Kinetics and Mechanism of Hydrolysis of Insecticidal *O*-(Methylcarbamoyl)oximes

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The hydrolysis of various insecticidal benzaldoxime and acetophenoxime carbamates was investigated for hydroxide ion concentrations ranging from 0.01 to 5.0 N at 25 °C. The reactions were found to be first order with respect to both hydroxide ion and the ester. The data suggest the involvement of an E1cB elimination mechanism with formation of an isocyanate intermediate. The Hammett ρ values were different from those usually reported for such a reaction scheme since the imine bond weakens the substituent effects.

Interest in oxime carbamates originated from the outstanding anticholinesterase activity exhibited by such compounds as 2-methyl-2-(methylthio)propionaldehyde *O*-(methylcarbamoyl)oxime (aldicarb), 1-(methylthio)-acetaldehyde *O*-(methylcarbamoyl)oxime (methomyl), and 3,3-dimethyl-1-(methylthio)-2-butanone *O*-(methylaminocarbonyl)oxime (thiofanox).

The alkaline hydrolysis of oxime carbamates leads to the oxime as the major final product (Payne et al., 1966; Fukuto et al., 1969; Jones et al., 1972). As *N*-methylcarbamates have a labile proton on the atom α to the carbonyl group, their hydrolysis mechanism depends on the reactivity of the carbanion obtained through proton abstraction:

$$CH_3NHCOOR \underset{K_a}{\rightleftharpoons} CH_3\bar{N}COOR + H^+$$

If the anion is unreactive, slow hydroxide ion addition on the neutral species of the substrate gives rise to a tetrahedral intermediate ($B_{AC}2$ mechanism):

$$CH_3NHCOR \underset{}{\overset{k_2(OH^-)}{\rightleftharpoons}} CH_3NH\underset{\bar{O}}{\overset{OH}{C}}OR \rightarrow CH_3NHCOOH + \bar{O}R$$

A reactive anion can undergo a unimolecular elimination process involving the formation of an isocyanate intermediate (E1cB mechanism):

$$CH_3\bar{N}COOR \rightarrow CH_3NCO + \bar{O}R$$

Isocyanates are very reactive toward nucleophilic groups and are therefore very difficult to isolate and characterize:

$$CH_3NCO + H_2O \xrightarrow{\text{fast}} CH_3NHCOOH \xrightarrow{\text{fast}} CH_3NH_2 + CO_2$$

However, Sartoré et al. (1977) could isolate this intermediate in the case of phenyl *N*-phenylthionocarbamates as phenyl isothiocyanates are more stable than phenyl isocyanates. The involvement of an E1cB mechanism in the hydrolysis of phenyl *N*-methylcarbamates had been suggested by various authors (Dittert and Higuchi, 1963; Vontor and Vecera, 1973; Fujita et al., 1974). Williams (1973) used physicochemical parameters to characterize $B_{Ac}2$ and E1cB mechanisms: *N*-methyl-*N*-phenylcarbamates, in contrast to *N*-phenylcarbamates, cannot hydrolyze via an E1cB pathway since they have no labile hydrogen. The use of the same parameters allowed the mechanism of hydrolysis of *N*-acetylcarbamates to be discussed (Bergon and Calmon, 1976). Nevertheless, the occurrence of a labile hydrogen on the nitrogen atom α to the carbonyl group is not a sufficient condition for the involvement of an E1cB mechanism. As a matter of fact, the leaving group is of major importance, both qualitatively and quantitatively, in the reactions of esters via an E1cB mechanism (Pratt and Bruice, 1970).

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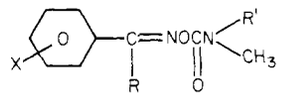
Table I. Melting Points (°C) of Oxime Carbamates $XC_6H_4C(R)$:NOCONHCH$_3$ and Their Oximes



	R	R'	X	carbamate mp obsd, °C	carbamate mp lit, °C	oxime mp obsd, °C	oxime mp lit, °C
1	H	H	H	89	89–90	35	35
2	H	H	*p*-iPr	94–5	93–5	50–4	52
3	H	H	*p*-Br	142–4	141–4	110	111
4	H	H	*m*-NO_2	168–9	162–3	122	122
5	H	H	*p*-NO_2	180–2	162–4	130	129–33
6	Me	H	H	97	93–7	58–9	59
7	Me	H	*p*-Me	104–5	100–4	88	86–8
8	Me	H	*m*-MeO	97	92–5	50	44–5
9	Me	H	*p*-Br	132–4	130–4	130	127–9
10	Me	H	*m*-NO_2	169	165–8	138	131–2
11	Me	H	*p*-NO_2	190	188–90	172	172–4
12	H	Me	H	135		35	35
13	Me	Me	H	79–81		58–9	59

The investigations reported in this paper were carried out on *O*-(methylcarbamoyl)oximes, $XC_6H_4C(R)$=NOCON(R')CH_3, to elucidate their mechanism of hydrolysis and to compare them with phenyl esters. The data obtained will be used later on in structure–activity relationships and the correlation between the mechanisms of alkaline hydrolysis and acetylcholinesterase inhibition will then be discussed.

EXPERIMENTAL SECTION

Synthesis and Structure of *O*-(Methylcarbamoyl)oximes. Benzaldoximes, acetophenoxime, and the corresponding *N*-methylcarbamates were synthesized according to the procedures used by Jones et al. (1972) and Fukuto et al. (1969), respectively. However, a different method (Schlittler and Müller, 1948) was used for *m*-methoxyacetophenoxime. The melting points of the various derivatives investigated are listed in Table I.

The syn configuration of benzaldoximes was checked by IR spectroscopy, using the data of Palm and Werbin (1953, 1954), particularly the stretching vibration frequencies (ν_{OH} 3250 cm^{-1}), as well as by NMR spectroscopy: the signal at lower field for –CH=N– was observed at 8.1 ppm (Lustig, 1961). The NMR spectra of *O*-(methylcarbamoyl)oximes exhibited the same characteristics of the syn structure as those of the corresponding oximes (δ 8.5).

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Synthesis of *O*-(Dimethylcarbamoyl)oximes. The oxime (0.02 M) dissolved in 40 mL of anhydrous ether was converted into its sodium salt after addition of 1 mL of a toluene solution of $NaNH_2$ (50%). After continuous shaking for 5 h, the solid product was washed with ether until the excess of amide was removed. The sodium oximate formed was resuspended in 40 mL of anhydrous ether to which were added 2.3 mL of *N,N*-dimethylcarbamoyl chloride and 1 mL of triethylamine (catalyst). The mixture was refluxed for 24 h. *O*-(Dimethylcarbamoyl)benzaldoximes were recrystallized from an ether–petroleum ether mixture and *O*-(dimethylcarbamoyl) acetophenoximes from a benzene–hexane mixture.

Determination of the Rate Constants. The reaction progress was followed by measuring the increase in absorbance of the oxime released at the wavelength for which the absorbance difference between the carbamate and the oxime was the highest. The carbamate dissolved in ethanol was introduced in the reaction medium by means of a microsyringe; the final concentration of ethanol in the aqueous solution was 1%. For the slowest rates ($k_{obsd} < 0.1$ s^{-1}), a Unicam Model SP 800 spectrophotometer, equipped with a thermostated multiple cell compartment, was used. A Durrum-Gibson Model D-110 spectrophotometer, equipped with a Gould Advance OS-4000 Digital storage oscilloscope, allowed the fastest hydrolyses ($k_{obsd} > 0.1$ s^{-1}) to be followed. As the measurements were carried out in strongly alkaline solutions, calibrated syringes with a 1:10 volume ratio were preferred to the standard 1:1 syringes. This procedure allowed lower initial concentrations of sodium hydroxide: the heat released during dilution was thus kept to a minimum and any cloudiness which might have disturbed the measurements could be avoided.

All reactions were carried out at 25 ± 0.1 °C (unless otherwise specified). The initial carbamate concentration was 10^{-4} mol/L. 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 from the following equation: $\log (A_\infty - A_t) = \log A_\infty - (k_{obsd}/2.303)t$, where A_∞ and A_t are the absorbance readings at infinity and at time t, respectively.

Entropy of Activation. The entropies of activation $\Delta S^\ddagger$ were obtained from the equation $\Delta S^\ddagger = 2.303R(\log k_{obsd} - \log T - \log eK/h) + E_o/T$ and regression lines from a weighted least-squares program written for the Hewlett-Packard HP 2921.

RESULTS

Characterization of the Final Product. Repetitive scans of the UV region established that the hydrolyses were characterized by tight isosbestic points, indicating the absence of intermediates. The UV spectra recorded at the completion of the hydrolyses of *O*-(methylcarbamoyl)-oximes at all pH values were identical with the spectra of authentic samples of the corresponding oximes, run at the same concentration and under the same conditions. Therefore, bond cleavage does occur at the level of the ester function and not of the imine bond.

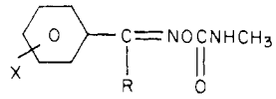
Effect of pH. The rate constants k_{obsd} for the alkaline hydrolysis of *O*-(methylcarbamoyl)oximes were measured for hydroxide ion concentrations ranging from 0.01 to 5.0 N (Table II). Figure 1 shows a plot of the logarithms of the observed pseudo-first-order rate constants k_{obsd} against H_- for the hydrolysis of oxime carbamate **5**. (H_- is the acidity function of Hammett; $H_- = -\log h_-$ with $h_- = a_H\gamma_A^-/\gamma_{AH}$). This H_-–rate profile shows two distinct regions: a straight line of slope unity (in agreement with a first-order reaction rate with respect to hydroxide ion),

Table II. Pseudo-First-Order Rate Constants k_{obsd} (s^{-1}) for the Alkaline Hydrolysis of Oxime Carbamates 1 and 11 at 25 °C

	[OH⁻]	0.01[a]	0.05[a]	0.10[a]	0.50[a]	1.00	1.50	2.00	2.50	3.00	4.00	5.00
	H_-[b]	12.10	12.71	13.00	13.71	14.02	14.20	14.37	14.54	14.65	14.95	15.20
1		6.20×10^{-4}	3.10×10^{-3}	6.69×10^{-3}	4.11×10^{-2}	8.89×10^{-2}	0.13	0.20	0.315	0.41	0.71	1.18
2		4.37×10^{-4}	2.12×10^{-3}	5.02×10^{-3}	2.56×10^{-2}	5.82×10^{-2}	9.14×10^{-2}	0.14	0.20	0.31	0.55	
3		1.08×10^{-3}	5.90×10^{-3}	1.09×10^{-2}	6.77×10^{-2}	0.13	0.19	0.29	0.44	0.59	1.04	1.66
4		2.92×10^{-3}		3.33×10^{-2}	0.17	0.34	0.57	0.75	1.02	1.26	1.64	2.09
5		5.46×10^{-3}	3.15×10^{-2}	6.26×10^{-2}	0.35	0.81	1.23	1.57	1.62	1.84	2.185	2.26
6		6.99×10^{-5}	3.60×10^{-4}	7.52×10^{-4}	4.02×10^{-3}	8.98×10^{-3}	1.48×10^{-2}	2.48×10^{-2}	4.08×10^{-2}	4.29×10^{-2}	8.54×10^{-2}	0.16
7		5.86×10^{-5}	3.01×10^{-4}	6.14×10^{-4}	3.18×10^{-3}	7.30×10^{-3}	9.98×10^{-3}	1.70×10^{-2}	2.86×10^{-2}	3.15×10^{-2}	5.65×10^{-2}	9.51×10^{-2}
8		1.00×10^{-4}	5.45×10^{-4}	1.09×10^{-3}	5.66×10^{-3}	1.27×10^{-2}	2.10×10^{-2}	3.16×10^{-2}	5.30×10^{-2}	5.63×10^{-2}	0.11	0.175
9		1.24×10^{-4}	6.86×10^{-4}	1.42×10^{-2}	7.40×10^{-3}	1.75×10^{-2}	2.73×10^{-2}	4.34×10^{-2}	6.71×10^{-2}	9.23×10^{-2}	0.205	0.27
10		3.36×10^{-4}	1.71×10^{-3}	3.51×10^{-3}	1.87×10^{-2}	4.28×10^{-2}	6.60×10^{-2}	0.11	0.16	0.235	0.465	0.66
11		4.94×10^{-4}	2.56×10^{-3}	5.23×10^{-3}	2.79×10^{-2}	6.42×10^{-2}	9.80×10^{-2}	0.16	0.23	0.34	0.61	1.02

[a] μ 1.0, KCl. [b] Coussemant et al. (1969).

Table III. Bimolecular Rate Constants k_{OH} ($l\ mol^{-1}\ s^{-1}$) for *O*-(Methylcarbamoyl)oximes $XC_6H_4C(R)$:NOCONHCH$_3$ at 25 °C (μ 1.0, KCl)



	X						
	p-NO_2	*m*-NO_2	*p*-Br	*m*-MeO	H	*p*-Me	*p*-iPr
σ[a]	0.780	0.710	0.232	0.115	0	−0.170	−0.150
benzaldoximes	0.780	0.345	0.127		0.0882		0.0552
acetophenoxymes	0.0562	0.0377	0.0186	0.00115	0.080	0.0064	

[a] McDaniel and Brown (1958).

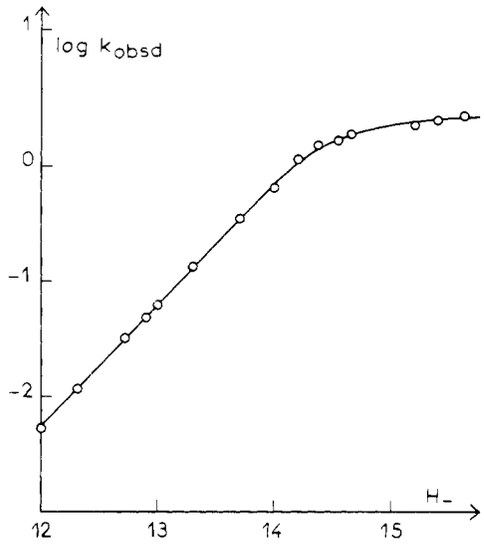


Figure 1. Plot of the logarithms of the observed rate constants k_{obsd} vs. H_- for the hydrolysis of *p*-$NO_2C_6H_4CH$:NOCONHCH$_3$ at 25 °C (μ 1.0, KCl, when [OH^-] <1.0 N).

followed by a plateau at higher values of H_- ($H_- > 14$). The shape of this profile suggests the ionization of the substrate.

Effect of the Leaving Group. This investigation was carried out over the H_- range where the rate constant is proportional to the hydroxide ion concentration (Figure 1: straight line of slope unity). The effect of the substituents X on the hydrolysis of *O*-(methylcarbamoyl)-oximes is reflected upon the bimolecular rate constant $k_{OH} = k_{obsd}/[OH^-]$ which can be used in two kinds of correlations.

1. The k_{OH} values (Table III) led to the following Hammett relationships. For *O*-(methylcarbamoyl)benzaldoximes (R = H):

$$\log k_{OH} = 1.09\sigma - 1.10 \qquad n = 5,\ r = 0.975,\ s = 0.118$$

where n is the number of compounds, r the correlation coefficient, and s is the standard deviation.

This correlation was improved when σ^- (instead of σ) was used for the *p*-nitro derivative:

$$\log k_{OH} = 0.82\sigma^- - 1.09 \qquad n = 5,\ r = 0.996,\ s = 0.045$$

For *O*-(methylcarbamoyl)acetophenoxymes:

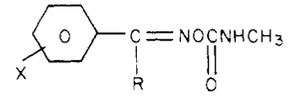
$$\log k_{OH} = 0.96\sigma - 2.04 \qquad n = 6,\ r = 0.988,\ s = 0.063$$

2. The bimolecular rate constants also fitted a Bronsted relationship when the pK_a values of the leaving groups were employed: $\log k_{OH} = \beta pK_a + k';\ \beta = -1.32$ (Table IV).

Effect of Temperature. Entropy of Activation. The hydrolyses of four derivatives were investigated in 0.1 N (1) or 1.0 N (**6**, **12**, **13**) sodium hydroxide at three different temperatures (15, 25, and 35 °C) (Table V). The synthesis of *O*-(dimethylcarbamoyl)oximes **12** and **13**, which hydrolyze via a $B_{Ac}2$ pathway, allowed the value of the entropy of activation to be assessed for such a reaction scheme.

Deuterium Oxide Solvent Isotope Effects. The isotope effects for the hydrolyses of four derivatives (**1**, **6**, **12**, **13**) were measured in 1.0 N sodium hydroxide solutions (Table VI).

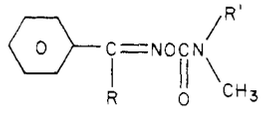
Table IV. pK_a Values of the Leaving Group and Logarithms of the Bimolecular Rate Constants k_{OH} for Oxime Carbamates $XC_6H_4C(R)$:NOCONHCH$_3$ at 25 °C (μ 1.0, KCl).



	R	X	$\log k_{OH}$	pK_a
1	H	H	−1.054	10.68[a]
4	H	*m*-NO_2	−0.462	10.15[a]
5	H	*p*-NO_2	−0.108	9.97[a]
6	Me	H	−2.096	11.48[b]

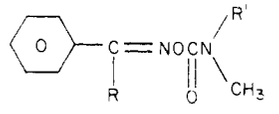
[a] Brady and Goldstein (1926). [b] Bell and Higginson (1949).

Table V. Pseudo-First-Order Rate Constants k_{obsd} (s^{-1}) at Various Temperatures and Entropies of Activation $\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1}) for the Alkaline Hydrolysis of Oxime Carbamates $C_6H_5C(R)$:NOCON(R')CH$_3$ (μ 1.0, KCl)



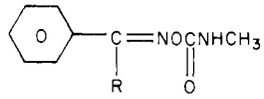
	R	R'	35 °C	25 °C	15 °C	$\Delta S^{\ddagger}$
1	H	H	1.82×10^{-2}	6.69×10^{-3}	1.89×10^{-3}	0
6	Me	H	2.57×10^{-2}	8.98×10^{-3}	2.60×10^{-3}	0.8
12	H	Me	4.02×10^{-3}	1.32×10^{-3}	4.54×10^{-4}	−8.5
13	Me	Me	6.46×10^{-4}	2.92×10^{-4}	1.32×10^{-4}	−29.7

Table VI. Pseudo-First-Order Rate Constants k_{obsd} (s^{-1}) for the Hydrolysis of Oxime Carbamates $XC_6H_4C(R)$:NOCONR'CH$_3$ in 1.0 N NaOH and NaOD Solutions at 25 °C



	R	R'	$k_{obsd}(H_2O)$	$k_{obsd}(D_2O)$	k_{H_2O}/k_{D_2O}
1	H	H	8.89×10^{-2}	0.125	0.71
6	Me	H	8.99×10^{-3}	1.42×10^{-2}	0.63
12	H	Me	1.32×10^{-3}	2.05×10^{-3}	0.64
13	Me	Me	2.92×10^{-4}	4.45×10^{-4}	0.66

Table VII. Effect of Triethylamine Buffer Concentration on the Observed Rate Constants k_{obsd} (s^{-1}) for the Hydrolysis of Oxime Carbamates $C_6H_5C(R)$:NOCONHCH$_3$ at 25 °C (μ 1.0, KCl)



R	[B],[a] mol l^{-1} 0.050	0.075	0.100	0.125	0.150	0.200	[B]/[BH$^+$]	pH
H	1.99×10^{-4}		2.03×10^{-4}		1.95×10^{-5}	1.88×10^{-4}	2.0	11.40
	1.05×10^{-4}		1.00×10^{-4}		9.65×10^{-5}	9.04×10^{-5}	1.0	11.09
	4.60×10^{-5}		4.60×10^{-5}		3.99×10^{-5}	3.85×10^{-5}	0.5	10.80
Me	1.05×10^{-5}	1.09×10^{-5}	1.14×10^{-5}	1.15×10^{-5}			1.0	11.16

[a] [B] refers to the free base component of the buffer.

Effect of Buffer Concentration. Although no general base catalysis is involved in E1cB and $B_{Ac}2$ mechanisms, the investigation of the effect of buffer concentration was needed so as to discard any possibility of a mechanism subjected to such a catalysis. No catalysis could be observed in triethylamine buffers for derivatives 1 and 6: the reaction rate was independent of the buffer concentration (Table VII).

DISCUSSION

The two reaction schemes considered earlier lead to the following rate equations for the hydrolysis of *O*-(methylcarbamoyl)oximes: $k_{obsd} = k_1K_a/(a_H + K_a)$ for the E1cB mechanism, and $k_{obsd} = k_2K_w/(a_H + K_a)$ for the $B_{Ac}2$ mechanism. Therefore, k_{obsd} depends on the value of the ionization constant K_a of the substrate. These two rate laws are in agreement with the experimental data and account for the shape of the plot of log K_{obsd} against H_- (Figure 1). However, these two equations are kinetically equivalent at all pH values and cannot be used to distinguish the two pathways. Moreover, as these molecules have high pK_a values (circa 16), in mildly alkaline media the proton activity a_H satisfies the condition $a_H \gg K_a$, whence $k_{obsd} = k_1K_a[OH^-]/K_w$ (E1cB) and $k_{obsd} = k_2[OH^-]$ ($B_{Ac}2$). In both cases, the pH–rate profile is then a straight line of slope unity (Figure 1).

In strongly alkaline media ([OH$^-$] > 1.0 N), the activities of the various reacting species have to be taken into account:

$$K_a = a_{A^-}a_H/a_{AH} = \gamma_{A^-}[A^-]a_H/\gamma_{AH}[AH]$$

The acidity of the medium can then be expressed in terms of the Hammett equation $h_- = a_H\gamma_{A^-}/\gamma_{AH}$. The substrate can thus be considered as an indicator of the H_- scale. The rate laws are expressed as:

$$k_{obsd} = k_1K_a/(K_a + h_-) \qquad \text{(E1cB)}$$

and

$$k_{obsd} = \gamma_{A^-}k_2K_w/\gamma_{AH}(K_a + h_-) \qquad (B_{Ac}2)$$

when $h_- \gg K_a$, these expressions become

$$k_{obsd} = k_1K_a/h_- = \gamma_{AH}k_1K_aa_{OH^-}/\gamma_{A^-}K_w$$

and

$$k_{obsd} = \gamma_{A^-}k_2K_w/\gamma_{AH}h_- = k_2a_{OH^-}$$

The general form of these rate laws is analogous to that calculated for moderately alkaline media.

When $h_- \ll K_a$, the observed rate constants become pH independent and the H_-–rate profile exhibits a plateau:

$$k_{obsd} = k_1K_a/K_a = k_1 \qquad \text{(E1cB)}$$

and

$$k_{obsd} = \gamma_{A^-}k_2K_w/\gamma_{AH}K_a \qquad (B_{Ac}2)$$

In order to distinguish between these two reaction mechanisms, it is necessary to call upon physicochemical parameters such as electronic effects, entropies of activation, and isotope effects.

1. The Hammett ρ value obtained for change of substituent on the leaving group of *O*-(methylcarbamoyl)-oximes is close to unity and might therefore be assigned to a $B_{Ac}2$ mechanism since such a value was observed for the alkaline hydrolysis of substituted phenylacetates (Tommila et al., 1938). This ρ value is quite different from those usually found for an E1cB mechanism: for instance, Fujita et al. (1974) reported a ρ value of 2.7 for phenyl *N*-methylcarbamates. Such a high value reflects a higher degree of C–OC$_6$H$_4$X bond cleavage in the transition state where the structure of the phenyl moiety is close to that of the phenolate ion. Likewise, if the hydrolysis of *O*-(methylcarbamoyl)oximes is assumed to proceed via an E1cB mechanism, the structure of the leaving group in the transition state should be close to that of the oximate ion. The substituent effect on ionization is known to be 2.2 for phenols, whereas it is only 0.86 for benzaldoximes (Jaffe, 1953). The electronic effect is then weakened by the interposition of the C=N bond between the phenyl ring and the reaction center. This decrease in the substituent effect can be assessed by means of an attenuation ratio τ = 0.86/2.2 = 0.4. A theoretical ρ value for *O*-(methylcarbamoyl)oximes can thus be calculated from the ρ value observed for phenyl *N*-methylcarbamates: 2.7 × 0.4 = 1.2. As a matter of fact, Hladka et al. (1977) found a ρ value of 1.4 for an E1cB reaction scheme in the case of the hydrolysis of *O*-(*N*-4-nitrophenylcarbamoyl)benzaldoximes. Therefore, a ρ value near unity is not necessarily inconsistent with an E1cB mechanism.

For *O*-(methylcarbamoyl)benzaldoximes, the oximate character of the leaving group is further corroborated by the value of the correlation coefficient which is higher when σ^- is used instead of σ. However, for *O*-(methylcarbamoyl)acetophenoximes, the occurrence of a methyl group α to the imine bond does not result in a better regression when σ^- is used instead of σ and leads to a slightly different ρ value.

2. The Bronsted β coefficient of −1.32 is close to that reported by Williams and Douglas (1973) for *N*-phenylcarbamates PhNHCOOC$_6$H$_4$X which hydrolyze via an E1cB mechanism (β = −1.34). According to him, such a Bronsted coefficient is too large to account for a mechanism where simple C–O bond breaking would occur, as in a $B_{Ac}2$ scheme (β = −0.25 for *N*-methyl-*N*-phenylcarbamates PhN(Me)COOC$_6$H$_4$X). The β value found for *O*-(methylcarbamoyl)oximes is therefore an important argument favoring an E1cB mechanism. Moreover, it can be pointed out that, since this parameter is actually the ratio of two ρ values, $\beta = \rho_{k_{OH}}/\rho_{pK_a}$, it is thus independent from the attenuation coefficient τ.

3. The values found for the entropy of activation of O-(methylcarbamoyl)oximes are close to zero whereas those of the N,N-dimethyl derivatives are markedly negative. Entropy values lying between −20 and −35 cal deg^{-1} mol^{-1} have been reported in the literature for $B_{Ac}2$ mechanisms (Christenson, 1964; Sartoré et al., 1977; Bergon and Calmon, 1976). Such values are interpreted in terms of the formation of a relatively hindered tetrahedral intermediate in the transition state and of a decrease in the degrees of freedom of hydroxide ion. For E1cB mechanisms, the values of $\Delta S^{\ddagger}$ are generally positive and near zero, as shown by the previously mentioned authors. The values obtained for O-(methylcarbamoyl)oximes were measured over a pH range where the value of k_{obsd} is composite for the E1cB mechanism ($k_{obsd} = k_1K_a\,[OH^-]/K_w$) the observed entropy is therefore the sum of three individual contributions which can compensate each other.

4. Although the values of $k_{obsd}(H_2O)/k_{obsd}(D_2O)$ obtained for the solvent isotope effect are of the same order of magnitude for the four derivatives investigated (Table VI), this does not mean that the isotope effect is of the same kind in every case. As a matter of fact, the values observed for the N,N-dimethyl derivatives are consistent with those reported for reactions where hydroxide ion attack at a carbonyl group is rate determining. Thus, Gani and Viout (1976) measured an isotope effect of 0.69 for N-methyl-p-nitroacetanilides.

For E1cB mechanisms, when $a_H \gg K_a$, the isotope effect is composite, representing three individual contributions:

$$k_{obsd}(H_2O)/k_{obsd}(D_2O) = \frac{k_1(H_2O)K_a(H_2O)K_w(D_2O)}{k_1(D_2O)K_a(D_2O)K_w(H_2O)}$$

Each isotope effect can be evaluated: $k_1(H_2O)/k_1(D_2O) = 1$, since there is no isotope effect on the breakdown of the anion; $K_a(H_2O)/K_a(D_2O) = 5.4$ was determined from Bell's equation $\Delta pK = 0.41 + 0.020\ pK_H$ (Laughton and Robertson, 1969), assuming that the pK_a values of O-methylcarbamoyl)oximes are about 16; $K_w(D_2O)/K_w(H_2O) = 0.11$ was calculated from the variations of the free enthalpy of autoprotolysis (Laughton and Robertson, 1969).

The overall isotope effect is thus 0.60. Bender and Homer (1965) reported an isotope effect of 0.55 for p-nitrophenyl N-methylcarbamate which hydrolyzes via an E1cB mechanism. However, since isotope effect values are too close together, they cannot provide a decisive argument as to the reaction mechanism involved.

CONCLUSION

Although the investigation of the solvent isotope effect does not afford any decisive argument as to the mechanism involved in the alkaline hydrolysis of O-(methylcarbamoyl)oximes, the Hammett and Bronsted linear relationships as well as the entropies of activation suggest the involvement of an E1cB mechanism: oximes are therefore poorer leaving groups than phenols. The difference in the quality of the leaving group is reflected in the Hammet ρ value which is much lower than those usually reported for such a reaction mechanism. Moreover, the analogy between the mechanisms of hydrolysis of phenyl N-methylcarbamates and O-(methylcarbamoyl)-oximes suggests that their activity at the level of acetylcholinesterase might be of the same nature.

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