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Alkaline Hydrolysis of Some Carbamic Acid Esters

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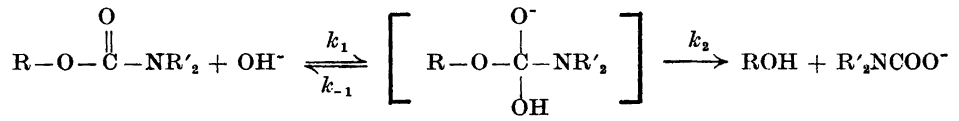
Several aliphatic and aromatic N-substituted and N,N-disubstituted carbamates are investigated. The hydrolytic reactions are generally studied in strongly basic or in buffer solutions, but sometimes also in the presence of 5–10 % of ethanol. The rate constants are determined at three or four different temperatures. The enthalpies and entropies of activation are calculated. The possible reaction mechanisms and the substituent effects are discussed.

Many carbamic acid esters, *e.g.* physostigmine, neostigmine, and pyridostigmine, are cholinesterase inhibitors and are used as drugs. More recently, various carbamates have been marketed as insecticides and also because of their anticholinesterase activity.

The decomposition of urethans has been investigated by several authors. The hydrolysis of physostigmine analogs has been studied qualitatively by Stedman [1] and by Aeschlimann and Reinert;[2] in the case of the singly N-substituted carbamates, they suggested an isocyanate intermediate. Ellis *et al.*[3] found the alkaline hydrolysis of physostigmine to be first-order with respect to both ester and hydroxyl ions. Mørch [4] investigated the stability of neostigmine methylsulfate under autoclave conditions. Chaikin [5] made a quantitative study of the decomposition of some physostigmine analogs. Casida *et al.*[6] determined the rate constants for the alkaline hydrolysis of several carbamate insecticides, including both N-alkyl and N,N-dialkylcarbamates. According to the findings of all these authors the N,N-disubstituted carbamates seem to be more stable towards alkaline hydrolysis than the singly N-substituted esters. Pedersen [7] determined the relationship between the rate constant, the Hammett H° acidity function, and the water activity for the hydrolysis of urethan in strongly acid solutions.

Faurholt *et al.*[8–10] have investigated the properties of carbamate ions in solution. Among the carbamates studied were, *e.g.*, ammonium carbamate and the carbamates formed by some alkylamines and dialkylamines. The authors found [8,9] that in acid solution the decomposition rate of the carbamates was too rapid to be measured. In weakly basic solution however, a measurable equilibrium was obtained at not too low amine concentrations.

At pH > about 10, the decomposition rate was rather slow, and above pH 12 it was found to vary inversely with the pH. Dittert [11] has recently carried out a kinetic and mechanistic investigation of the alkaline hydrolysis of some organic carbamates and carbonates. The carbamates studied were the ethyl, phenoxy, and *p*-nitrophenoxy esters of carbamic acid, N-methylcarbamic acid, and N,N-dimethylcarbamic acid. The reactions were carried out in buffer or strongly basic solutions at various temperatures. The author followed the hydrolysis of the aliphatic esters by titrating the amines formed. In the case of urethan he also determined the rate of formation of the carbonate ion and the rate of disappearance of the ester by water-free titration after chromatographic separation. The hydrolysis of the aromatic esters was studied by measuring the light absorption of the phenoxide or *p*-nitrophenoxide ions formed. Dittert found that the aromatic unsubstituted and singly N-substituted esters were decomposed at a much higher rate than the aliphatic esters and the N,N-disubstituted aromatic esters. He also found extremely low apparent heats of activation for the former compounds. For the hydrolysis of the aliphatic and the disubstituted aromatic esters, he suggested the following mechanism:

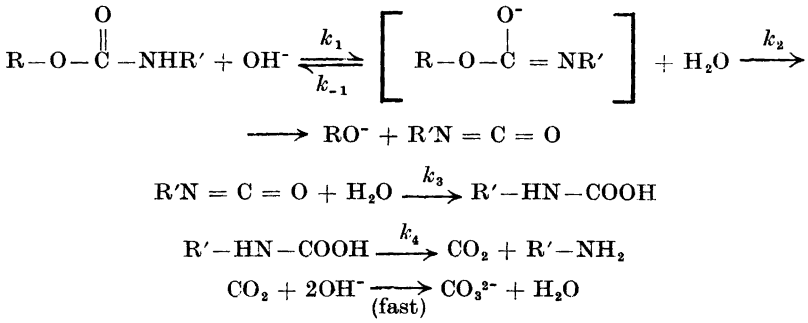


$$R'_2N-COO^- + H_2O \rightleftharpoons R'_2N-COOH + OH^-$$

$$R'_2N-COOH \xrightarrow{k_3} CO_2 + R'_2NH$$

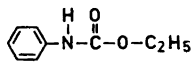
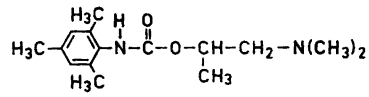
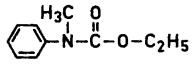
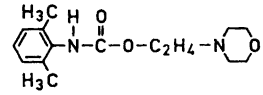
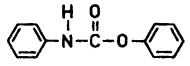
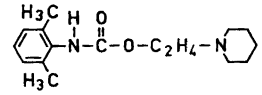
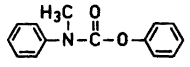
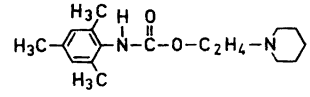
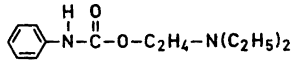
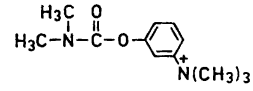
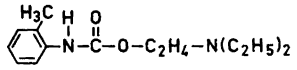
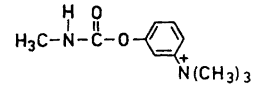
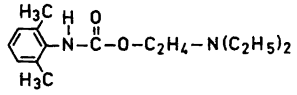
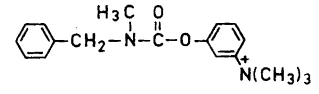
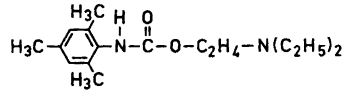
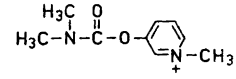
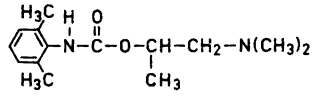
$$CO_2 + 2OH^- \xrightarrow[(fast)]{} CO_3^{2-} + H_2O$$

Thus, the initial hydroxyl ion attack on the carbonyl carbon results in cleavage of the CO—O bond. The carbamate ion formed then decomposes into amine and carbon dioxide at a rate that is inversely proportional to the hydroxyl ion concentration, as was found by Faurholt. Dittert proposed that if the rupture occurred at the C—N bond the substituted carbonate ion formed would decompose rapidly, according to Faurholt.[12] In the case of the disubstituted esters, however, he considered it probable that the hydroxyl ion attack would result in complete disintegration of the molecule, since it was shown by Faurholt [8] that the dimethyl carbamate ion did not exist in solutions under any conditions. As Dittert found very high velocity constants and extremely low apparent heats of activation for the hydrolysis of aromatic unsubstituted and monosubstituted carbamates, he assumed that these esters decompose according to a different mechanism, hence he suggested the following scheme involving an isocyanate intermediate:



Because of the low heats of activation, he considered it probable that the first step in the above scheme, *i.e.* the ionization of the ester, might have a negative temperature coefficient.

Table 1. Survey of the esters studied.

Ester No.	Formula	Ester No.	Formula
1		10	
2		11	
3		12	
4		13	
5		14	
6		15	
7		16	
8		17	
9			

Dahlbom and Österberg [13] have synthesized a series of basically substituted esters and amides of 2,6-dimethyl- and 2,4,6-trimethylphenylcarbamic acids. The esters were found to be powerful local anaesthetics though rather toxic, however. These carbamates are among the esters investigated in this work. The other esters studied were selected because they are drugs, *e.g.* neostigmine and pyridostigmine (esters Nos. 14 and 17), and/or because they are interesting from a kinetic and mechanistic point of view. Apparently, none of the esters investigated (Table 1) has been studied previously in this respect.

EXPERIMENTAL

Apparatus. The measurements of the UV absorption were made with a Beckman photometer model DU, using 1 cm cuvettes. The absorption in visible light was measured with a Beckman photometer model B in 1 cm cuvettes. The pH measurements were performed with a Radiometer PHM 4, using a glass electrode as indicator electrode and a calomel electrode as reference electrode.

Chemicals. Ester No. 1, phenylurethan, was the commercial product recrystallized from ethanol, m.p. 52°.

Ester No. 2 was prepared from N-methylaniline and ethyl chloroformate according to Dannley *et al.*;[14] b.p. 99–100°/2 mm (lit. 112–114°/60 mm[14]).

Ester No. 3 was made from phenylisocyanate and phenol according to Leuckart;[15] m.p. 126° (lit. 124°[15]).

Ester No. 4 was synthesized from methylphenylcarbamoyl chloride and potassium phenoxide according to Lellmann and Benz;[16] m.p. 58° (lit. 58°[16]). The methylphenylcarbamoyl chloride was prepared according to a modification of the method given by Weygand and Mitgau.[17] A solution of N-methylaniline in ethyl acetate was cooled to 0° and added slowly to an ice-cooled solution of phosgene in toluene. The reaction mixture was kept at 0° for 2 h, then at 25° for another 2 h. Gentle warming eliminated excess phosgene, which was absorbed in sodium hydroxide solution. The mixture was then subjected to vacuum distillation, the residual methylphenylcarbamoyl chloride being recrystallized from benzene; m.p. 86° (lit. 85–86°[17]).

Esters Nos. 6–13 were synthesized according to Dahlbom and Österberg.[13] The appropriate isocyanate was prepared from phosgene and *o*-toluidine, 2,6-xylidine, or mesidine. The esters were then synthesized from the isocyanates and the appropriate N-substituted alcohols. The oxalate of ester No. 6 melted at 101°. (Found: C 55.9; H 6.99; N 8.13. Calc. for $C_{16}H_{24}N_2O_6$: C 56.5; H 7.10; N 8.23).

Ester No. 5 was prepared from commercial phenylisocyanate (p.a.) and the amino alcohol, m.p. 114° (oxalate). (Found: C 54.8; H 6.81; N 8.24. Calc. for $C_{15}H_{22}N_2O_6$: C 55.2; H 6.80; N 8.59). The melting points of esters Nos. 7–13 agreed with those given in the literature cited.[13]

Ester No. 14 was provided by Leo, Hälsingborg, whilst esters Nos. 15–17 were provided by Hoffmann-la Roche, Basel. These four esters were not further purified.

The other chemicals used were reagent grade. The buffer solutions with pH below 10 were prepared according to the Swedish Pharmacopeia Ed. XI, the others according to Britton.[18]

Kinetic methods. Some of the esters studied have protolytic properties, hence it may be expected that their basic and acidic forms would be hydrolyzed at different velocities. However, in the present investigation, hydrolysis was carried out in strongly alkaline solutions, hence the reaction velocities determined were those of the basic forms.

The ester under investigation was treated with a solution containing the hydroxyl ion at the desired concentration, which was maintained constant during the whole reaction time. At appropriate intervals, aliquots were withdrawn, and their content of formed amine or hydroxy compound was determined. In some cases, the amount of residual ester was determined as well.

Ester No. 1 (phenylurethan). In the alkaline hydrolysis of this ester, it may be assumed that the phenylcarbamate ion ($C_6H_5NHCOO^-$) is initially formed. This ion gradually decomposes further in basic solutions to give aniline, but in acidic solutions, the decom-

position into aniline and carbon dioxide is instantaneous. These facts form the basis for the experimental determination of the alkaline decomposition rate of phenylurethan, as follows:

(*a*) About 4×10^{-4} moles of ester was dissolved in carbon dioxide-free water at 25°C. Sodium hydroxide solution was added till the desired hydroxyl ion concentration was attained, and the solution made up to one litre with carbon dioxide-free water. The flask was immersed in a water-bath at 25 ± 0.1°C, and aliquots withdrawn at known intervals. The aliquots were run into that quantity of hydrochloric acid which gave a pH of about 1 to the final solution. The unreacted ester was extracted with chloroform, and the remaining aniline diazotized by a modification of the method of Bratton and Marshall.[19] (The coupling reagent was increased tenfold, and the reaction time extended to 2 h at 25°C). The absorbance of the final diazotized solution was measured at 550 mμ (see Table 2). A standard curve was prepared from authentic aniline treated in the same manner.

The pseudo first-order rate constants were obtained by plotting log(% residual ester), *i.e.* $\log[100(E_s - E_t)/E_s]$, as a function of time. E_t is the absorption of the diazotized solutions at times t; E_s is the final theoretical absorption, calculated from the standard curve.

In the studies carried out at 50 and 75°C, a slightly modified technique was used: The reaction mixture was made up at 25°C and dispensed under nitrogen in 10 ml ampoules, which were placed in a water-bath of the desired temperature. At periodic intervals, the ampoules were rapidly cooled to 25°C, and an appropriate volume was treated as described above. The increase in volume of the warmed solutions was neglected.

(*b*) The amounts of aniline and of phenylcarbamate ion formed in a strongly basic solution of phenylurethan were determined separately in the following manner: Hydrolysis was carried out under the conditions described above, the hydroxyl ion concentration being 1 M. The samples withdrawn from the reaction mixture were shaken with chloroform, extracting the aniline and unreacted ester. The aqueous phase containing the phenylcarbamate ion was acidified, and the aniline thus formed was diazotized and treated as described above. The aniline in the chloroform phase was extracted with 0.1 M hydrochloric acid, diazotized, and determined in the usual manner. Thus the amounts of phenylcarbamate ion and aniline were estimated separately.

(*c*) In order to investigate the rate of appearance of aniline in solutions of phenylcarbamate ions, the following experiment was carried out: Phenylisocyanate was shaken vigorously with 1 M sodium hydroxide solution for about 5 min, until a clear solution was obtained. An appropriate portion of the solution was brought to the desired hydroxyl ion concentration with carbon dioxide-free water or buffer solutions of 25°C. The flask was placed in a 25°C water-bath, aliquots were withdrawn periodically, and the aniline formed was extracted with chloroform. A portion of the chloroform phase was shaken with 0.1 M hydrochloric acid, and the aniline in the aqueous phase was determined as above. Experiments were run with solutions of twelve different hydroxyl ion concentrations, ranging from 1.000 M − 0.001 M. In buffer solutions of pH 10 and below, the decomposition rate of the phenylcarbamate ion was too fast to be measured. The pseudo first-order rate constants were determined as in study (*a*). In some cases, the samples from the reaction mixture were not extracted with chloroform but instead were acidified, and the amount of aniline was determined. The final value, E_s, was then always obtained, showing that the phenylcarbamate ion, or more correctly the carbanilic acid, is immediately decomposed into aniline and carbon dioxide under these conditions.

Esters Nos. 2—4. As seen from Table 2, these esters were all studied by measuring the amount of amine formed. In the case of esters Nos. 2 and 3, the residual ester was also determined and in the case of ester No. 4 the amount of phenol formed. The reaction solutions contained 5 − 10 % ethanol, which was assumed (and in some cases proved) not to have a significant effect on the rate of hydrolysis. The molar concentrations of the esters ranged from $10^{-4} - 6 \times 10^{-4}$. Usually the reaction solutions were dispensed in ampoules under nitrogen.

As is seen from Table 4, esters Nos. 2 and 4 were studied in strongly alkaline solutions, while ester No. 3 was investigated in borate buffers of pH 8 − 9. The studies at pH 8 were carried out in three different buffer concentrations (0.05, 0.1, and 0.2 M) to determine, if the buffer had any catalytic effect. This was found to be so slight that it could be neglected. The N-methylaniline formed in the hydrolysis of esters Nos. 2 and 4 was de-

termined by reading the absorbance at 240 mμ after the unreacted ester (and the phenol formed in the case of ester No. 4) had been extracted with chloroform from the acidified sample, which was again made alkaline before measuring.

The phenol was determined according to a modification of the method given by Gibbs.[22] A stock solution of the reagent was prepared by dissolving an appropriate amount of 2,6-dichloro-quinonechloroimide in ethanol. Immediately before use, a portion of this solution was diluted with distilled water and added to a sample from the reaction mixture, from which the unreacted ester and the amine had first been extracted with chloroform. To the solution was added a 0.05 M borate buffer of pH 9.6, and the mixture kept in the dark at 25°C for 4 h. The absorbance was then read at 610 mμ, as is seen from Table 2. A standard curve was prepared from authentic phenol treated in a similar

Table 2. Absorption of products or of residual starting material in the hydrolysis of urethans.

Hydrolysis of ester No.	Absorption measured on	pH of solution measured	ε	λ mμ
1	Amine *	0.4	40 920	550
2	Amine	9	6 270	240
	Ester	1	5 770	229
3	Amine *	0.4	40 920	550
	Ester	2	17 170	233
4	Amine	9	6 270	240
	Phenol *	9.6	21 340	610
5	Amine	8.5	1 410	280
6	Amine	8.5	1 740	280
7, 9, 11, 12	Amine	8.5	1 750	280
8, 10, 13	Amine	8.5	1 940	285.5
14	Phenol	11	3 430	294
15	Phenol	3	2 130	272
16	Amine	11	10 800	241
	Phenol	11	3 430	294
17	Pyridol	8.5	5 420	320

* measured on a coloured derivative thereof.

manner. The pseudo first-order rate constants were obtained as in the determination of aniline.

In the studies of esters Nos. 2 and 3 the absorbance of the unreacted ester was read without first separating it from the reaction products. The measurements were made in acidic solutions, where the esters were found to be stable and where the reaction products have very low or no extinction at the wavelengths used. The pseudo first-order rate constants were determined from a plot of $\log[100(E_t-E_s)/(E_0-E_s)]$ *versus* time. E_t is the extinction of the reaction mixture when it was added to hydrochloric acid. E_0, the extinction at zero time, was determined by measuring the ester dissolved in hydrochloric acid. The final extinction value, E_s, was obtained by reading the absorbance of a solution of N-methylaniline in hydrochloric acid in the case of ester No. 2, and of a mixture of aniline and phenol in the case of ester No. 3. The former value was found to be zero.

The method of measuring the extinction of a solution at a wavelength where one component has an absorption maximum and other components have some low extinction has been used before by, *e.g.*, Higuchi *et al.*[20] and Karlén and Ågren.[21]

In order to determine if the methylphenylcarbamate ion appears as an intermediate in the decomposition of ester No. 2, an experiment similar to that described in the phenylurethan study (*b*) was carried out. Aliquots from the hydrolysis mixture were first extracted with chloroform and then treated with acid; under these conditions, the postulated methylphenylcarbamate ion would be expected to decompose into methylaniline and carbon dioxide. In practice, however, no amine was detected in the aqueous phase, whilst the chloroform phase contained about as much N-methylaniline as was detected after the corresponding time-lapse by the standard procedure involving direct acidification of the aliquot.

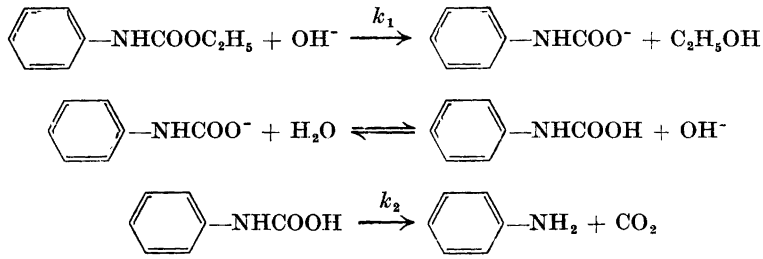
A similar experiment was carried out with ester No. 3, to detect the possible formation of the phenylcarbamate ion. The hydrolysis mixture contained about 10^{-4} moles ester in one litre and the hydroxyl ion concentration was 1 M. The acidified aliquot was first extracted with chloroform, to remove phenol, before determining the aniline by diazotization.

Esters Nos. 5—17 were all studied according to the direct photometric method. The ester concentrations ranged from 4×10^{-4} to 2×10^{-3} M, and the solutions were usually filled into ampoules under nitrogen. In those cases where the amine was determined, the samples were first acidfied to decompose the carbamate ions. The absorbance was then usually read in buffer solution as appears from Table 2. The pseudo first-order rate constants were obtained from a plot of $\log[100(E_s-E_t)/(E_s-E_0)]$ *versus* time.

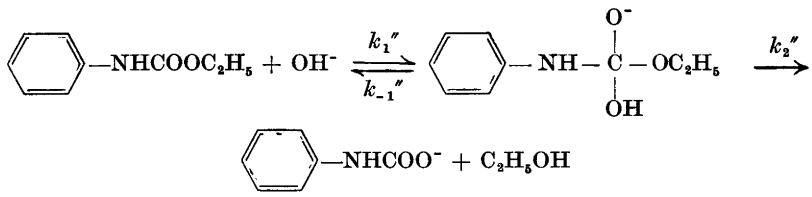
RESULTS AND DISCUSSION

The results of the studies are summarized in Tables 3—5 and Figs. 1—8.

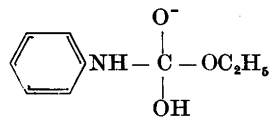
In the case of phenylurethan, the experimental results strongly suggest that the predominant hydrolytic reaction proceeds according to the following scheme:



(Actually, the first step in the above scheme consists of two stages:



If the steady-state approximation is applied to the intermediate



it may be shown that the constant k_1 is equal to $k_1'' \cdot k_2''/(k_{-1}'' + k_2'')$, or if $k_2'' \gg k_{-1}''$, k_1 is equal to k_1'').

In the phenylurethan study (*a*) the hydrolytic reaction was followed by determining the amount of aniline after acidifying the samples from the reaction mixture. This determines the rate constant of the first step, since the phenylcarbamate ion is instantaneously decomposed into aniline and carbon dioxide in acidic solution, as shown in experiment (*c*). Under these conditions, the rate of formation of aniline is equal to the rate of decomposition of phenylurethan, and the rate expression

$$\frac{\mathrm{d(aniline)}}{\mathrm{d}t} = -\frac{\mathrm{d(ester)}}{\mathrm{d}t} = k_1(\mathrm{ester})\,(\mathrm{OH^-}) = k_1'(\mathrm{ester})$$

is valid, as will be shown below. The integrated rate equation can be transformed to

$$k_1' \cdot t/2.303 = 2 - \log C \cdot 100/C_0$$

where $\log C \cdot 100/C_0$ is equal to log (% residual ester). To determine the pseudo first order rate constants k_1' this quantity was plotted *versus* time, as was

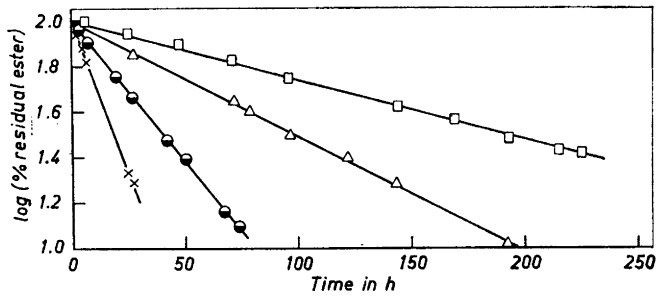


Fig. 1. Hydrolysis of phenylurethan with various hydroxyl ion concentrations at 25.0°C. M OH^-: □ 0.0500, △ 0.1000, ◒ 0.2500, × 0.5000.

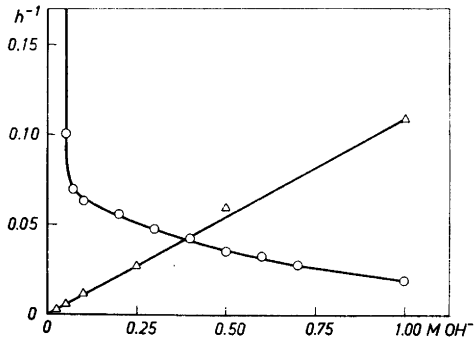


Fig. 2. Pseudo first-order rate constants at 25.0°C in the hydrolysis of phenylurethan *versus* hydroxyl ion concentration. △ k_1', referring to the first step, ○ k_2', referring to the second step.

described before. Fig. 1 shows the plots obtained for phenylurethan at four different hydroxyl ion concentrations at 25°C. Such straight lines were also obtained for the other esters studied. However, for want of space, they are not reproduced here. The constants were obtained by multiplying the slope of the line by -2.303. The second-order rate constants k_1 were calculated from the equation $k_1' = k_1(OH^-)$. The results are shown in Table 4.

In Fig. 2 the k_1' values for phenylurethan are plotted *versus* hydroxyl ion concentration; this yields a straight line through the origin, showing that the reaction is first-order with respect to hydroxyl ions. (Varying the ester concentration showed that the reaction is first-order with respect to ester too, which was expected).

In experiment (*c*) the decomposition rate of the phenylcarbamate ion obtained by the action of hydroxyl ions on phenylisocyanate was measured at various hydroxyl ion concentrations. Some of the results are shown in Fig. 3.

The reaction between phenylisocyanate and potassium- or barium hydroxide was studied by Mohr.[23] He found that the hydrolysis of phenylisocyanate proceeds in two steps, the first one being a rapid formation of phenylcarbamate and the second one a rather slow decomposition of this into aniline and carbonate. More recently, Naegeli *et al.*[24] investigated the interaction between water and aromatic isocyanates. They found the disubstituted ureas to be the main

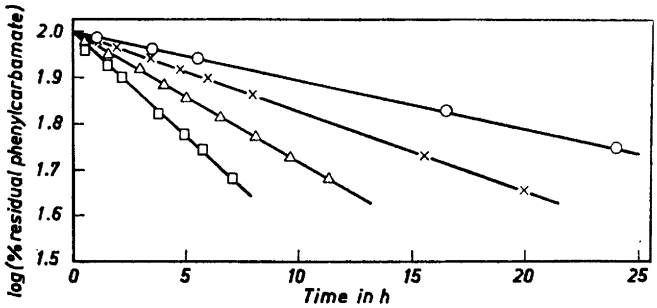


Fig. 3. Decomposition of phenylcarbamate ion with various hydroxyl ion concentrations at 25.0°C. M OH^-: □ 0.0500, △ 0.1000, × 0.5000, ○ 1.000.

end products in most cases. However, if they treated the isocyanates with a 2 % potassium hydroxide solution these were all, with the exception of one, transformed within a few minutes into carbamates which, after acidifying, were quantitatively decomposed into amines.

As seen in the scheme outlined above, the decomposition of the phenylcarbamate ion is the second step in the hydrolysis of phenylurethan. Table 3 and Fig. 2 show the relationship between the pseudo first-order rate constants k_2' for this step and the hydroxyl ion concentration. At hydroxyl ion concentrations of 1 M to about 0.4 M, the reaction rate is approximately inversely proportional to the hydroxyl ion concentration. At lower concentrations, the rate rises more steeply, and from about 0.01 M to 0.001 M the rate is again inversely proportional to the hydroxyl ion concentration. The first 3 values in Table 3 are not plotted in the figure. At pH 10 and below, the rate is too fast to be measured.

As is evident from Fig. 2, the first step in the hydrolysis of phenylurethan is the rate-determining step up to a hydroxyl ion concentration of about 0.4 M. At higher hydroxyl ion concentrations the second step is the slowest one. The rate equations valid for these two consecutive pseudo first-order reactions can be expressed as follows

$$\begin{aligned} -\mathrm{d}A/\mathrm{d}t &= k_1' A \\ \mathrm{d}B/\mathrm{d}t &= k_1' A - k_2' B \\ \mathrm{d}C/\mathrm{d}t &= k_2' B \end{aligned}$$

where A is the ester concentration, B is that of the phenylcarbamate ion, and C the concentration of aniline. k_1' and k_2' are the pseudo first-order rate constants for the first and second steps, respectively.

These differential equations may be integrated according to Esson [25] yielding:

$$B = A_0 \frac{k_1'}{k_2' - k_1'} [\exp(-k_1' t) - \exp(-k_2' t)]$$

and

$$C = A_0 \frac{k_2'[1-\exp(-k_1' t)] - k_1'[1-\exp(-k_2' t)]}{k_2' - k_1'}$$

Table 3. Pseudo first-order rate constants for the formation of aniline in alkaline solutions of phenylcarbamate ion at 25.0°C.

M OH^-	k_2' (h^{-1})	M OH^-	k_2' (h^{-1})
0.0010	3.15	0.300	4.82×10^{-2}
0.0050	6.90×10^{-1}	0.400	4.30×10^{-2}
0.0100	3.57×10^{-1}	0.500	3.51×10^{-2}
0.0500	1.04×10^{-1}	0.600	3.29×10^{-2}
0.0700	7.00×10^{-2}	0.700	2.80×10^{-2}
0.100	6.27×10^{-2}	1.000	1.91×10^{-2}
0.200	5.66×10^{-2}		

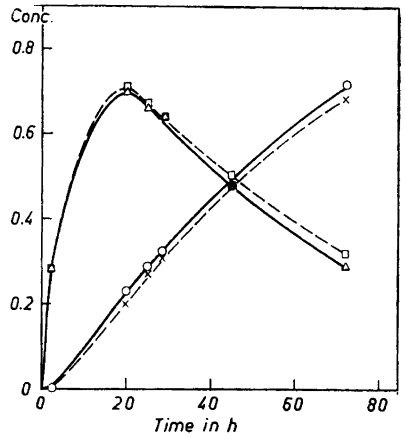


Fig. 4. Hydrolysis of phenylurethan with 1.000 M sodium hydroxide solution at 25.0°C. Concentration of: □ △ phenylcarbamate ion, × O aniline, relative to the initial ester concentration as a function of time.
— experimental values found in study (*b*).
— — — values calculated from the velocity constants determined in studies (*a*) and (*c*).

where A_0 is the initial concentration of the ester. As the values of k_1' and k_2' have been determined in the phenylurethan studies (*a*) and (*c*) the amounts of aniline and phenylcarbamate ion formed may be calculated at any time using these equations. In the phenylurethan study (*b*) the concentrations of aniline and phenylcarbamate ion were estimated separately.

In Fig. 4, these concentrations relative to the initial ester concentration are plotted *versus* time. As is evident, the curves obtained by the two methods agree rather well, indicating that the predominant hydrolytic reaction proceeds according to the scheme proposed above.

In the case of esters Nos. 2—4 the rate constants were determined in two ways as has been described. This gave agreeing values within the limits of experimental error. Apparently the methylphenylcarbamate ion does not exist even in the strongly alkaline solutions used. However, it seems most probable that the mechanism of hydrolysis for esters Nos. 2 and 4 is the same as that for phenylurethan, although the second step, *i.e.* the decomposition of the carbamate ion is here always the fastest step, independent of hydroxyl ion concentration.

As far as unsubstituted and singly N-substituted aromatic carbamates are concerned, Dittert [11] suggested an isocyanate intermediate. Esters Nos. 3 and 15 belong to the latter category of carbamates. As will be discussed below a shift in the mechanism of hydrolysis of these esters is very probable. However, if an isocyanate intermediate is formed the electrophilic carbon atom in the isocyanate group would be readily attacked by the hydroxyl ions, the isocyanate being rapidly transformed to a carbamate ion. Thus, a possible isocyanate intermediate is very hard to detect under the conditions used. In one experiment ester No. 3 was treated with 1 M sodium hydroxide solution. Measurements of the amount of phenylcarbamate ion formed showed that the ester was instantaneously transformed to the ion, which was then decomposed giving the same pseudo first-order rate constant as in the phenylurethan study (*c*). The other hydrolytic studies of ester No. 3 were carried out in buffer solutions of pH 8 and 9. Under these conditions the formation of phenylcarba-

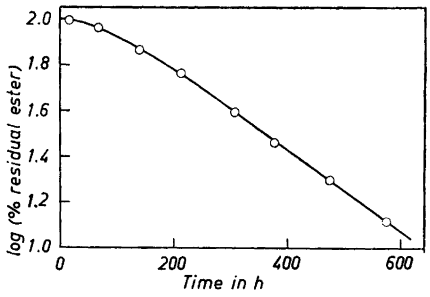


Fig. 5. Hydrolysis of ester No. 12 with 1.000 M sodium hydroxide solution at 25.0°C.

mate ion (or phenylisocyanate) might be the rate-determining step, as the decomposition of the carbamate at these pH values proceeds at a rate that is too fast to be measured. This was shown in the phenylurethan study (*c*). Thus, the mechanism seems to consist of formation of phenylcarbamate, possibly with phenylisocyanate as intermediate, followed by decomposition of the phenylcarbamate into aniline and carbonate.

The decomposition rate of esters Nos. 5—13 was followed by measuring the amount of amine formed after acidification.

The formation of a carbamate ion intermediate was indicated when the samples to be measured were not acidified before, which resulted in an induction period, or lag time, in the appearance of the amine in hydroxyl ion concentrations of above about 0.5 M. This is shown in Fig. 5. The plotting of log (% residual ester) is not quite adequate in this case, as the rate of formation of the amine does not strictly coincide here to the rate of decomposition of the ester. However, for the sake of uniformity, this notation is retained. Evidently, the mechanism is the same as for phenylurethan.

The velocity constants of esters Nos. 14—17 were determined by studying the rate of formation of the hydroxy compounds. In the case of ester No. 16 the rate of appearance of the amine was also measured; the two constants agreed rather well. Isocyanate formation may be considered to be out of the question for the N,N-disubstituted esters Nos. 14, 16, and 17. Acyl oxygen scission is the most probable mechanism for these esters. However, since Faurholt found no evidence for the occurrence of dimethylcarbamate ions it seems probable that rupture of the CO—N bond occurs immediately after. In the case of ester No. 15 a shift in the mechanism is indicated, which will be discussed in the following section.

The temperature dependence. According to the Arrhenius equation in its logarithmic form,

$$\log k = \log(PZ) - E_a/2.303\,RT$$

when the logarithms of the second-order rate constants k_1 were plotted *versus* $1/T$, straight lines were obtained, the slopes of which multiplied by $-2.303\,R$ give the Arrhenius activation energy E_a (Figs. 6—8).

Table 4. Kinetic data for the alkaline hydrolysis of urethans.

Ester No.	Temp. °C	M OH^-	k_1' h^{-1}	k_1 l. $mole^{-1}$ h^{-1}
1	25.0	0.0250	2.99×10^{-3}	1.20×10^{-1}
		0.0500	5.82×10^{-3}	1.16×10^{-1}
		0.1000	1.20×10^{-2}	1.20×10^{-1}
		0.2500	2.79×10^{-2}	1.12×10^{-1}
		0.5000	6.32×10^{-2}	1.26×10^{-1}
		1.000	1.09×10^{-1}	1.09×10^{-1}
	50.0	0.1000	9.31×10^{-2}	9.31×10^{-1}
	75.0	0.0500	3.17×10^{-1}	6.34
2	25.0	1.006	1.75×10^{-2}	1.74×10^{-2}
		1.000	1.84×10^{-2}	1.84×10^{-2}
	50.0	0.0960	1.34×10^{-2}	1.40×10^{-1}
		1.153	1.48×10^{-1}	1.28×10^{-1}
	75.0	1.153	8.76×10^{-1}	7.60×10^{-1}
3	25.0	1.047×10^{-6}*	1.74×10^{-1}	1.66×10^{5}
		1.175×10^{-5}*	2.06	1.75×10^{5}
	30.0	5.370×10^{-6}*	1.59	2.96×10^{5}
	35.0	1.778×10^{-6}*	7.33×10^{-1}	4.12×10^{5}
	45.0	3.160×10^{-6}*	2.99	9.46×10^{5}
4	25.0	0.1119	1.71×10^{-2}	1.53×10^{-1}
		0.9725	1.50×10^{-1}	1.54×10^{-1}
	50.0	0.1119	1.38×10^{-1}	1.23
		1.158	1.52	1.31
	75.0	0.1128	7.31×10^{-1}	6.48
5	25.0	0.1000	9.52×10^{-3}	9.52×10^{-2}
		1.000	9.10×10^{-2}	9.10×10^{-2}
	50.0	0.4889	5.12×10^{-1}	1.05
	75.0	0.0948	6.98×10^{-1}	7.36
6	25.0	0.0500	2.25×10^{-3}	4.50×10^{-2}
	50.0	0.9681	4.68×10^{-1}	4.83×10^{-1}
	75.0	0.2471	1.15	4.65

* Calculated from electrometrically determined pH-values.

Ester No.	Temp. °C	M OH^-	k_1' h^{-1}	k_1 l. $mole^{-1}$ h^{-1}
7	25.0	0.5000	2.78×10^{-3}	5.56×10^{-3}
		1.007	5.25×10^{-3}	5.21×10^{-3}
	50.0	0.9942	1.22×10^{-1}	1.23×10^{-1}
	75.0	0.1000	2.18×10^{-1}	2.18
		0.2500	5.19×10^{-1}	2.08
	100.0	0.0485	1.12	2.31×10^{1}
8	25.0	0.5000	1.71×10^{-3}	3.42×10^{-3}
		1.000	3.10×10^{-3}	3.10×10^{-3}
	50.0	0.5000	4.85×10^{-2}	9.70×10^{-2}
		1.000	9.64×10^{-2}	9.64×10^{-2}
	75.0	0.1000	1.50×10^{-1}	1.50
		0.2500	0.348	1.39
	100.0	0.0500	9.60×10^{-1}	1.92×10^{1}
9	25.0	0.5000	4.09×10^{-4}	8.18×10^{-4}
		1.000	7.71×10^{-4}	7.71×10^{-4}
	50.0	1.006	1.53×10^{-2}	1.52×10^{-2}
	75.0	1.000	3.37×10^{-1}	3.37×10^{-1}
	100.0	0.1000	3.95×10^{-1}	3.95
		0.2500	1.02	4.08
10	25.0	1.005	5.20×10^{-4}	5.17×10^{-4}
	50.0	0.5000	6.10×10^{-3}	1.22×10^{-2}
		1.005	1.19×10^{-2}	1.18×10^{-2}
	75.0	0.5000	1.01×10^{-1}	2.14×10^{-1}
		1.000	2.03×10^{-1}	2.03×10^{-1}
	100.0	0.2485	5.02×10^{-1}	2.02
11	25.0	0.1000	9.93×10^{-4}	9.93×10^{-3}
		0.5000	5.16×10^{-3}	1.03×10^{-2}
		1.010	1.02×10^{-2}	1.01×10^{-2}
	50.0	0.2500	5.76×10^{-2}	2.30×10^{-1}
		0.5000	1.09×10^{-1}	2.18×10^{-1}
	75.0	0.2500	7.74×10^{-1}	3.10
	100.0	0.02346	6.31×10^{-1}	2.69×10^{1}
		0.05056	1.41	2.79×10^{1}

Ester No.	Temp. °C	M OH^-	k_1' h^{-1}	k_1 l. $mole^{-1}$ h^{-1}
12	25.0	0.5000	2.23×10^{-3}	4.46×10^{-3}
		1.003	4.75×10^{-3}	4.74×10^{-3}
	50.0	0.1000	1.13×10^{-2}	1.13×10^{-1}
		1.003	1.20×10^{-1}	1.20×10^{-1}
	75.0	0.2548	4.92×10^{-1}	1.93
	100.0	0.0260	5.28×10^{-1}	2.03×10^{1}
		0.0507	9.43×10^{-1}	1.86×10^{1}
13	25.0	1.000	2.21×10^{-3}	2.21×10^{-3}
	50.0	1.000	9.21×10^{-2}	9.21×10^{-2}
	75.0	0.2500	3.28×10^{-1}	1.31
		0.5035	6.49×10^{-1}	1.29
	100.0	0.1000	1.92	1.92×10^{1}
14	10.0	0.1000	2.40×10^{-2}	2.40×10^{-1}
		1.000	2.28×10^{-1}	2.28×10^{-1}
	25.0	0.1000	1.00×10^{-1}	1.00
		1.000	1.02	1.02
	45.0	0.1000	4.80×10^{-1}	4.80
		1.000	4.58	4.58
15	20.0	2.845×10^{-6}*	0.389	1.37×10^{5}
	25.0	4.093×10^{-6}*	0.966	2.36×10^{5}
	30.0	5.370×10^{-6}*	2.15	4.01×10^{5}
16	25.0	0.0100	5.70×10^{-3}	5.70×10^{-1}
		0.0986	5.81×10^{-2}	5.89×10^{-1}
		0.9835	5.54×10^{-1}	5.63×10^{-1}
	35.0	0.4694	6.95×10^{-1}	1.48
	45.0	0.0993	3.38×10^{-1}	3.40
17	10.0	0.0100	9.80×10^{-2}	9.80
		0.1000	1.02	1.02×10^{1}
		1.000	9.60	9.60
	25.0	0.0100	3.61×10^{-1}	3.61×10^{1}
		0.1000	3.37	3.37×10^{1}
		1.000	3.22×10^{1}	3.22×10^{1}
	45.0	0.0100	1.56	1.56×10^{2}
		0.1000	1.44×10^{1}	1.44×10^{2}

* calculated from electrometrically determined pH-values.

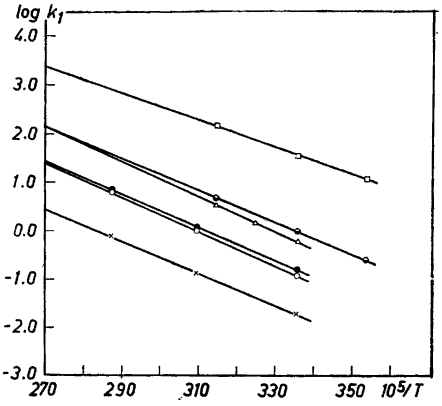


Fig. 6. log k_1 *versus* $1/T$. O ester No. 1, × ester No. 2, ● ester No. 4, ◒ ester No. 14, △ ester No. 16, □ ester No. 17.

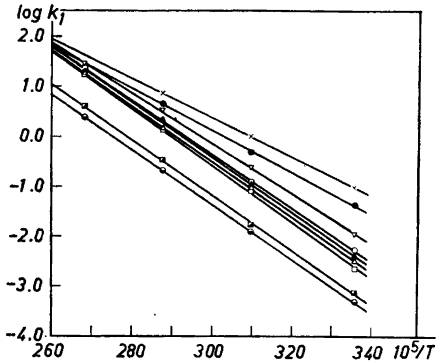


Fig. 7. log k_1 *versus* $1/T$. × ester No. 5, ● ester No. 6, O ester No. 7, △ ester No. 8, ◪ ester No. 9, ◒ ester No. 10, ▽ ester No. 11, ▲ ester No. 12, □ ester No. 13.

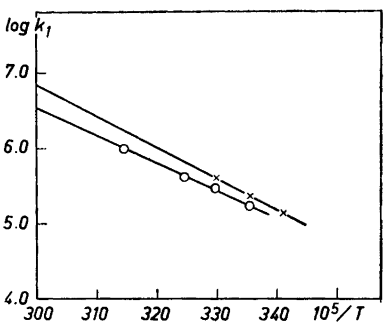


Fig. 8. log k_1 *versus* $1/T$. × ester No. 3, O ester No. 15.

The frequency factor PZ was calculated from the Arrhenius equation. The enthalpies and entropies of activation $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were, respectively, obtained from the equations

$$E_a = \Delta H^{\ddagger} + RT$$

and

$$PZ = e \times RT/Nh \times \exp(\Delta S^{\ddagger}/R)$$

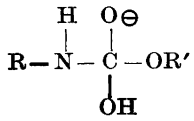
The results are shown in Table 5 together with the k_1 values at 25.0°.

As is apparent from Table 5, the second-order rate constants of esters Nos. 3 and 15 are about 10^5—10^6 times larger than those obtained for the corresponding disubstituted esters (Nos. 4 and 14). Dittert [11] also found very high velocity constants for the aromatic singly N-substitutd carbamates he studied, apparently due to very low heats of activation. In the case of esters Nos. 3 and 15, however, the $\Delta H^{\ddagger}$ values as compared to the other esters are normal. On the other hand the entropies are high, having positive signs. The positive $\Delta S^{\ddagger}$ values indicate an increase in the degrees of freedom of the system when the

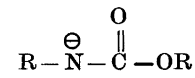
Table 5.

Ester No.	k_1 at 25.0°C l. mole^{-1} h^{-1}	$\Delta H^{\neq}$ kcal.	$\Delta S^{\neq}$ E.U.
1	1.2×10^{-1}	15.9	−25.5
2	1.8×10^{-2}	12.9	−39.3
3	1.7×10^{5}	16.6	5.0
4	1.5×10^{-1}	15.0	−28.0
5	9.3×10^{-2}	17.5	−20.8
6	4.5×10^{-2}	18.4	−19.1
7	5.4×10^{-3}	24.1	− 4.4
8	3.3×10^{-3}	24.7	− 3.3
9	7.9×10^{-4}	24.8	− 5.9
10	5.2×10^{-4}	24.1	− 8.7
11	1.0×10^{-2}	23.1	− 6.1
12	4.6×10^{-3}	24.1	− 4.7
13	2.2×10^{-3}	25.3	− 2.0
14	1.0	14.2	−27.0
15	2.4×10^{5}	18.3	11.4
16	5.7×10^{-1}	15.9	−22.4
17	3.4×10^{1}	12.8	−24.8

reactants pass into the transition state. The other esters studied in this work have all negative $\Delta S^{\neq}$ values. Thus the formation of the activated complex is here accompanied by a loss of degrees of freedom. This may indicate a shift in the mechanism of hydrolysis in the case of esters Nos. 3 and 15. Bender [26] has shown that the alkaline hydrolysis of several esters, which undergo acyl oxygen scission, is not a S_N2 reaction, and that the intermediate formed by the attack of the hydroxyl ions upon the ester is a real one. In the mechanism elucidated for phenylurethan, the intermediate has the structure



However, this intermediate may be supposed to be very like the activated complex, the steric conditions, *e.g.*, being about the same. The isocyanate mechanism, proposed by Dittert, does not involve any nucleophilic attack upon the carbonyl carbon by the hydroxyl ions, but rather elimination of a proton. The first intermediate formed has the formula



The spatial arrangements in the activated complex corresponding to this intermediate may be more favourable, giving a positive sign to $\Delta S^{\neq}$. In the isocyanate mechanism the formation of the intermediate is accompanied by

the release of a water molecule. This may have the same effect as a decrease in solvation, *i.e.* an increase in $\Delta S^{\ddagger}$.

In the following discussion of the substituent effects upon the enthalpy and entropy of activation, esters Nos. 3 and 15 are not included. As far as the N,N-disubstituted esters are concerned, the isocyanate mechanism is not probable. As the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values found for the singly N-substituted aliphatic esters do not deviate from those found for the disubstituted esters, the isocyanate mechanism is not probable even here.

The rate constant of ester No. 2 is about 7 times lower than that of ester No.1, as seen from Table 5. Apparently, this is due to steric hindrance from the methyl group rather than due to the electron-releasing effect, as there is a decrease in the entropy of activation of ester No. 2 by 13.8 E.U., while its enthalpy of activation is lower than that of ester No. 1. Comparing esters Nos. 2 and 4, the velocity constant is about 8 times larger for the latter; apparently the phenolic ester has the larger $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values. However, the phenyl group is expected to cause more steric hindrance and to be more electron-attracting than the ethyl group.

The introduction of a tertiary amino group in the alcoholic part of the ester, as in ester No. 5, has no pronounced effect upon the velocity constant. There is, however, a small increase in $\Delta H^{\ddagger}$ compared to phenylurethan, reflecting the electron-releasing effect of the tertiary amino group.

The introduction of an *ortho*-methyl group in ester No. 6 causes a somewhat lower velocity constant, due to a higher $\Delta H^{\ddagger}$ value, evidently indicating the positive inductive effect of the methyl group. However, introduction of a second *ortho*-methyl group, as in ester No. 7, has a more striking effect, the rate constant of this ester being about 8 times lower that of ester No. 6; this retarding effect seems therefore to be mainly steric. The *para*-methyl group in ester No. 8 has only a slight influence on the velocity of hydrolysis, as the effect of this group is exclusively inductive. The methyl group in the β-position of the alcohol in esters Nos. 9 and 10 seems to cause steric hindrance, the rate constants and $\Delta S^{\ddagger}$ values being rather low for these two esters. However, also ester No. 11 has a rather low entropy of activation. This ester is decomposed most rapidly of esters Nos. 7—13 and has a relative low $\Delta H^{\ddagger}$ value, possibly due to the electron-attracting oxygen atom in the morpholine ring. The influence of the diethylamino group seems to be about the same as that of the piperidine ring. The rather high $\Delta H^{\ddagger}$ values of esters Nos. 7—13 indicate that the methyl groups in the benzene ring might have an inductive effect.

Esters Nos. 14, 16, and 17 have rather low $\Delta S^{\ddagger}$ values indicating steric hindrance from the benzyl and methyl groups attached to the nitrogen in the acidic part of the ester. These esters have relatively low $\Delta H^{\ddagger}$ values, probably due to the electron-withdrawing effect of the positively charged nitrogen atom in the phenolic (or pyridolic) part of the esters. This is most pronounced in ester No. 17, where the nitrogen atom is located within the ring itself.

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