; 2, 20222-51-9; 3, 20222-52-0; p-$MeC_6H_4NHCO_2C_6H_4$(3-$NHCO_2Me$), 13684-46-3; *m*-

$MeC_6H_4NHCO_2C_6H_4(3\text{-}NHCO_2Me)$, 13684-63-4; $C_6H_5NHCO_2C_6H_4(3\text{-}NHCO_2Me)$, 19961-72-9; *p*-$ClC_6H_4NHCO_2C_6H_4(3\text{-}NHCO_2Me)$, 13684-02-1; *m*-$CF_3C_6H_4NHCO_2C_6H_4(3\text{-}NHCO_2Me)$, 23198-98-3; *m,p*-$Cl_2C_6H_3NHCO_2C_6H_4(3\text{-}NHCO_2Me)$, 13684-68-9; *p*-$No_2C_6H_4NHCO_2C_6H_4(3\text{-}NHCO_2Me)$, 17184-56-4; 3-$MeC_6H_4NHCO_2C_6H_4NO_2$-*p*, 96445-16-8; 3-$MeC_6H_4NHCO_2C_6H_4Ac$-*p*, 96445-17-9; 3-$MeC_6H_4NHCO_2C_6H_4Ac$-*m*, 96445-18-0; 3-$MeC_6H_4NHCO_2C_6H_4Cl$-*p*, 96445-19-1; 3-$MeC_6H_4NHCO_2C_6H_4Cl$-*m*, 96445-20-4; 3-$MeC_6H_4NHCO_2C_6H_5$, 33275-27-3; 3-$MeC_6H_4NHCO_2C_6H_4OMe$-*p*, 96445-21-5; 3-$MeC_6H_4NHCO_2CH_2CF_3$, 96445-22-6; 3-$MeC_6H_4NHCO_2CH_2CH_2OCH$, 96445-23-7; 3-$MeC_6H_4NHCO_2CH_3$, 39076-18-1; *p*-$MeOC_6H_4NHCO_2Me$, 14803-72-6; *p*-$MeC_6H_4NHCO_2Me$, 5602-96-0; $C_6H_5NHCO_2Me$, 2603-10-3; *p*-$ClC_6H_4NHCO_2Me$, 940-36-3; *m*-$ClC_6H_4NHCO_2Me$, 2150-88-1; *m*-$CF_3C_6H_4NHCO_2Me$, 18584-93-5; *m,p*-$Cl_2C_6H_3NHCO_2Me$, 1918-18-9; *m*-$NO_2C_6H_4NHCO_2Me$, 2189-61-9; *m*-$O^-C_6H_4NHCO_2Me$, 96445-24-8; *m*-$HOC_6H_4NHCO_2Me$, 13683-89-1; *m*-tolyl isocyanate, 621-29-4.

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