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ACKNOWLEDGMENTS AND ADDRESSES

Received July 25, 1973, from the *Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612*

Accepted for publication October 11, 1973.

[x] To whom inquiries should be directed.

Mechanisms of Hydrolysis of Salicylanilide *N*-Methylcarbamates

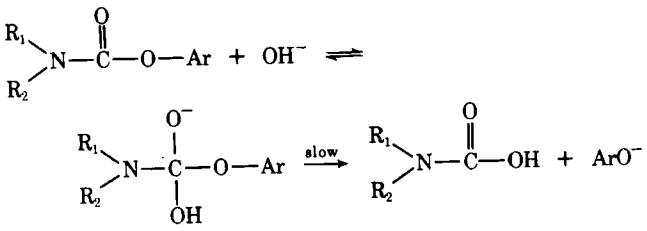
LEO W. BROWN, RICHARD S. P. HSI, and ARLINGTON A. FORIST[x]

Abstract □ The facile hydroxide-ion-catalyzed hydrolysis of the carbamoyl group in salicylanilide *N*-methylcarbamate (I) and analogs unsubstituted on the anilide nitrogen proceeds by a reaction mechanism involving anchimeric assistance by the *o*-carboxanilide group. Substitution of an alkyl or aryl group for the anilide proton greatly reduces the hydrolysis rate; the reaction rate constant for I is ~7 × 10^2 times that for *N*-methylsalicylanilide *N*-methylcarbamate (II). To characterize the mechanism for II, comparative parameters of activation were determined for I and II. The entropy of activation ($\Delta S\ddagger$) for II was 8.6 eu more negative than that for I, suggesting steric hindrance in the transition state for II. The observed reaction rate constant for II was consistent with estimates based on the electronic *ortho*-substituent effect of the carboxanilide group. It is concluded that II is hydrolyzed *via* the established mechanism for simple aryl *N*-monosubstituted carbamates (rapid proton extraction followed by a rate-determining conversion of the carbamate anion to an isocyanate) rather than by the mechanism followed by I.

Keyphrases □ Salicylanilide *N*-methylcarbamates—mechanisms of hydrolysis □ Hydrolysis mechanisms—salicylanilide *N*-methylcarbamates □ Carbamoyl group hydrolysis—mechanisms of salicylanilide *N*-methylcarbamate hydrolysis

A growing body of literature (1–7) has established a duality of mechanism for the alkaline hydrolysis of aryl carbamates. In the absence of a proton on the nitrogen atom (*N,N*-disubstituted carbamates), the reaction follows Scheme I, characteristic of simple ester hydrolysis. However, for compounds containing a proton on the nitrogen atom (*N*-monosubstituted carbamates), hydrolysis occurs *via* Scheme II (the ElcB mechanism).

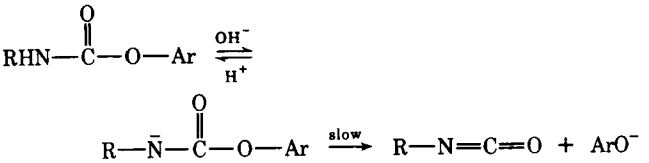
Reports from these laboratories described the kinetics of hydrolysis of a number of aryl carbamates possessing anti-inflammatory activity (8–10). Hsi *et al.* (9) showed that the extremely rapid hydroxide-ion-catalyzed hydrolysis of the carbamoyl group of



Scheme I

salicylanilide *N*-methylcarbamate (I) and a number of analogs with *para*-substituents in the phenyl ring of the anilide moiety involved participation by the neighboring *o*-carboxanilide group. Reaction rate constants, k_{OH^-}, were logarithmically related to the Hammett σ-constants (ρ = 0.46 at 37°). A special case of the mechanism shown in Scheme II, involving rapid proton extraction from the carbamate nitrogen followed by a rate-limiting intramolecular cyclization and subsequent ring opening and fragmentation, was indicated (Scheme III).

Substitution of an alkyl or aryl group for the proton on the anilide nitrogen of I produces a dramatic reduction in the carbamate hydrolysis rate (9). Reaction rate constants for *N*-methylsalicylanilide *N*-methylcarbamate (II) and *N*-phenylsalicylanilide *N*-methylcarbamate (III) are nearly identical and only about 15 times that for phenyl *N*-methylcarbamate



Scheme II

Table I—Reaction Conditions and Kinetic Constants for Carbamate Hydrolysis in 50% Aqueous Ethanol

Compound	Concentration, $M \times 10^5$	Apparent pH	Temperature	$k_{OH^-} \pm SD$, M^{-1} min^{-1}
I	9.26	5.4	30°	$1.29 \pm 0.01 \times 10^5$
	9.26	5.4	37°	$1.97 \pm 0.02 \times 10^5$
	8.60	5.4	47°	$4.48 \pm 0.02 \times 10^5$
II	21.9	8.6	30°	$1.82 \pm 0.01 \times 10^2$
	19.2	8.6	37°	$3.05 \pm 0.01 \times 10^2$
	18.9	8.6	47°	$7.15 \pm 0.05 \times 10^2$
III[a]	10.4	8.6	37°	$2.89 \pm 0.03 \times 10^2$
IV[a]	42.3	10.2	37°	$1.90 \pm 0.01 \times 10^1$

[a] Reference 9.

(IV) (37°, 50% aqueous ethanol). By contrast, I is hydrolyzed at a rate 10^4 times that for IV. Hydrolysis of II (and III) predominantly *via* Scheme II is suggested by these results.

Limited studies to date indicate that the entropy of activation ($\Delta S\ddagger$) for Scheme II is considerably more positive than that for Scheme I (2, 6). Parameters of activation have not been reported for the *o*-carboxanilide-assisted carbamate hydrolysis (9) or for the more recently described intramolecular nucleophilic attack on carbamates by the phenoxide ion (11) and the carboxylate ion (12). Therefore, to provide such information for Scheme III and to clarify the reaction mechanism for II, comparative parameters of activation for the hydrolysis of I and II were determined and are reported, together with estimated rate constants for nonanchimerically assisted hydrolysis based on electronic substituent effects.

EXPERIMENTAL

Solutions of I and II were prepared in 50% aqueous ethanolic acetate and phosphate (0.025 *M*) buffers, respectively, at the concentrations and apparent pH values shown in Table I. Each solution was placed in a UV spectrophotometer equipped with a constant-temperature cell compartment maintained at the temperatures indicated in Table I. Absorbances (A_t) were determined at appropriate times at the absorption maximum of the product phenols (300 and 285 nm for I and II, respectively) until no further absorbance increases occurred (A_∞). Pseudo-first-order reaction rate constants (k') were obtained from the slopes of log ($A_\infty - A_t$) *versus* time curves fitted by linear least-squares regression analysis. Based on the previously established fact that the hydrolysis of I, II, and other aryl carbamates displays first-order dependence on the hydroxide ion (8–10), specific reaction rate constants (k_{OH^-}) were calculated from the equation:

$$\log k' = \log k_{OH^-} + \text{pH} - \text{pKw} \qquad \text{(Eq. 1)}$$

Activation energies (ΔE_a) were determined from the classical Arrhenius equation by linear least-squares regression; $\Delta H\ddagger$ and $\Delta S\ddagger$ were determined similarly from the absolute reaction rate equation.

RESULTS AND DISCUSSION

Specific reaction rate constants (k_{OH^-}) for hydrolysis of the carbamoyl groups in I and II in 50% aqueous ethanol are shown in Table I; similar data for III and IV from previous work (9) are included for comparison. Derived parameters of activation for I and II are presented in Table II. Activation energies (ΔE_a) and enthalpies of activation ($\Delta H\ddagger$) are not significantly different for the two compounds. Vontor *et al.* (6) observed a ΔE_a value of 16.5 kcal mole^{-1} for the alkaline hydrolysis of 1-naphthyl *N*-methylcarbamate in aqueous solution; Christenson (2) reported a $\Delta H\ddagger$ value of 16.6 kcal mole^{-1} for phenyl *N*-phenylcarbamate hydrolysis in 5–10% ethanol. The corresponding parameters for I and II are slightly less, but direct comparisons are complicated by the different solvents employed. In studies (13) of the alkaline hydrolysis of formate esters, $\Delta H\ddagger$ in water was significantly smaller than in 85% ethanol. By analogy, predicted ΔE_a and $\Delta H\ddagger$ values for the hydrolysis of I and II in aqueous solution would be significantly smaller than the values observed in 50% ethanol and, hence, less than those reported for other aryl carbamates in aqueous solution.

Table II—Activation Parameters for the Hydrolysis of I and II in 50% Aqueous Ethanol

Parameter	I	II
ΔE_a (kcal mole^{-1})	14.2 ± 1.3	15.6 ± 0.8
$\Delta H^\ddagger$ (kcal mole^{-1})	13.6 ± 1.3	15.0 ± 0.8
$\Delta S^\ddagger$ (eu)	1.6 ± 4.3	−7.0 ± 2.7

Entropies of activation ($\Delta S\ddagger$) of 0.6 and 5.0 eu were reported for the hydrolysis of 1-naphthyl *N*-methylcarbamate (6) and phenyl *N*-phenylcarbamate (2), respectively, consistent with expectations for the mechanism shown in Scheme II (14). The value of $\Delta S\ddagger$ for I, 1.6 eu, is intermediate in magnitude and indicates that its facile hydrolysis *via* Scheme III is not the consequence of a more favorable $\Delta S\ddagger$ but rather of a reduced $\Delta H\ddagger$.

The value of $\Delta S\ddagger$ for the hydrolysis of II, −7.0 eu, is considerably more negative than for I. In addition, it is the most negative of those cited from the literature as well as those found in these laboratories[1] for various aryl *N*-methylcarbamates hydrolyzed *via* Scheme II. The $\Delta S\ddagger$ alone does not provide unequivocal proof of mechanism. However, considered with other evidence (*vide infra*), the observed negative $\Delta S\ddagger$ is consistent with steric hindrance in the transition state (14, 15) and hydrolysis of II *via* Scheme II.

For hydrolysis of II by Scheme II, it should be possible to relate k_{OH^-} to the electronic substituent effect of the *ortho*-substituted phenyl *N*-methylcarbamate. Williams (7) correlated hydrolysis rate constants for *para*- and *meta*-substituted phenyl *N*-phenylcarbamates with Hammett σ (or σ^-) constants and obtained ρ =

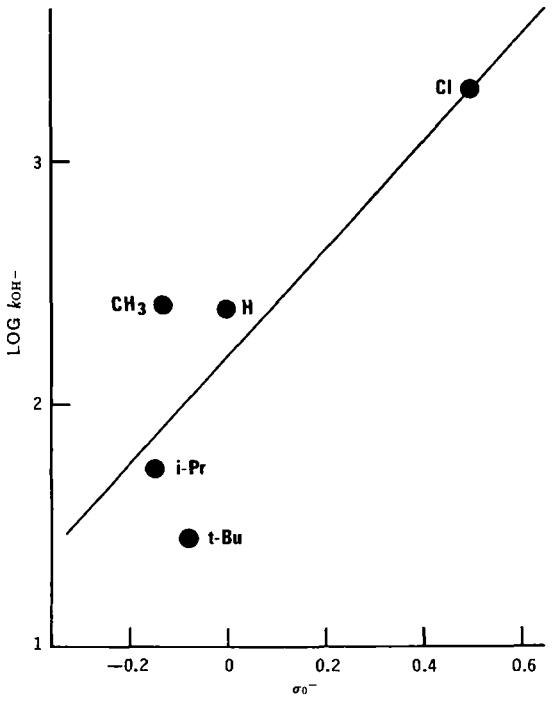
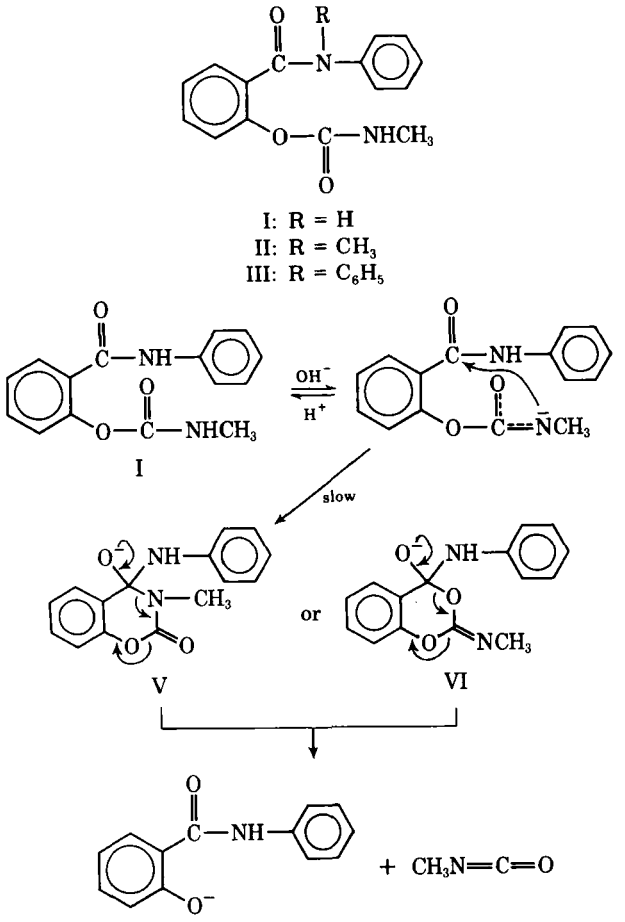


Figure 1—*Linear least-squares regression of log* k_{OH^-} *for the hydrolysis of* o*-substituted phenyl* N*-methylcarbamates (37.5°, aqueous solution) (17) versus* σ_0^- *(16).*

[1] Unpublished results.



Scheme III

2.86. No similar study of *ortho*-substituent effects has been reported.

The *ortho*-substituent constants (σ_o-) for a large number of functional groups were recently determined (16). Therefore, utilizing these σ_o- values and the k_{OH}- values (37.5°) reported (17) for five *ortho*-substituted phenyl *N*-methylcarbamates, a linear least-squares regression of log k_{OH}- *versus* σ_o- was obtained (Fig. 1). The fit was acceptable (r = 0.83), considering the limited number of data points, and gave a ρ value of +2.2, in reasonable agreement with that obtained by Williams (7) based on *para*- and *meta*-substituents.

With the k_{OH}- for IV hydrolysis (37°, 50% aqueous ethanol, Table I), σ_o- for the *N*-phenylcarboxamide group (0.79), and the previously determined ρ, k_{OH}- reflecting only *ortho*-substituent effects was calculated for I (and for II, assuming a similar σ_q- for the *N*-methyl-*N*-phenylcarboxamide group). The resulting value, $1.04 \times 10^3\ M^{-1}\ min^{-1}$, is markedly less than that observed for I ($1.97 \times 10^5\ M^{-1}\ min^{-1}$, Table I), as expected. However, the calculated k_{OH}- is actually larger (by a factor of 3.4) than that found for II ($3.05 \times 10^2\ M^{-1}\ min^{-1}$, Table I). In view of the inherent assumptions, this is considered quite reasonable agreement and argues strongly against anchimeric assistance (Scheme III) in the hydrolysis of II. Apparently, the presence of a methyl (II) or phenyl (III) group on the anilide nitrogen exerts sufficient steric influence to preclude formation of the cyclic intermediate of Scheme III. This is supported by the negative $\Delta S^{\ddagger}$ for II.

In Scheme III, V is considered the more likely intermediate by analogy to the cyclization of salicylaldehyde *N*-methylcarbamate to yield 3,4-dihydro-4-hydroxy-3-methyl-2*H*-1,3-benzoxazin-2-one (18). This intermediate is also consistent with the results (19) on intramolecular reactions involving ureido group participation.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 18, 1973, from the *Research Laboratories, The Upjohn Company, Kalamazoo, MI 49001*

Accepted for publication October 30, 1973.

[x] To whom inquiries should be directed.