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Mechanisms of Hydrolysis of Carbonyl Chlorides[1]

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The rates of hydrolysis of dimethylcarbamyl chloride and ethyl chloroformate were studied, and the results were compared with those for acetyl and benzoyl chlorides obtained by previous investigators. The latter three chlorides are highly reactive toward hydroxyl ion and amines in water, but dimethylcarbamyl chloride is inert. Nevertheless, products resulting from attack by amines on a dimethylcarbamylium ion can be isolated. It is suggested that the carbamyl chloride hydrolyzes by an SN1 mechanism, while the other three chlorides react by SN2 mechanisms.

The kinetics and mechanisms of the hydrolysis of carbonyl chlorides, ZCOCl, have not been studied as extensively as those of the alkyl halide series, primarily because of inconveniently high rates. A considerable amount of information has, however, been accumulated on aromatic acyl chlorides (Z = $C_6H_5^-$, etc.), and some data on acetyl chloride (Z = CH_3^-) and ethyl chloroformate (Z = $C_2H_5O^-$) were also available.

The hydrolysis of benzoyl chloride[2] in aqueous acetone was first studied by Berger and Olivier.[3] Hudson and his co-workers have made an extensive study of the hydrolysis of benzoyl chloride and various substituted derivatives, chiefly in aqueous acetone.[4a-e] Their conclusion was that in solvents rich in acetone the hydrolysis of benzoyl chloride proceeded by an SN2 mechanism, while the water-rich solvents brought about a change to an SN1 mechanism. Even in the latter solvent the halide was susceptible to nucleophilic attack by hydroxyl ion.[5] The behavior of substituted benzoyl chlorides was held to be compatible with this view.[4c]

Swain and Scott[6a,b] studied the reactivity of benzoyl chloride toward hydroxide ion and aniline and concluded that bond making preceded bond breaking. They also studied acetyl chloride, and proved that it hydrolyzes much more rapidly than benzoyl chloride. The hydrolysis of acetyl chloride also has been studied recently by Zimmermann and Yuan[7] in 5% water–95% acetone.

Recently the existence of intermediates in the hydrolysis of benzoyl chloride has been demonstrated by two groups of investigators. Gold, Hilton and Jefferson[8] showed that a weakly nucleophilic aromatic amine could trap an intermediate which they felt to be benzoylium ion, $C_6H_5CO^+$. Bunton and his collaborators,[9] using the methods developed by Bender,[10] demonstrated the occurrence of a symmetrical intermediate in this reaction, presumably $C_6H_5C(OH)_2Cl$.

It has been overlooked by the proponents of an ionization process that Böhme and Schürhoff[11] have measured the rate of hydrolysis of ethyl chloroformate and found it to be quite slow ($k_1 = 2.0 \times 10^{-4}$ sec.$^{-1}$ in water at 25°). It appeared improbable to us that a reaction proceeding by ionization should not be greatly accelerated by the substitution of alkoxyl for phenyl. We have therefore investigated the hydrolysis of ethyl chloroformate more thoroughly and extended the study to dimethylcarbamyl chloride (Z = $(CH_3)_2N$–).

Experimental

Materials.—Dimethylcarbamyl chloride (Monsanto) was redistilled under vacuum, b.p. 34° (1 mm.), n^{20}_D 1.4511. It was necessary to use a low pressure to prevent decomposition during distillation. Ethyl chloroformate (Eastman Kodak Co.) was redistilled, b.p. 93.5°. The amines were Eastman Kodak Co. White Label materials.

Kinetic Methods.—The concentration cell method of Swain and Ross[12] was used for most runs. The equipment consisted of a Leeds and Northrup Type K-2 potentiometer and a Leeds and Northrup mirror galvanometer, type 2430-d. The electrodes were 22-gage silver wire. They were coated with silver chloride by electrolyzing 0.5 *N* HCl for 10–15 minutes using two dry cells connected in series. A Gilmont 1-ml. pipet was used to add 0.5 *N* HCl to the titration cell. The salt bridge contained an agar gel containing 5% sodium perchlorate. The solutions in the 500 ml. reaction and titration cells were stirred by electrically driven stirrers.

The method of intermittent titration was used in several runs. The titrant, 0.5 *N* sodium hydroxide, was added directly to the reaction flask from a Gilmont 1-ml. pipet with vigorous stirring. Ethyl chloroformate could be studied by this method, but not dimethylcarbamyl chloride. The buffering action of dimethylamine, and perhaps incomplete hydrolysis of the carbamic acid, cause erroneous results for the latter compound.

The silver electrodes could not be used in solutions of amines since the silver chloride coating was removed. In alkaline solution, the electrodes were very short-lived, but by working quickly some rate data could be obtained. A conductimetric method was more satisfactory, although of lower precision, for these experiments. An Industrial Instruments Co. conductivity bridge, model RC-IB (1000 cycles), was used. The reactions were conducted in a 1-liter 3-neck flask fitted with an electrically driven stirrer and a dip-type cell (cell constant 0.773).

Calculation of Rate Constants.—From the concentration cell and intermittent titration data, the rate constants were evaluated by a method similar to that of Swain and co-

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[1] Kinetics of Reactions of Acyl Chlorides. I.

[2] The discussion will be confined to aqueous solvents, although considerable data is known for alcoholic media.

[3] G. Berger and S. C. J. Oliver, *Rec. trav. chim.*, **46**, 516, 861 (1927).

[4] (a) R. F. Hudson and J. E. Wardill, *J. Chem. Soc.*, 1729 (1950); (b) B. L. Archer and R. F. Hudson, *ibid.*, 3259; (c) D. A. Brown and R. F. Hudson, *ibid.*, 883 (1953); (d) B. L. Archer, R. F. Hudson and J. E. Wardill, *ibid.*, 888 (1953); (e) D. A. Brown and R. F. Hudson, *ibid.*, 3352 (1953).

[5] The ratio k_{OH^-}/k_{H_2O} is substantial for benzoyl chloride but there is disagreement as to its actual value. Ref. 4a gives it as 20 (for 50% aq. acetone at 0°) but ref. 4e as 600. Ref. 6b, on the other hand, sets the ratio at 3.5×10^4. The variance is in k_{OH^-}, since k_{H_2O} shows good agreement.

[6] (a) C. G. Swain and C. B. Scott, THIS JOURNAL, **75**, 141 (1953); (b) 247 (1953).

[7] G. Zimmermann and C. Yuan, *ibid.*, **77**, 332 (1955).

[8] V. Gold, J. Hilton and E. G. Jefferson, *J. Chem. Soc.*, 2756 (1954).

[9] C. A. Bunton, T. A. Lewis and D. R. Llewellyn, *Chem. and Ind.*, **73**, 1154 (1954).

[10] M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

[11] H. Böhme and W. Schürhoff, *Chem. Ber.*, **84**, 28 (1951).

[12] C. G. Swain and S. D. Ross, THIS JOURNAL, **68**, 658 (1946).

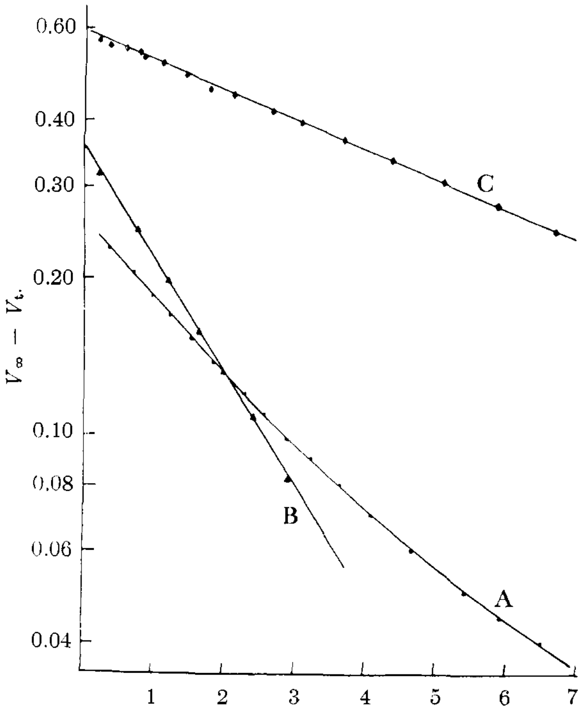


Fig. 1.—Representative first-order hydrolysis rate plots: A, dimethylcarbamyl chloride (Table I, expt. 4); B, dimethylcarbamyl chloride in presence of alkali (expt. 10); C, ethyl chloroformate (expt. 18) (multiply time scale by ten).

workers.[13] A plot of log (V_∞ − V_t) *vs.* time, in minutes was prepared and extrapolated to zero time. The quantity (V_∞ − V_0) at zero time was read off and divided by 2. The time corresponding to the quotient, *i.e.*, the half-life, was read from the graph. Division of 0.01155 by the half-life in minutes gave the first-order rate constant in reciprocal seconds. From the conductimetric data, a plot of log (K_∞ − K_t) *vs. t*, where K_∞ and K_t are the reciprocals of the observed resistance at times ∞ and *t*, respectively, was prepared. The rate constant was obtained as described above.

Products.—To a solution of 21.5 g. of *p*-anisidine, 2.1 g. of sodium lorol sulfate and 177.6 g. of sodium sulfate in 5 l. of water at 8.0° was added 1.44 g. of dimethylcarbamyl chloride in 36 ml. of acetone. After 35 minutes at 6–8° the solution was acidified with 150 ml. of concd. sulfuric acid in 750 ml. of water. It was extracted five times with 1-liter portions of methylene chloride. These were combined, dried over $MgSO_4$, and evaporated. Essentially nothing was left. The water layer was extracted continuously overnight with methylene chloride. No product was found in the methylene chloride solution.

A reaction was conducted as above, using 2.00 g. of benzylamine in 410 ml. of water, and a solution of 1.000 g. of dimethylcarbamyl chloride in 10 ml. of acetone. No product could be isolated by a procedure like that above.

A solution of 10.0 g. of hydroxylamine hydrochloride in 600 ml. of distilled water was stirred with 180 g. of Amberlite IR-4B(OH) until the *p*H was 7.5. A portion of the filtrate, 200 ml., was diluted with 250 ml. of water and treated with 3.2 g. of dimethylcarbamyl chloride at 8.5°. When the reaction was complete a portion of the solution was found to give an intense purple color with ferric chloride solution. To the remainder was added 10 g. of potassium nitrate and then 10 ml. of glacial acetic acid. The solution turned green and gas was evolved. The solution was extracted five times with 100-ml. portions of ether, dried over $MgSO_4$ and evaporated to a mobile yellow oil. This was left in a desiccator over P_2O_5 for two weeks. It eventually left 0.10 g. of a pale brown oil. This was not further investigated.

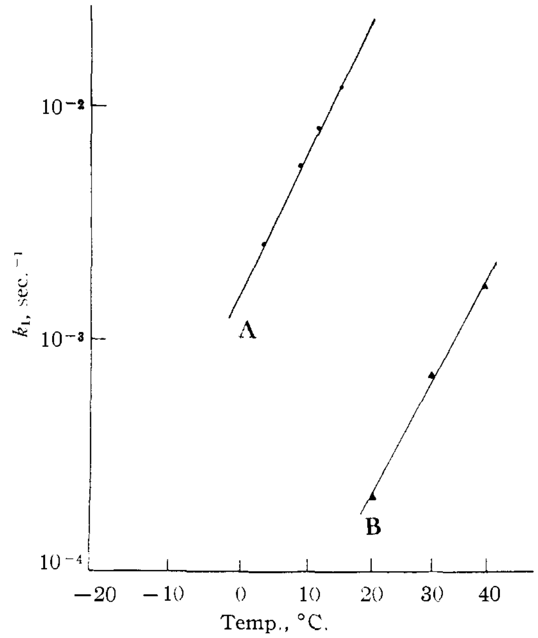


Fig. 2.—Arrhenius plots for the neutral hydrolysis of dimethylcarbamyl chloride (A) and ethyl chloroformate (B).

In a similar experiment, 135 ml. of the filtrate was diluted with 300 ml. of water and reacted with 1.94 g. of dimethylcarbamyl chloride. The final solution gave the characteristic deep purple color of a hydroxamic acid with aqueous ferric chloride solution, whereas the starting solution only gave a brown precipitate of ferric hydroxide. The expedient of freeing hydroxylamine from its salt with alkali was unsuitable, since the solutions were too conducting to follow the rates accurately. Use of an ion-exchange resin avoided this difficulty.

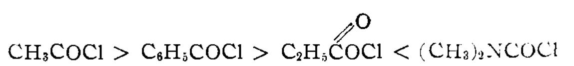
Dimethylcarbamyl Chloride–Pyrrolidine.—In a 4-l. beaker fitted with a stirrer was placed 3 liters of water at 8.5°. To it were added with stirring 22.0 g. (0.31 mole) of pyrrolidine and then, over 1 minute, 15.0 g. (0.14 mole) of dimethylcarbamyl chloride. The solution was stirred for 30 minutes at 7–8°, allowed to warm to room temperature, and was extracted continuously overnight with methylene chloride. The methylene chloride extract was dried with magnesium sulfate and distilled. There was obtained 10.38 g. (52.3%) of 1,1-dimethyl-3,3-tetramethyleneurea, b.p. 103–105° (9 mm.), $n^{20}\mathrm{D}$ 1.4852.

An authentic sample, prepared in 69.5% yield by the reaction of dimethylcarbamyl chloride with pyrrolidine in benzene solution, had the following properties: b.p. 103–109° (9 mm.), $n^{20}\mathrm{D}$ 1.4850–1.4860.

Anal. Calcd. for $C_7H_{14}N_2O$: C, 59.12; H, 9.92. Found: C, 58.65, 58.85; H, 9.78, 9.52.

Results

The kinetics data are given in Table I. The rate sequence for neutral hydrolysis is



$$\mathrm{CH_3COCl > C_6H_5COCl > C_2H_5\overset{\overset{O}{/\!/}}{C}OCl < (CH_3)_2NCOCl}$$

The decline in rate on passing from acetyl chloride to ethyl chloroformate, followed by a steep rise to dimethylcarbamyl chloride, suggests a change in mechanism. The phenomenon is reminiscent of the behavior observed in the alkyl halide series, where the introduction of progressively more electron-donating groups eventually changes the reaction mechanism from S_N2 to S_N1. We therefore propose the following reaction mechanisms

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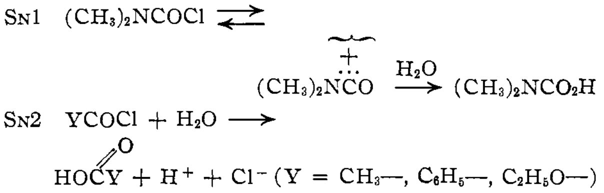
[13] C. G. Swain, C. B. Scott and K. H. Lohmann, This Journal, **75**, 136 (1953).

TABLE I

Expt.	Temp., °C.	Halide	Initial concn. 10^3, *M*	Concn. of added substances, *M*	Kinetic method	$k_1 \times 10^4$ sec.$^{-1}$
1	3.2	Dimethylcarbamyl chloride	1.81	$NaClO_4$, 0.065	Concn. cell	25.8
2	3.2	Dimethylcarbamyl chloride	0.715	NaOH, 0.157	Concn. cell	35
3	3.2	Dimethylcarbamyl chloride	0.734	NaOH, 0.205	Concn. cell	37
4	8.5	Dimethylcarbamyl chloride	1.97	$NaClO_4$, 0.065	Concn. cell	55.5
5	8.5	Dimethylcarbamyl chloride	4.10	$NaClO_4$, 0.0054	Conductivity	72.2
6	8.5	Dimethylcarbamyl chloride	4.17	$NaClO_4$, 0.0054	Conductivity	63.5
7	8.5	Dimethylcarbamyl chloride	0.70	Na_2SO_4, 0.25	Concn. cell	66.4
8	8.5	Dimethylcarbamyl chloride	0.972	NaOH, 0.205	Concn. cell	53
9	8.5	Dimethylcarbamyl chloride	0.850	NaOH, 0.1465	Concn. cell	67
10	8.5	Dimethylcarbamyl chloride	0.477	NaOH, 0.1036	Concn. cell	84.3
11	8.5	Dimethylcarbamyl chloride	0.532	*p*-Anisidine, 0.0348	Concn. cell	59
12	8.5	Dimethylcarbamyl chloride	22.7	Benzylamine, 0.0455	Conductivity	72
13	8.5	Dimethylcarbamyl chloride	45.1	Pyrrolidine, 0.053	Conductivity	83
14	8.5	Dimethylcarbamyl chloride	41.5	Hydroxylamine, 0.075	Conductivity	64
15	9.5	Dimethylcarbamyl chloride	0.79	*m*-Cresol, 0.0617 NaOH, 0.0613	Concn. cell[a]	36.7
16	11.4	Dimethylcarbamyl chloride	1.37	$NaClO_4$, 0.065	Concn. cell	81.4
17	15.0	Dimethylcarbamyl chloride	1.90	$NaClO_4$, 0.065	Concn. cell	120.5
18	20.1	Ethyl chloroformate	0.863	$NaClO_4$, 0.047	Concn. cell	2.15
19	30.0	Ethyl chloroformate	1.04	$NaClO_4$, 0.065	Concn. cell	6.92
20	39.7	Ethyl chloroformate	1.50	$NaClO_4$, 0.065	Concn. cell	16.7
21	8.5	Ethyl chloroformate	1.0	NaOH, 0.040	Conductivity	>400
22	8.5	Ethyl chloroformate	34.5	Pyrrolidine, 0.053	Conductivity	>760

[a] Solvent 86.1% water–13.9% dioxane.



$$S_N1 \quad (CH_3)_2NCOCl \rightleftarrows (CH_3)_2N\overset{+}{C}O \xrightarrow{H_2O} (CH_3)_2NCO_2H$$

$$S_N2 \quad YCOCl + H_2O \longrightarrow HO\overset{O}{\overset{\|}{C}}Y + H^+ + Cl^- \; (Y = CH_3—, C_6H_5—, C_2H_5O—)$$

The first-order plots in the hydrolysis of ethyl chloroformate were linear throughout each run, up to 80% completion. Those for dimethylcarbamyl chloride showed a marked downward drift within each run. The plots were extrapolated to zero time, and the rate constants were calculated from the initial slopes.

This drift was not caused by hydrogen ion formed in the reaction because solutions acidified to *p*H 2 with perchloric acid behave similarly. It was not caused by a reaction of higher order, because the extrapolated initial first-order rate constants did not depend on the initial concentration of dimethylcarbamyl chloride. Significantly, this draft was not observed when reactive nucleophiles were present, even though the latter did not affect the rate. Under these conditions the first-order plot was linear over 80% of the total reaction.

It appears reasonable to ascribe the above behavior to a "mass law" effect of chloride ion, which reacts with the dimethylcarbamylium ion to form starting material. If hydroxide or phenoxide ions, which are much more active than chloride ion, are present, they compete effectively for the acyl ion.

Several attempts were made to measure the rate of hydrolysis of diethylcarbamyl chloride, $(C_2H_5)_2NCOCl$, at 8.5°, but the reaction was too rapid to measure.

Investigation of the behavior of these halides toward nucleophilic reagents provided strong evidence in favor of a duality of mechanism. Acetyl chloride and benzoyl chloride are known to be highly reactive toward hydroxyl ion and aniline.[4,6] The data of Table I show the same to be true of ethyl chloroformate, since the ratios k_{OH^-} and k_p/k_{H_2O} can be shown to be of the order of at least 10^4. On the other hand, the rate of hydrolysis of dimethylcarbamyl chloride is completely unaffected by 0.205 *M* hydroxyl ion, 0.053 *M* pyrrolidine or 0.075 *M* hydroxylamine.

Proof of an intermediate in the hydrolysis of dimethylcarbamyl chloride was obtained by examining the products formed when dimethylcarbamyl chloride was hydrolyzed in the presence of pyrrolidine or hydroxylamine. Hantzsch and Sauer[14] showed that the reaction of dimethylcarbamyl chloride with hydroxylamine formed the hydroxamic acid, $(CH_3)_2NCONHOH$. Their experiment was repeated using the conditions of the kinetic experiments. The hydroxamic acid cannot be extracted owing to its high water solubility, but tests with ferric chloride gave the characteristic deep purple color of a hydroxamic acid.

Conclusive evidence was obtained from the use of 0.053 *M* pyrrolidine. The product, isolated in 52.3% yield by continuous extraction of the reaction mixture with ether, was 1,1-dimethyl-3,3-tetramethyleneurea. Although the amine cannot compete with water, an electrophilic reagent, for the acyl chloride, it can compete with water nucleophilically for the dimethylcarbamyl ion.

Benzylamine (pK_a 9.4) and *p*-anisidine (pK_a 5.29) were also without effect on the rate. Here no product was isolable by continuous extraction of the reaction mixture. It was not ascertained whether these amines, possessing less nucleophilic character, could not compete with water for the acylium

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[14] A. Hantzsch and A. Sauer, *Ann.*, **299**, 85 (1898).

ion; or whether the ureas produced, possessing N–H bonds, could not be extracted from water.

The activation energies and entropies for the neutral hydrolysis of the various halides are given, along with those of earlier investigators in Table II. It is seen that the value of $\Delta S^{\ddagger}$ for dimethylcarbamyl chloride differs markedly from those of the other halides. It is, however, close to that observed for the solvolysis of *t*-butyl chloride in 90% water–10% dioxane[15] (+8 e.u.) and that of the acid-catalyzed hydrolysis of *t*-butyl mesitoate[16] (+10 e.u.) (*cf.* −8 e.u. for methyl chloride[15]).

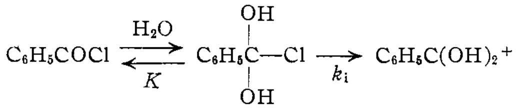
TABLE II

Halide	Solvent	$\Delta E^{\ddagger}$, kcal./mole	$\Delta S^{\ddagger}$, e.u.	Reference
Acetyl chloride	25% water–75% acetone	13.9	−14	6b
Benzoyl chloride	50% water–50% acetone	18.8	− 7.1	6b
Ethyl chloroformate	Water	19.0	−12.4	Present work
Dimethylcarbamyl chloride	Water	21.6	+ 5.6	Present work

Discussion

The fact that ethyl chloroformate hydrolyzes at a rate at least one-fiftieth as fast as benzoyl chloride, as found by Böhme and Schürhoff, definitely excludes an SN1 mechanism for the latter compound. For an alkoxyl group to be so much less effective at stabilizing a carbonium ion than a phenyl group would be without precedent. The observed high reactivities of both of these halides to nucleophiles makes it likely that both of them are undergoing an SN2 type of hydrolysis.

The SN2 reaction in neutral hydrolysis, at least for benzoyl chloride, is not a simple irreversible displacement. The work of Bunton, *et al.*, and of Gold, *et al.*, has proven the existence of intermediates in the hydrolysis of benzoyl chloride. A symmetrical molecule has been shown to exist by the tracer work. It seems reasonable in view of the structure of this molecule that it should give rise to the intermediate observed by Gold[17]



$$C_6H_5COCl \underset{K}{\overset{H_2O}{\rightleftharpoons}} C_6H_5\overset{OH}{\underset{OH}{C}}{-}Cl \xrightarrow[k_1]{} C_6H_5C(OH)_2^+$$

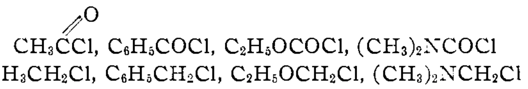
Reaction of this ion with amine or with water accounts for the observed kinetics. It would be interesting to know whether similar intermediates occur in the hydrolysis of ethyl chloroformate.

Berger and Olivier[3] and Brown and Hudson[4c] have given the rate constants for the hydrolysis of *p*-substituted benzoyl chlorides in 50% aqueous acetone. As noted by the latter investigators, the rate constants, when plotted against Hammett's sigma constants for the substituents, do not give a single straight line. Instead a pronounced minimum in the region of $\sigma = +0.23$ is noted. The strong acceleration caused by introduction of electron-releasing substituents (negative ρ) was taken as an indication of an SN1 reaction by Brown and Hudson.[4c] It is also, however, consistent with the process postulated above, since k_1 (obs) will be the product Kk_1. The observed ρ value will be the sum of the observed ρ values for the reversible hydration and the ionization. The former will be slightly positive or negative,[18] and the latter strongly negative.[19] The sum will therefore be strongly negative.

Acetyl chloride may also react by a hydration mechanism.

Swain and Dittmer[20] showed that the reactivities toward solvolysis of a wide variety of halides could be expressed by the values of a parameter *a*. The value of *a* for benzoyl chloride is very close to that of methyl and ethyl bromides and differs markedly from those of *t*-butyl chloride and bromide.

In comparing the two series



$$\overset{O}{\overset{\nearrow}{CH_3CCl}},\ C_6H_5COCl,\ C_2H_5OCOCl,\ (CH_3)_2NCOCl$$
$$CH_3CH_2Cl,\ C_6H_5CH_2Cl,\ C_2H_5OCH_2Cl,\ (CH_3)_2NCH_2Cl$$

it is clear that the point of mechanistic change occurs further to the right in the carbonyl chloride series. This is what would be expected from a comparison of the electrophilic characteristics of a carbonyl group and an alkyl group.

Acknowledgments.—We are indebted to Dr. P. W. Morgan for advice and encouragement and to Mr. Donald G. Preis for excellent technical assistance.

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(15) C. G. Swain, R. Cardinaud and A. D. Ketley, THIS JOURNAL, **77**, 934 (1955).

(16) V. R. Stimson and E. J. Watson, *J. Chem. Soc.*, 2848 (1954).

(17) A hydration mechanism for the hydrolysis of benzoyl chloride was first suggested by Berger and Oliver.[3] A referee has criticized this formulation on the grounds that in all ester and amide hydrolysis studied by oxygen exchange methods, the addition of water proceeds as the slow step, followed by a fast breakdown of the intermediate. In amide and ester hydrolyses, however, the intermediate cannot ionize in the manner postulated here. Also, electron donation by O or N in the former cases might well cause the addition of water to be the slow step.

(18) C. W. L. Bevan, E. D. Hughes and C. K. Ingold, *Nature*, **171**, 301 (1953).

(19) J. K. Kochi and G. S. Hammond, THIS JOURNAL, **75**, 3445 (1953).

(20) C. G. Swain and D. C. Dittmer, *ibid.*, **75**, 4627 (1953).