Rates of Hydrolysis of Carbamate and Carbonate Esters in Alkaline Solution

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The rate of the alkaline hydrolysis of several aliphatic and aromatic carbamate and and carbonate esters was studied at various temperatures. The reactions were found to be first order with respect to both hydroxyl ion and the ester. The data seemed to indicate two mechanisms for the hydrolysis of the carbamates: that initiated by an hydroxyl ion attachment on the central carbon atom followed by a carbamate ion intermediate, and that involving direct ionization of an amide hydrogen followed by formation of an isocyanate intermediate. Since the latter mechanism appears to proceed with much greater ease for carbamates of strongly electrophilic alcohols, the N-unsubstituted and N-monosubstituted carbamates of these compounds undergo cleavage at rates several orders of magnitude greater than those of the corresponding disubstituted carbamates.

A LTHOUGH several drugs are marketed which contain the carbamate ester linkage, e.g., physostigmine, neostigmine, carbachol, etc., no exhaustive kinetic or mechanistic study on the general stability of this linkage toward alkaline hydrolysis appears to have been carried out. The specific stability of physostigmine in solution has, however, been the object of many qualitative investigations (1–6). Ellis and his co-workers (7) in a quantitative study showed that the destruction of physostigmine in aqueous solution was first order in hydroxyl ions and first order in physostigmine. A physostigmine analog, neostigmine methylsulfate (8), was reported by Morch (9) to be hydrolyzed in very dilute alkaline solutions under autoclave conditions, but Chaiken (10) was unable to find any decomposition of an analogous compound (a dimethylcarbamate) in pH 7.4 phosphate buffer at 38°. The results of these studies indicate that the dimethylcarbamate esters are much more stable toward alkaline hydrolysis than are the N-methylcarbamate esters.

More recently, because of their potent anticholinesterase activity, carbamates have been employed as insecticides, e.g., Sevin,[1] Isolan,[2] Pyrolan,[2] Pyramat,[2] etc. Casida and his co-workers (11) have studied the alkaline hydrolysis of these and similar compounds and have also found the dimethylcarbamate esters to be more stable than the N-methylcarbamate esters.

It has been known for many years that carbamate esters in alkaline solution hydrolyze according to

$$R\text{---}O\text{---}\overset{\overset{\displaystyle O}{\|}}{C}\text{---}NR'_2 + 2OH^- = ROH + CO_3^- + HNR'_2$$
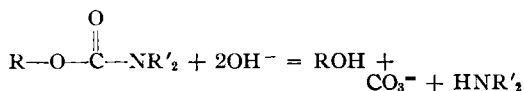
Although Werner (12), in 1918, proposed a mechanism for the destruction of urethane in aqueous alkali at 100°, no exhaustive kinetic or mechanistic study on urethane appears to have been carried out since that time.

It was the purpose of the present investigation to explore the general kinetics and mechanisms of the alkaline hydrolysis of urethane, ethyl N-methylcarbamate, ethyl dimethylcarbamate, phenyl carbamate, phenyl N-methylcarbamate, phenyl dimethylcarbamate, p-nitrophenyl carbamate, p-nitrophenyl N-methylcarbamate, p-nitrophenyl dimethylcarbamate, phenyl ethyl carbonate, and p-nitrophenyl ethyl carbonate, and to determine the effect of temperature and structure on the hydrolytic reaction.

EXPERIMENTAL

Materials

Ethyl N-Methylcarbamate and Ethyl Dimethylcarbamate.—The compounds were synthesized by the method of Schreiner (13) and purified by fractional distillation through a 30-cm. Vigreaux column. The following fractions were collected: ethyl N-methylcarbamate 167–168° (lit. 170° (13)), ethyl dimethylcarbamate 142–144° (lit. 139–140 (13)).

Phenyl N-Methylcarbamate.—The compound was synthesized by the method of Schreiner (13) and purified by repeated crystallization from 5% benzene in petroleum ether, m.p. 85-87°.

Phenyl Dimethylcarbamate and p-Nitrophenyl Dimethylcarbamate.—The compounds were synthesized by reacting dimethyl carbamyl chloride with the appropriate phenol in pyridine solution. Phenyl dimethylcarbamate was recrystallized repeatedly from petroleum ether, m.p. 44 to 45.5° (lit. 44–45° (14)). p-Nitrophenyl dimethylcarbamate was recrystallized repeatedly from ethanol, m.p. 107–109°.

Phenyl Ethyl Carbonate and p-Nitrophenyl Ethyl Carbonate.—The compounds were prepared

TABLE I.—PSEUDO FIRST-ORDER RATE CONSTANTS AND SECOND-ORDER RATE CONSTANTS FOR THE DISAPPEARANCE OF URETHANE ($k_{URETHANE}$) AND THE APPEARANCE OF CARBONATE IONS ($k_{CARBONATE}$) IN STRONGLY BASIC SOLUTIONS OF URETHANE AT 30°C.

N OH⁻	$k_{urethane}$·[OH⁻] (Hr.⁻¹)	$k_{urethane}$ (L.·Mole⁻¹·Hr.⁻¹)	$k_{carbonate}$·[OH⁻] (Hr.⁻¹)	Approx. Lag Time, Hr.⁻¹
0.10	1.2×10^{-2}	0.12	1.4×10^{-2}	2
0.15	1.8×10^{-2}	0.12	...	...
0.20	2.4×10^{-2}	0.12	2.4×10^{-2}	5
0.25	3.1×10^{-2}	0.12	...	...
0.30	3.8×10^{-2}	0.13	3.8×10^{-2}	6
0.35	4.4×10^{-2}	0.13	...	...
0.40	5.1×10^{-2}	0.13	5.2×10^{-2}	8
0.50	...	...	5.3×10^{-2}	11
0.70	...	...	5.0×10^{-2}	14
1.00	...	...	3.4×10^{-2}	17
		av. 0.12		

by reacting ethyl chloroformate with the appropriate phenol in pyridine solution. Phenyl ethyl carbonate was purified by fractional distillation through a 30-cm. Vigreaux column, b.p. 226–228° (lit. 227–230° (15)). *p*-Nitrophenyl ethyl carbonate was recrystallized repeatedly from ethanol, m.p. 64–66° (lit. 67–68° (16)).

p-Nitrophenyl Carbamate and p-Nitrophenyl N-Methylcarbamate.—The compounds were prepared by nitration of the corresponding phenyl esters after the method of Ransom (16). *p*-Nitrophenyl carbamate was recrystallized repeatedly from ethanol, m.p. 110–140° (lit. 161° (17)). *p*-Nitrophenyl N-methylcarbamate was recrystallized repeatedly from ether-acetone solution, m.p. 105–109°.

Procedures

1. The Rate of Disappearance of Urethane from Strongly Basic Solutions at 30°.—The reaction mixture was prepared by dissolving urethane in sodium hydroxide–barium hydroxide solution of the desired normality. Periodically, 5 to 20-ml. portions of this solution containing about 15 mg. of urethane were neutralized by dropwise addition of 60% perchloric acid and distributed in 1 Gm. of silicic acid per ml. of urethane solution. The silicic acid was slurried with chloroform, quantitatively transferred to a chromatography column, packed down, and developed with 300 to 500 ml. of chloroform. The eluate was boiled down to a small volume, and 10 ml. of 0.1 N perchloric acid in glacial acetic acid and 25 ml. of chlorobenzene were added. The mixture was boiled until the temperature of the solution reached 104°. The solution was refluxed for 2 hours at 104°, cooled, and titrated with 0.05 N sodium acetate in glacial acetic acid to the α-naphthol benzein end point. The amount of perchloric acid consumed represented the amount of urethane present in the aliquot.

2. Rate of Appearance of Carbonate Ions in Strongly Basic Solutions of Urethane at 30°.—The reaction mixture was prepared as described in the preceding paragraph, and 20-ml. aliquots of the solution were filled into 8-dr. vials with a hypodermic syringe. The vials were sealed with rubber stoppers and placed in a 30° thermostat. Periodically, the vials were removed from the thermostat; sufficient barium chloride solution was added to precipitate all the carbonate ion which had formed. The contents of the vials were then filtered through Pyrex glass medium porosity fritted disk Buchner funnels. The barium carbonate precipitate was washed well and

dissolved in standard hydrochloric acid. This solution was washed through the funnel and the excess acid titrated with standard carbonate-free sodium hydroxide solution to the bromcresol green end point.

3. Rate of Alkaline Hydrolysis of Urethane, Ethyl N-Methylcarbamate, and Ethyl Dimethylcarbamate in Strongly Basic Solutions at Various Temperatures.—The reaction mixture was prepared by dissolving the ester in sodium hydroxide–barium hydroxide solution so that the concentration of hydroxyl ions was twice the concentration of the ester. Five-milliliter aliquots of this solution were filled into 5-ml. ampuls with a hypodermic syringe, and the ampuls were sealed and placed in a thermostat at the desired temperature. At zero time, and periodically thereafter, the ampuls were removed from the bath and crushed under standard hydrochloric acid. The excess acid was titrated with standard carbonate-free sodium hydroxide solution to the bromcresol green end point.

4. Rate of Alkaline Hydrolysis of Various Aromatic Carbamates and Carbonates at Various Temperatures in Buffered and Strongly Basic Solutions.—The reactions were followed spectrally by measuring
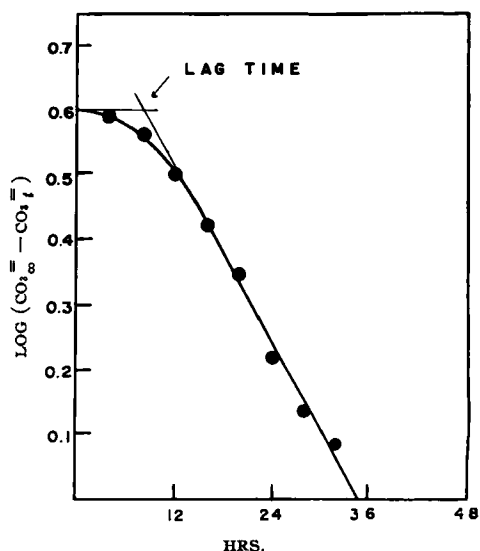

Fig. 1.—Plot showing the rate of appearance of carbonate ions in a 0.4 N OH⁻ solution of urethane at 30°C.

TABLE II.—SECOND-ORDER RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF ALIPHATIC CARBAMATE ESTERS IN STRONGLY BASIC SOLUTION

Ester	T, °C.	k(L.·Mole^{-1}·Min.$^{-1}$)	Apparent ΔHa (Kcal./Mole)
Urethane	55°	2.4×10^{-2}	
	30°	2.0×10^{-3}	20
	25°a	1.2×10^{-3}	
Ethyl N-methyl-carbamate	55°	5.1×10^{-3}	
	30°	5.5×10^{-4}	17.5
	25°a	3.4×10^{-4}	
Ethyl dimethyl-carbamate	96°	4.2×10^{-2}	
	55°	3.0×10^{-3}	
	25°a	2.7×10^{-4}	15.5

a The k's at 25°C. were extrapolated from the higher temperature data.

the absorbance due to the phenate ion (at 235 mμ wavelength) or the *p*-nitrophenate ion (at 400 mμ wavelength) using a model 11 MS Cary recording spectrophotometer. The reactions were allowed to proceed until no further change in the absorbance could be detected. Pseudo first-order rate constants were determined from the slopes of plots of log (A_∞ − A_t) versus time. Borate and phosphate buffers and sodium hydroxide–barium hydroxide solutions were employed and several pH's or hydroxyl ion concentrations were studied for each compound. All buffer results were extrapolated to infinite dilution.

RESULTS AND DISCUSSION

Experimental studies on the hydrolytic rate of urethane and various substituted carbamates strongly suggest that, as would be expected, the initial cleavage occurred at the CO—O bond.

Urethane.—The pseudo first-order rate constants (k_{urethane}. [OH$^-$]) for the rate of disappearance of urethane from strongly basic solutions at 30° and the dependency of this reaction on the base concentration are shown in Table I. These data were procured by *Procedure 1*. A plot of pseudo first-order rate constant *versus* hydroxyl ion concentration yielded a straight line through the origin with a slope of unity, showing that the reaction was first order with respect to hydroxyl ions. The second-order rate constant (k_{urethane}) for this reaction at 30° is also shown in Table I. This rate constant corresponds to the rate of the initial attack on the urethane molecule.

A typical plot showing the rate of appearance of carbonate ions in strongly basic solutions of urethane at 30° is shown in Fig. 1. These data were procured by *Procedure 2*. The reactions were allowed to proceed until no further change in the amount of barium carbonate could be detected. The plot of log
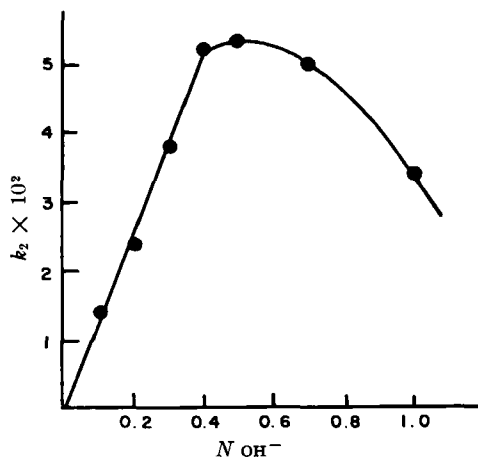

Fig. 2.—Plot showing the relationship between pseudo first-order rate constants for the rate of appearance of carbonate ions in strongly basic solutions of urethane at 30°C. and hydroxyl ion concentration.

($CO_{3\infty}^{=}$ − $CO_{3t}^{=}$) *versus* time, shown in Fig. 1, goes through a lag period, then a straight line portion. The dependency of the slopes of the straight line portions, calculated as pseudo first-order rate constants, on the base concentration is shown in Table I and Fig. 2. The dependency of the lag time on the base concentration is also shown in Table I.

Faurholt (18) pointed out that in solutions of pH above 12.5, the rate of conversion of carbamate ions into carbonate ions and ammonia decreases as the pH increases. This is shown in Table I as an increase in the lag time with increasing hydroxyl ion concentration. The effect is also shown in Fig. 2 as a decrease in $k_{\text{carbonate}}$ with increasing hydroxyl ion concentration above 0.5 N OH$^-$. The fact that k_{urethane} equals $k_{\text{carbonate}}$ between 0.1 and 0.4 N OH$^-$ shows that the rate of rupture of the CO—O bond in the ester linkage is the rate-determining step in the appearance of carbonate ions at these OH$^-$ concentrations. The decrease in $k_{\text{carbonate}}$ with increasing hydroxyl ion concentration beyond 0.5 N OH$^-$ indicates that at these OH$^-$ concentrations the conversion of carbamate ions into carbonate ions is the rate-determining step in the appearance of carbonate ions.

Werner (12) stated that in refluxing sodium hydroxide solution the major intermediate in the hydrolysis of urethane was alkali cyanate. When a solution of urethane in 0.5 N OH$^-$, which had stood at room temperature until the precipitate of barium carbonate was in evidence, was tested for cyanate ions by Werner's method (19), the test was so faint that it could hardly be distinguished from the blank. According to Jensen (20), the decomposition of cyanate ion in such strongly basic solutions is extreme-

TABLE III.—SECOND-ORDER RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF AROMATIC CARBAMATE ESTERS

Ester	k(L.·Mole^{-1}·Min.$^{-1}$)		Apparent ΔHa (Kcal./Mole)
	34°C.	25°C.	
p-Nitrophenyl dimethylcarbamate	5.5×10^{-2}	2.4×10^{-2}	17
p-Nitrophenyl N-methylcarbamate	3.9×10^{4}	3.5×10^{4}	2
p-Nitrophenyl carbamate	1.5×10^{7}	1.5×10^{7}	2
Phenyl dimethylcarbamate	6.0×10^{-3}	2.8×10^{-3}	16
Phenyl N-methylcarbamate	1.9×10^{2}	1.2×10^{2}	8
Phenyl carbamate	2.2×10^{4}	1.6×10^{4}	7

ly slow. If cyanate ion had been the true intermediate in the hydrolysis of urethane at 30°, carbonate ions probably never would have been detected.

Effect of Temperature on the Rate of Alkaline Hydrolysis of Urethane, Ethyl N-Methylcarbamate, and Ethyl Dimethylcarbamate in Strongly Basic Solutions.—The second-order rate constants for the alkaline hydrolysis of the three aliphatic carbamate esters at several temperatures are shown in Table II. These data were procured by *Procedure 3.*

This method for following the aliphatic carbamates was considered completely reliable for studies at any hydroxyl ion concentration, even though appreciable quantities of carbamate ions may have been present in the reaction mixture. The aliquots to be analyzed were first placed in strong acid solution which, according to Faurholt (18), would instantaneously decompose any carbamate ions into ammonia and carbon dioxide and include them in the titer. According to Jensen (20), any cyanate ion present would also have been rapidly converted into ammonia and carbon dioxide under these conditions, although the change would not have been instantaneous. The decomposition of urethane itself was studied by *Procedure 3* at 30°, and the resulting *k* was exactly the same as the value previously determined by following the disappearance of the ester.

Methylation of the amide nitrogen of urethane produced significant changes in the hydrolytic rate, but the changes were not sufficient to indicate major changes in the basic mechanism. In the case of ethyl dimethylcarbamate, the only mechanism possible is a direct hydroxyl ion attack on the carbonyl carbon atom followed by either a dimethylcarbamate ion or a monoethylcarbonate ion intermediate

$$\text{Et—O—}\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{—N(Me)}_2 + \text{OH}^- \rightleftharpoons$$

$$\left[\text{Et—O—}\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{\text{C}}}\text{—N(Me)}_2 \right] \rightarrow$$

$$\text{EtOH} + \text{(Me)}_2\text{N—COO}^-$$

$$\text{Et—O—}\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{—N(Me)}_2 + \text{OH}^- \rightleftharpoons$$

$$\left[\text{Et—O—}\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{\text{C}}}\text{—N(Me)}_2 \right] \rightarrow$$

$$\text{(Me)}_2\text{NH} + \text{Et—O—COO}^-$$
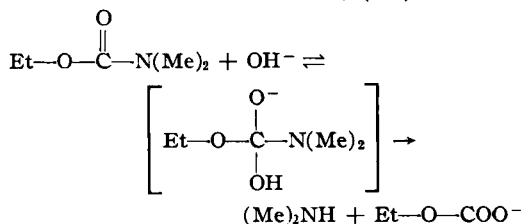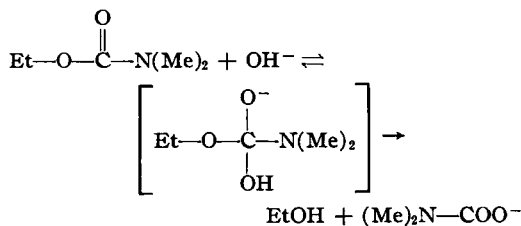
Faurholt (18) has shown that the dimethyl-

TABLE IV.—SECOND-ORDER RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF CARBONATE ESTERS

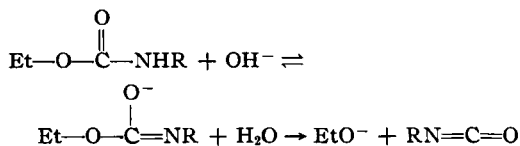| Ester	k(L.·Mole^{-1}·Min.$^{-1}$) 34°C.	25°C.	Apparent ΔHa (Kcal./ Mole)
p-Nitrophenyl ethyl carbonate	400	320	5
Phenyl ethyl carbonate	37	24	9
Diethyl carbonate[a]	5.5(35°C.)	2.8	13

[a] After Miller and Case (22).

TABLE V.—INFLUENCE OF THE ELECTROPHILICITY OF THE ALCOHOLIC OR PHENOLIC GROUPS ON THE STABILITY OF ETHYL CARBONATE AND ACETATE ESTERS TOWARD HYDROXYL ION ATTACK

Ester	pKa of ROH	k(L.·Mole^{-1}· Min.$^{-1}$) (25°C.)
p-Nitrophenyl ethyl carbonate	~6	320
Phenyl ethyl carbonate	~10	24
Diethyl carbonate[a]	~16	2.8
p-Nitrophenyl acetate[b]	~6	1600 (22°C.)
Phenyl acetate	~10	...
Ethyl acetate[c]	~16	5.6 (21°C.)

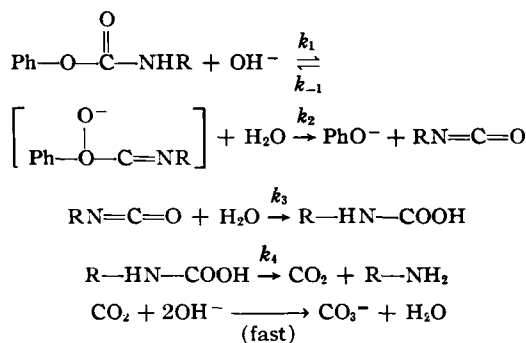[a] Miller and Case (22). [b] Casida, *et al.* (11). [c] Warder (23).

carbamate ion does not exist in solution under any conditions and (21) that the monoethylcarbonate ion is rapidly converted into carbamate ions and ethyl alcohol under the conditions of these experiments. Thus, the initial hydroxyl ion attack on the ethyl dimethylcarbamate ester is probably followed by complete disintegration of the molecule. In the urethane and ethyl N-methylcarbamate cases the formation of an isocyanate intermediate is possible

$$\text{Et—O—}\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{—NHR} + \text{OH}^- \rightleftharpoons$$

$$\text{Et—O—}\overset{\overset{\displaystyle O^-}{|}}{\text{C}}\text{=NR} + \text{H}_2\text{O} \rightarrow \text{EtO}^- + \text{RN=C=O}$$

but the rate constants for these compounds were so close to that for ethyl dimethylcarbamate that this possibility seems remote. The apparent heats of activation for the three compounds are essentially equal, suggesting no major difference in mechanism between them. The small differences in rates which were observed are probably because of the inductive and steric effect of the methyl groups.

Rate of Alkaline Hydrolysis of Various Aromatic Carbamates.—The second-order rate constants obtained for several aromatic carbamates are shown in Table III. These data were procured by following the appearance of the phenate or *p*-nitrophenate ions spectrally and therefore correspond to the rate of cleavage of only the CO—O bond.

Unlike the case of urethane, methylation of the amide nitrogen of phenyl carbamate and *p*-nitrophenylcarbamate has a very marked effect on the hydrolytic rate. The second-order *k* for phenyl carbamate is nearly 10[7] times that for phenyl dimethylcarbamate. The second-order *k* for *p*-nitrophenyl carbamate is nearly 10[9] times that for *p*-nitrophenyl dimethylcarbamate. The apparent heats of activation for the hydrolysis of these two types of carbamates are also very different. These facts strongly suggest some shift in the mechanism of the hydrolysis. It has already been pointed out in the case of ethyl dimethylcarbamate, that the hydrolysis of the dimethylcarbamates can only occur by direct hydroxyl ion attack on the carbonyl carbon, probably followed by complete disintegration of the molecule. It therefore seems likely that the alternative mechanism, *i.e.*, the formation of an isocyanate intermediate, may be responsible for the great increase in the hydrolytic rate seen with the aromatic N-unsubstituted and N-monosubstituted carbamate esters. If the hydrolysis proceeds according to

$$Ph-O-\overset{\overset{O}{\|}}{C}-NHR + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$$

$$\left[\overset{O^-}{\underset{}{Ph-O-C=NR}}\right] + H_2O \overset{k_2}{\rightarrow} PhO^- + RN=C=O$$

$$RN=C=O + H_2O \overset{k_3}{\rightarrow} R-HN-COOH$$

$$R-HN-COOH \overset{k_4}{\rightarrow} CO_2 + R-NH_2$$

$$CO_2 + 2OH^- \xrightarrow[\text{(fast)}]{} CO_3^- + H_2O$$

it is possible that the initial ionization of the carbamate ester has a negative temperature coefficient, since the apparent heat of activation of the overall hydrolysis reaction is rather small. The relative closeness of the rates and apparent heats of activation for phenyl carbamate and phenyl N-methylcarbamate and for *p*-nitrophenyl carbamate and *p*-nitrophenyl N-methylcarbamate suggests that the isocyanate mechanism is dominant in these cases.

Rate of Alkaline Hydrolysis of Various Aromatic Carbonates.—The pseudo first-order rate constants and second-order rate constants obtained for two aromatic ethyl carbonates are shown in Table IV. These data were procured by following the appearance of the phenate or *p*-nitrophenate ions spectrally and therefore correspond to the rate of rupture of only the CO—O bond vicinal to the phenol group.

Miller and Case (22) studied the rate of alkaline hydrolysis of diethyl carbonate and determined a value of 2.8 L.·mole^{-1}·minute^{-1} for the second-order rate constant for the initial cleavage at 25° and an apparent heat of activation of 13 Kcal./mole for this reaction. The differences in rates of hydrolysis of the various carbonate esters seem to parallel the electrophilicity of the alcoholic or phenolic moieties. This
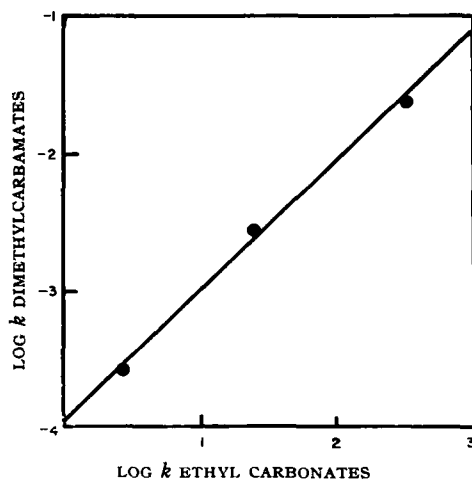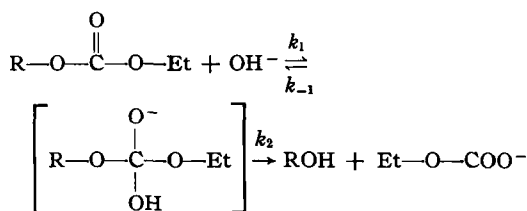

Fig. 3.—Plot showing the proportionality of effect of R—O— groups on the rate of hydrolysis of dimethylcarbamate and ethyl carbonate esters.

effect is illustrated in Table V. It can be seen that the effect of the alcoholic or phenolic groups on the stability of the ethyl carbonate esters and the acetate esters toward hydroxyl ion attack is essentially the same. This suggests that the increased hydrolytic rate in each case is because of an increased polarization of the carbonyl carbon atom which facilitates the initial hydroxyl ion attack. In the carbonate case, this initial attack is followed by a mono-alkylcarbonate ion intermediate, probably mono-ethylcarbonate ion

$$R-O-\overset{\overset{O}{\|}}{C}-O-Et + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$$

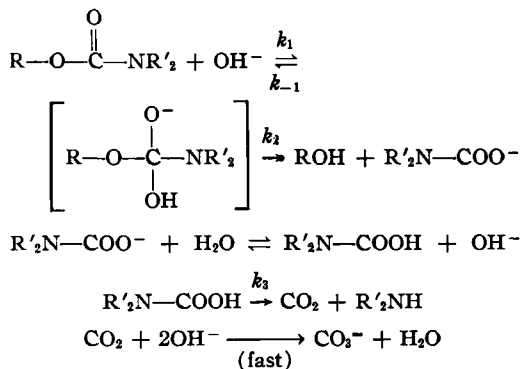$$\left[\overset{O^-}{\underset{OH}{R-O-C-O-Et}}\right] \overset{k_2}{\rightarrow} ROH + Et-O-COO^-$$

and the effect of the R group suggests that the rate-determining step in this mechanism is probably k_1. Faurholt (21) has already shown that the resulting monoethylcarbonate ion is rapidly converted to carbonate ions and ethyl alcohol in the solutions employed in our studies. Thus, the carbonate esters can be considered to be completely destroyed after the initial cleavage.

Comparison with the Work of Casida, et al.— Casida and his co-workers (11) have studied the hydrolysis of some of the compounds listed in Tables III and IV in 0.05 *M* phosphate buffer at pH 7.8 and 22°. Their results are shown in Table VI. The rate constants in Table VI are somewhat higher than might be expected from the data of Tables III and IV. This is probably because of buffer catalytic effects.

TABLE VI.—SECOND-ORDER RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF CARBAMATE AND CARBONATE ESTERS IN 0.05 *M* PHOSPHATE BUFFER AT pH 7.8 AND 22°C. AFTER CASIDA, *et al.* (11)

Ester	k(L.·Mole^{-1}·Min.$^{-1}$)
p-Nitrophenyl dimethylcarbamate	2.0×10^{-2}
p-Nitrophenyl N-methylcarbamate	1.3×10^5
Phenyl dimethylcarbamate	3.9×10^{-3}
p-Nitrophenyl ethyl carbonate	5.5×10^2

TABLE VII.—INFLUENCE OF THE ELECTROPHILICITY OF THE ALCOHOLIC OR PHENOLIC GROUPS ON THE STABILITY OF DIMETHYLCARBAMATE AND ETHYL CARBONATE ESTERS TOWARD HYDROXYL ION ATTACK

Ester	pKa of ROH	k(L.·Mole^{-1}·Min.$^{-1}$) (25°C.)
p-Nitrophenyl dimethyl-carbamate	~6	2.4×10^{-2}
Phenyl dimethylcarbamate	~10	2.8×10^{-3}
Ethyl dimethylcarbamate	~16	2.7×10^{-4}
p-Nitrophenyl ethyl carbonate	~6	320
Phenyl ethyl carbonate	~10	24
Diethyl carbonate	~16	2.8

CONCLUSIONS

On the basis of the data presented above, two mechanisms appear to be responsible for the alkaline hydrolysis of the carbamate esters: (*a*) hydroxyl ion attack followed by a carbamate ion intermediate

$$R—O—\overset{\overset{\textstyle O}{\|}}{C}—NR'_2 + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$$

$$\left[R—O—\overset{\overset{\textstyle O^-}{|}}{\underset{\underset{\textstyle OH}{|}}{C}}—NR'_2 \right] \overset{k_2}{\rightarrow} ROH + R'_2N—COO^-$$

$$R'_2N—COO^- + H_2O \rightleftharpoons R'_2N—COOH + OH^-$$

$$R'_2N—COOH \overset{k_3}{\rightarrow} CO_2 + R'_2NH$$

$$CO_2 + 2OH^- \xrightarrow[\text{(fast)}]{} CO_3^- + H_2O$$

(*b*) hydroxyl ion attack followed by an isocyanate intermediate

$$R—O—\overset{\overset{\textstyle O}{\|}}{C}—NHR' + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$$

$$\left[R—O—\overset{\overset{\textstyle O^-}{|}}{C}=NR' \right] + H_2O \overset{k_2}{\rightarrow} RO^- + R'N=C=O$$

$$R'N=C=O + H_2O \overset{k_3}{\rightarrow} R'—NH—COOH$$

$$R'—NH—COOH \overset{k_4}{\rightarrow} CO_2 + R'—NH_2$$

$$CO_2 + 2OH^- \xrightarrow[\text{(fast)}]{} CO_3^- + H_2O$$
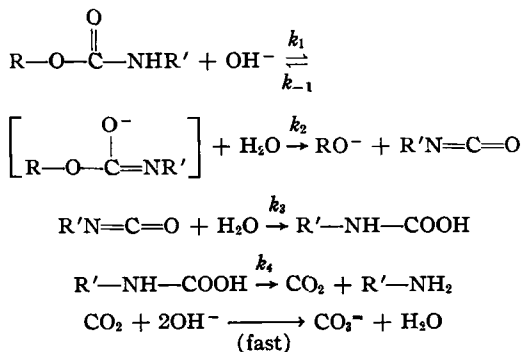
The second mechanism appears to predominate in the extremely fast reactions of the N-unsubstituted and N-monosubstituted aromatic carbamates, whereas the first mechanism appears to be the only one possible in the slower reactions of the dimethylcarbamates. The data seem to indicate that mechanism (*a*) predominates in the hydrolysis of all the aliphatic carbamates. The apparent heats of activation for the compounds which proceed *via* mechanism (*a*) are of the same order of magnitude as those which might be expected for ordinary hydrolytic reactions. The extremely low apparent heats of activation for the compounds which proceed *via* mechanism (*b*) seem to indicate that some step in this mechanism has a negative temperature coefficient. That step is very likely the initial ionization of the carbamate ester, since in this step a molecule of water is formed releasing 13 Kcal. of energy.

The electrophilicity of the alcoholic or phenolic moiety appears to exert considerable influence on the stability of the dimethylcarbamate and ethyl carbonate esters toward hydroxyl ion attack. This effect is illustrated in Table VII and Fig. 3 and is probably the result of an increased polarization of the carbonyl carbon atom, since more electrophilic R—O— groups cause greater polarization of the carbonyl group. The Hammett-type plot of log *k* for a dimethylcarbamate ester *versus* log *k* for the corresponding ethyl carbonate ester, shown in Fig. 3, is a straight line with a slope very nearly unity, showing that the effect of the alcoholic or phenolic group

TABLE VIII.—INFLUENCE OF THE ELECTROPHILICITY OF THE ALCOHOLIC OR PHENOLIC GROUPS ON THE STABILITY OF CARBAMATE AND N-METHYLCARBAMATE ESTERS TOWARD HYDROXYL ION ATTACK

Ester	pKa of ROH	k(L.·Mole^{-1}·Min.$^{-1}$) (25°C.)
p-Nitrophenyl N-methyl- carbamate	~6	3.5×10^4
Phenyl N-methylcarbamate	~10	1.2×10^2
Ethyl N-methylcarbamate	~16	3.4×10^{-4}
p-Nitrophenyl carbamate	~6	1.5×10^7
Phenyl carbamate	~10	1.6×10^4
Ethyl carbamate (urethane)	~16	1.2×10^{-1}

follows a linear free-energy relationship (24). Since the polarity of the carbonyl group seems largely to determine the rate, k_1 is probably the rate-determining step in mechanism (*a*).

The effect of the R—O— group is even more marked in the case of intermediate isocyanate formation, *i.e.*, mechanism (*b*). This is illustrated in Table VIII. The greater effect in this case is probably because this mechanism requires the loss of the R—O$^-$ ion, and *p*-nitrophenate ion is a better leaving group than phenate ion. This suggests that k_2 is probably the rate-determining step in mechanism (*b*). The two aliphatic compounds are included in Table VIII to show that they do not fit this theory. This is further evidence that the N-unsubstituted and N-monosubstituted aliphatic compounds probably hydrolyze *via* the carbamate ion intermediate, *i.e.*, mechanism (*a*), at ordinary temperatures. It should be noted that the *k*'s for the aliphatic compounds at 25° are practically equal. The small differences are probably because of the inductive and steric effects of the methyl groups. Even the apparent heats of activation for all the aliphatic compounds are essentially the same and correspond most closely to those values determined for the compounds which can only hydrolyze *via* mechanism (*a*).

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