

gest that an initial protonation determines the structure of the reduction products. Indirect evidence for significant basicity in the β -position of the pyrrole ring has been inferred from reaction products with other electrophilic reagents, *e.g.*, nitration.¹⁹ This is also apparent in the fact that all the hydrogen atoms in pyrrole are readily exchanged with deuterium in acid solutions.¹ Finally, the mechanism proposed²⁰ for the trimerization of pyrrole, which assumes β -protonation, is indirectly supported by our direct observation of this step in a closely related system.

Experimental^{21,22}

Materials.—2,5-Dimethylpyrrole was prepared by passing a slow stream of dry ammonia gas through a refluxing solution of 10 g. of acetylacetone in 30 ml. of benzene; water was removed azeotropically. The pure product, b.p. 164–166° (755 mm.) (reported²³ b.p. 165°), weighed 7.6 g. (92%); v.p.c. analysis at 150° showed a single sharp peak, retention time 6.5 min. The infrared spectrum (pure liquid) had bands at 2.98 μ (NH) and 6.25 μ (double bonds).

1,2,5-Trimethylpyrrole, prepared by the above method with methylamine instead of ammonia, was a colorless liquid, b.p. 168–170° (755 mm.) (reported²⁴ b.p. 173° (746 mm.)); v.p.c. analysis at 150° showed a single sharp peak with a retention time of 9 min.

2,5-Dimethyl-1-phenylpyrrole was prepared by the method of Yanovskaya.²⁵

Fisher certified reagent sulfuric acid and perchloric acids were used for all measurements. Concentrations were determined by titration with 0.2 *N* sodium hydroxide (standardized against potassium acid phthalate) using phenolphthalein as indicator.

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N.m.r. Spectra.—Samples (0.2 g.) of the freshly distilled pyrrole and 1.0 ml. of aqueous sulfuric acid of the concentration specified containing a few crystals of tetramethylammonium chloride were degassed separately and mixed under vacuum. Sealed 5-mm. o.d. precision ground thin wall sample tubes containing the mixed solutions were examined using a Varian HR-60 spectrometer (59.997 m.c.) and Hewlett-Packard 200-J audio-oscillator calibrated against a 524-C frequency counter. The frequency separation between the tetramethylammonium ion internal reference and tetramethylsilane is 198.7 c.p.s., the latter occurring at higher field. Areas were determined with a H. A. Philbrick model UPA-2 integrator using an ac-lock in detector operating at 1200 c.p.s. according to the circuit described by Johnson.²⁶

pK_a Measurements.—Stock solutions (10^{-2} *M*) of the freshly distilled pyrrole in 95% ethanol were prepared immediately before each determination. In the indicator measurements, 0.1 ml. of the stock was pipetted into 10-ml. volumetric flasks and diluted to volume with the appropriate acid. Ultraviolet measurements were conducted at 25° in 1-cm. silica cells in a Beckman DU spectrophotometer equipped with double therino-spacers except for preliminary work carried out on a Beckman model DK-2 recording spectrophotometer. All bases and conjugated acids were found to obey Beer's law. The reversibility of the spectra was demonstrated by approaching intermediate acid concentrations either from neutral or strongly acidic media. Indicator ratio determinations were made about 2 minutes after mixing the pyrrole and acid, and readings rechecked 4 minutes later showed less than 1% change in absorbance. The pK_a 's listed were determined at 237, 242 and 275 $m\mu$, respectively, for 2,5-dimethyl-, 1,2,5-trimethyl- and 1-phenyl-2,5-dimethylpyrrole. In the first two cases, direct extrapolation using the eq. 10

$$pK_{BH^+} = \lim_{C_a \rightarrow 0} [\log (C_{BH^+}/C_B) - \log C_{H^+}] \quad (10)$$

was possible, the value for C_{H^+} being corrected for the second ionization of sulfuric acid using a constant of 0.02.²⁷ A least squares technique assuming the linearity of the equation above was used to obtain pK_{BH^+} from the experimental points. The extrapolation of the data for 1-phenyl-2,5-dimethylpyrrole was based on the indicator ratio plot for 2,5-dimethylpyrrole, the two curves being parallel in the region of overlap; 50% protonation of 1-phenyl-2,5-dimethylpyrrole occurs in 2.83 *M* H_2SO_4 , and the slope of $\log I$ vs. molarity of H_2SO_4 is 0.80 at the 50% protonation point.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, NORTHWESTERN UNIVERSITY, EVANSTON, ILL., AND ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL.]

Acylium Ion Formation in the Reactions of Carboxylic Acid Derivatives. III. The Hydrolysis of 4-Substituted-2,6-dimethylbenzoyl Chlorides¹

BY MYRON L. BENDER² AND MARK C. CHEN

RECEIVED JULY 11, 1962

The kinetics of hydrolysis of five 4-substituted-2,6-dimethylbenzoyl chlorides in 99% acetonitrile-water were determined. The hydrolysis of mesitoyl chloride was shown to be subject to both hydronium ion (the first instance of acid catalysis of an acid chloride) and hydroxide ion catalysis. Tetra-*n*-butylammonium chloride depresses the rate presumably due to a common-ion rate effect. Other salts have relatively little effect on the reaction. Electron-donating 4-substituents accelerate the neutral and acid-catalyzed hydrolysis but depress the base-catalyzed hydrolysis. The Hammett ρ -constants for the neutral, acid-catalyzed and base-catalyzed reactions are -3.85 , -3.73 and $+1.20$, respectively, the former two obtained from plots employing σ^+ -constants and the latter one obtained from a plot employing σ -constants. In neutral and acid-catalyzed hydrolysis, no carbonyl oxygen exchange was found to accompany the reaction. On the basis of the above evidence it is postulated that two distinct pathways occur in the hydrolysis of these acid chlorides: (1) in neutral and acid-catalyzed hydrolysis, a unimolecular heterolytic fission occurs, with the formation of an acylium ion in the rate-determining step; and (2) in base-catalyzed hydrolysis, addition of hydroxide ion to the carbonyl group occurs, with the formation of a tetrahedral addition intermediate in the rate-determining step.

Introduction

Previous papers in this series have presented experimental evidence for the formation of acylium ion intermediates in two reactions, the diazotization of benzamide³ and the hydrolysis of methyl mesitoate in sulfuric acid.⁴ The present paper attempts to pre-

sent evidence concerning an analogous reaction, the hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides.

The nucleophilic reactions of acid halides differ from those of esters principally in the speed of reaction, presumably because of the smaller resonance stabilization in the ground state of acid chlorides than of esters and of the ready ionization of the carbon-halogen bond. Acid chlorides may react with nucleo-

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(2) Alfred P. Sloan Foundation Research Fellow; present address Northwestern University.

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philes either through an S_N1 reaction with the intermediacy of an acylium ion or *via* a bimolecular reaction which can either be described as an S_N2 reaction or a carbonyl addition reaction. In highly polar solvents and in the absence of strong nucleophiles, the first mechanism tends to predominate, whereas in non-polar solvents and in the presence of strong nucleophiles the latter mechanism tends to predominate.⁵⁻⁷ Substituent effects on the nucleophilic reactions of substituted benzoyl chlorides indicate that electron-withdrawing groups facilitate the bimolecular reaction as expected.^{5,8,9}

In solvents of low polarity to which attention is devoted in this work, the bimolecular reactions of benzoyl halides are well characterized. The relative rates of solvolysis of various *p*-substituted benzoyl chlorides in 40% ethanol-60% diethyl ether show that electron-attracting groups accelerate the reaction.⁷ Furthermore, the bimolecular reactions of a series of substituted benzoyl chlorides with aniline in benzene solution shows the same substituent effect (Hammett $\rho = 1.2$).¹⁰⁻¹² The relative rates of reaction of a series of substituted anilines with benzoyl chloride in benzene solution show that the reaction is also proportional to the basicity of the amine^{10,13} (Hammett $\rho = 2.78^{11}$ (3.12^{12})). The rate of this reaction is dependent on the polarity of the solvent in benzene-nitrobenzene mixtures, indicating that the transition state of the amine-acid chloride reaction is more polar than the reactants.^{14,15} Thus the kinetic importance of nucleophilic attack on the carbonyl carbon atom of *p*-substituted benzoyl chlorides in non-polar solvents is established.

Although the nucleophilic reactions of *p*-substituted benzoyl chlorides appear to occur *via* a bimolecular pathway, the effects of di-*o*-substituents on the alcoholyses of benzoyl chlorides indicate that sterically hindered benzoyl chlorides may be hydrolyzed by an alternative mechanism. 2,6- and 2,4,6-substituents of benzoyl chlorides affect alcoholysis in such a way that electron-donating groups accelerate the reaction whereas electron-withdrawing groups retard it.¹⁶ Steric hindrance is known to cause large reductions in rate in S_N2 reactions, and also in the alkaline hydrolysis of benzoate esters, *e.g.*, methyl mesitoate.¹⁷ The fact that steric hindrance does not operate in the alcoholyses of 2,6- and 2,4,6-trimethyl-, -methoxy- and -ethoxybenzoyl chlorides shows that these reactions may proceed by a different mechanism. An accumulation of electron-donating groups on a benzene nucleus, despite apparent steric hindrance, causes the hydrolysis to proceed by an ionization mechanism even in solvents of low water content.⁷ Thus hydroxide ion has no effect on the rate of hydrolysis of mesitoyl chloride in 95% aqueous acetone⁷; alkoxide ion has very little catalytic effect on the rate of alcoholysis of mesitoyl chloride.¹⁸ These results seem to support the conclusion that mesitoyl chloride may be hydrolyzed by an S_N1 mechanism

whose rate-determining step is the formation of an acylium ion intermediate.

The results of other investigations, however, do not support the above hypothesis. In 95% (v./v.) aqueous dioxane a powerful acceleration of the rate of hydrolysis of mesitoyl chloride by hydroxide ion was found.¹⁹ Furthermore, the carbonyl oxygen atom of mesitoyl chloride was found to exchange with the solvent concurrently with the hydrolysis reaction.²⁰ From these results, Bunton and co-workers concluded that the hydrolysis of mesitoyl chloride should not be regarded as an S_N1 reaction involving the formation of an acylium ion, but rather as a reaction involving a tetrahedral intermediate. They pointed out that ordinarily it is found that aromatic carboxylic acid derivatives are less reactive than corresponding aliphatic compounds; however, the conjugation between the benzene ring and the carbonyl group of a benzoyl chloride, which is usually responsible for the lower reactivity of aromatic compounds, is not present in mesitoyl chloride because of steric hindrance to such conjugation. Therefore, the rate of reaction of mesitoyl chloride should not be thought of as inordinately high but rather that of benzoyl chloride as inordinately low. These experimental findings and conclusions were supported by a study of the kinetics of alcoholysis of some substituted benzoyl chlorides.²¹ In this reaction a similar large effect of alkoxide ion and no significant effect of added salts on the rate of alcoholysis of mesitoyl chloride was observed, as compared with that of other *p*-substituted benzoyl chlorides. In order to resolve these two divergent views of the hydrolysis of mesitoyl chloride the present kinetic and isotopic experiments were undertaken.

Experimental

Materials.—Spectrograde acetonitrile (Eastman Organic Chemicals) was used. The water content of this solvent was determined with Karl Fischer reagent (Fisher Scientific Co.) to be 0.02%. Perchloric acid solutions of desired molarity were diluted from concentrated perchloric acid (Allied Chemical, reagent grade). Diluted aliquots of the stock solutions were standardized by titration with standard sodium hydroxide. Tetramethylammonium hydroxide solutions of desired molarity were diluted from a 10% aqueous solution (Eastman Organic Chemicals). Diluted aliquots of the stock solutions were standardized by titration with standard hydrochloric acid. The tetra-*n*-butylammonium halide solutions of desired molarity were diluted from a 1 *M* aqueous solution of tetra-*n*-butylammonium chloride (K and K Lab.) or prepared from the solid salts, tetra-*n*-butylammonium bromide (Eastman Organic Chemicals, reagent grade) and tetra-*n*-butylammonium chloride obtained by evaporating commercial 1 *M* aqueous solutions. Labeled water containing 1.85 atom % ¹⁸O was obtained from the Weizmann Institute of Science, Rehovoth, Israel.

Benzoyl Chlorides.—Benzoyl chloride (Matheson, Coleman and Bell, reagent grade) was distilled under vacuum.

2,6-Dimethylbenzoyl chloride was prepared from 2,6-dimethylbenzoic acid and purified thionyl chloride²² (20% molar excess), the reaction being allowed to stand overnight. After 30 minutes of refluxing, the excess thionyl chloride and the gaseous by-products were removed under vacuum. The acid chloride was distilled under vacuum, b.p. 90-91° (5 mm.), lit.²³ b.p. 217° (752 mm.). Since the acid chloride hydrolyzes readily in air to the corresponding acid, the refractive index of the compound was not measured. 2,6-Dimethylbenzoic acid, the starting material for this preparation, was synthesized from 2,6-dimethylacetophenone²⁴ by means of the haloform reaction.²⁵ 2,6-Dimethylbenzoic acid which was obtained in 10% yield was recrystallized from ligroin; m.p. 115°, lit.²⁵ m.p. 115°.

Mesitoyl chloride was prepared from mesitoic acid (m.p. 153.5-155.8°) in the same manner as above. The acid chloride was dis-

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TABLE I
THE KINETICS OF HYDROLYSIS^a OF 4-SUBSTITUTED-2,6-DIMETHYLBENZOYL CHLORIDES^b AND BENZOYL CHLORIDE^c

Substituent	Spontaneous hydrolysis $k \times 10^3, ^\circ \text{sec.}^{-1}$	Perchloric acid catal.		Tetramethylammonium hydroxide catal.	
		$k \times 10^3, ^\circ \text{sec.}^{-1}$	$k_H \times 10, M^{-1} \text{sec.}^{-1}$	$k \times 10, ^\circ \text{sec.}^{-1}$	$k_{OH}, M^{-1} \text{sec.}^{-1}$
CH ₃ O	126	700-2100 ^e	520-1800
CH ₃	4.45	58.4	49.5	45.8	27.7
H	0.424	5.85	4.98	60.2	40.1
Br	0.0606 ^f	0.56	0.458	42.6 ^g	44.3
NO ₂	9.6×10^{-3j}	1.35×10^{-3j}	1.15×10^{-3}	184 ^h	369
Benzoyl chloride	1.30×10^{-3j}	1.20×10^{-3j}	..	1.32	0.885

^a 25.0° unless otherwise noted. 99% acetonitrile-water. ^b Initial concentration: 5×10^{-4} to $2 \times 10^{-5} M$. ^c Average of at least two runs. ^d $1.09 \times 10^{-2} M$ perchloric acid. ^e Estimated from the spectrophotometric observation that the reaction approaches completion a few seconds after mixing. ^f $1.49 \times 10^{-3} M$ tetramethylammonium hydroxide unless otherwise noted. ^g $0.961 \times 10^{-3} M$ tetramethylammonium hydroxide. ^h $0.497 \times 10^{-3} M$ tetramethylammonium hydroxide. ⁱ Initial concentration of acid chloride 10^{-4} to $6 \times 10^{-8} M$. ^j 25.5°.

titled *in vacuo*; b.p. 73° (0.5 mm.), lit.²⁸ b.p. 143-146° (60 mm.).

4-Methoxy-2,6-dimethylbenzoyl chloride was prepared from the corresponding acid by the method described above. The acid chloride, a colorless liquid, was distilled *in vacuo*; b.p. 105-107° (5-6 mm.). The chlorine content of the acid chloride was analyzed by hydrolyzing the acid chloride in water and titrating the hydrochloric acid produced with a standard solution of silver nitrate in the presence of 6 *N* nitric acid, ferric nitrate and potassium thiocyanate.²⁷ Since the acid chloride hydrolyzes very readily in air, there was considerable difficulty in weighing an accurate amount of the compound. Because the weighed sample of the acid chloride contained the product of hydrolysis in considerable amount, the chlorine content was 20% smaller than that calculated for C₁₀H₁₁ClO₂. However, since the method of synthesis from the corresponding acid is unequivocal, the identity of the acid chloride is assured. 4-Methoxy-2,6-dimethylbenzoic acid was synthesized from 3,5-xyleneol (Eastman Organic Chemicals) in three steps: bromination to produce 4-bromo-3,5-xyleneol, methylation to produce 4-methoxy-2,6-dimethylbromobenzene, and conversion to the Grignard reagent followed by carbonation producing 4-methoxy-2,6-dimethylbenzoic acid. The bromination of 3,5-xyleneol was carried out according to the directions of Auwers and Borsche.²⁸ The crude bromination product was methylated in the conventional way with 10% sodium hydroxide and dimethyl sulfate. After two consecutive methylations, the product was distilled under vacuum; 44% yield, b.p. 118-127° (12.5 mm.), lit.^{29,30} b.p. 131-134° (14-15 mm.). 4-Methoxy-2,6-dimethylbromobenzene was converted to 4-methoxy-2,6-dimethylbenzoic acid by conversion to the Grignard reagent followed by carbonation with Dry Ice. Ethyl bromide was used to facilitate the formation of the Grignard reagent. The product was recrystallized from ligroin-ether; yield 44%, m.p. 146°, lit.³¹ m.p. 144-146°.

4-Bromo-2,6-dimethylbenzoyl chloride was prepared from the corresponding acid with thionyl chloride according to the method outlined above. It was purified by sublimation under vacuum; m.p. 56°, lit.^{29,32} b.p. 56-57°. 4-Bromo-2,6-dimethylbenzoic acid was synthesized from 2,6-dimethylaniline by bromination to produce 4-bromo-2,6-dimethylaniline, diazotization and treatment with cuprous cyanide producing 4-bromo-2,6-dimethylbenzocyanide and hydrolysis of the nitrile with concentrated sulfuric acid to produce 4-bromo-2,6-dimethylbenzoic acid. 2,6-Dimethylaniline was brominated in glacial acetic acid.³² The crude product melted in the vicinity of 50°, lit. m.p.³² 50-51°. 4-Bromo-2,6-dimethylaniline was converted to 4-bromo-2,6-dimethylbenzocyanide according to the procedure for the preparation of *o*-tolunitrile from *o*-toluidine.³³ The product was obtained in 87% yield from the bromoaniline; m.p. 66-70°, lit.²⁹ m.p. 71-72°. 4-Bromo-2,6-dimethylbenzoic acid was prepared by hydrolysis of the nitrile in concentrated sulfuric acid.²⁹ The yield of the acid from the nitrile was 52%, m.p. 197°, lit.²⁹ m.p. 197-198°.

4-Nitro-2,6-dimethylbenzoyl chloride was prepared from the corresponding acid with thionyl chloride according to the above procedure. The acid chloride was purified by sublimation under vacuum; m.p. 40-41°. The chlorine content of the acid chloride

was analyzed as described above. Calcd. for C₉H₉ClNO₂: Cl, 16.63. Found: Cl, 16.67. 4-Nitro-2,6-dimethylbenzoic acid was prepared from 4-acetamido-2,6-dimethylbenzoic acid³⁴ by conversion to methyl 4-acetamido-2,6-dimethylbenzoate, hydrolysis of the acetoamido group to produce methyl 4-amino-2,6-dimethylbenzoate, conversion of the amino group to a nitro group by diazotization of the amine and treatment with cupric cobaltinitrite, and finally hydrolysis of the methyl ester to produce 4-nitro-2,6-dimethylbenzoic acid. Methyl 4-acetamido-2,6-dimethylbenzoate was synthesized from the acid by treatment with thionyl chloride, followed by treatment with excess methanol using pyridine as catalyst. The acetamido group was hydrolyzed by refluxing for 1 hour in a solution of 90% (v./v.) aqueous methanol containing 0.25 *N* sodium hydroxide. Methanol was then distilled off and the hydrolysate was diluted with water, extracted with ether and the ethereal extract was dried over anhydrous sodium sulfate. Hydrogen chloride was passed into the ethereal solution. The yield of the hydrochloride of methyl 4-amino-2,6-dimethylbenzoate from the acid was 51%. Methyl 4-nitro-2,6-dimethylbenzoate was prepared from the amino compound according to the method of Hodgson and Marsden.³⁵ The product melted at 87-91°, lit.³⁶ m.p. 91-91.2°. The crude methyl ester was then hydrolyzed for 20 hours by refluxing in 60% (v./v.) aqueous *t*-butyl alcohol containing 0.3 *N* sodium hydroxide. After recrystallization from water a 30% yield of 4-nitro-2,6-dimethylbenzoic acid was obtained (based on the hydrochloride of the amine); m.p. 179-180°, lit.³⁷ m.p. 180-181°.

Kinetic Measurements.—A direct spectrophotometric method was used for the determination of the kinetics of hydrolysis of the acid chlorides in this research. In order to determine a suitable wave length for the kinetics, the ultraviolet spectra of the reactant and the product of each reaction were measured in the same medium as that used for the kinetics. The wave length chosen for the kinetic study was the wave length at which the difference of molar absorptivities between the reactant and the product causes, if not the maximum change in absorbance, at least a large change during the kinetic run. All kinetic runs were carried out under first-order or pseudo first-order conditions. Usual first-order plots of Guggenheim³⁸ plots were used (when the absorbance at infinite time was not determined). The absorbance at infinite time was obtained both from the spectrophotometric measurements and from calculations using the initial concentration of the reactant and the molar absorptivity of the hydrolysis product. In general these two methods were in good agreement. The 99% acetonitrile solvent was prepared by adding water to a volumetric flask in the amount of 1% of the capacity of the flask and then diluting to the mark with acetonitrile. When a base, acid or salt was present, an aqueous solution of the appropriate substance was substituted for water. The reaction was initiated by the addition (with a micropipet or syringe), of the acid chloride to the solvent mixture which had previously been thermostated in the quartz cuvette (either 1 cm. or 5 cm.) in the cell compartment of either a Beckman spectrophotometer or a Cary 14 PM recording spectrophotometer. Each acid chloride was prepared immediately before kinetic measurements. A typical plot is shown in Fig. 1.

Isotopic Oxygen Exchange Experiments.—The solvent containing H₂¹⁸O was prepared in the same way as in the kinetic measurements except that H₂¹⁸O was substituted for normal water. The thermostated solution of 99% acetonitrile-water was added

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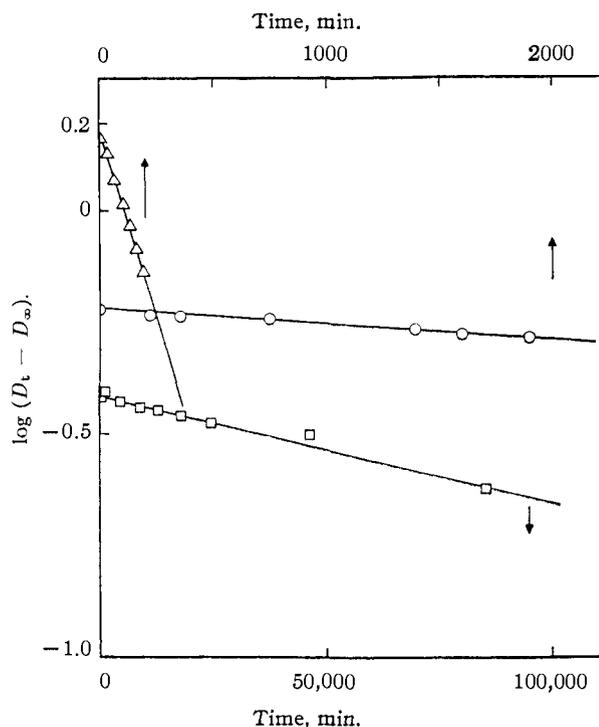


Fig. 1.—Kinetics of the hydrolysis of 4-X-2,6-dimethylbenzoyl chlorides and benzoyl chloride in 99% aq. CH_3CN at 25° : X = Br, Δ ; NO_2 , \square ; benzoyl chloride, \circ .

to the mesitoyl chloride, weighed in a 10-ml. volumetric flask. The mixture was rapidly shaken, and, if the reaction time was 1 minute, was immersed in a thermostat bath. After a time interval ranging from 20 seconds to 1 minute, the solution was added to ca. 15 ml. of liquid ammonia.³⁹ Subsequently the liquid ammonia was evaporated at room temperature and benzene was added to the solution. The benzene-acetonitrile solution was washed with 5% sodium carbonate and with water. The mesitamide was recrystallized from aqueous acetone; m.p. $188-89^\circ$, lit. m.p. $187-188^\circ$,³⁹ 189° .⁴⁰ The carbonate washing was acidified, extracted with methylene chloride and the latter evaporated to obtain mesitoic acid, which served to indicate the extent of reaction. The mesitamide was pyrolyzed to carbon dioxide with mercuric chloride (Fisher reagent grade) at 500° for 2 hours⁴¹ and the carbon dioxide was analyzed with a Consolidated Electrodynamic Corp. 21-130 mass spectrometer. The procedure used was identical with that of Rittenberg and Ponticorvo⁴¹ except that quinoline (Matheson, vacuum distilled) was used in place of 5,6-benzoquinoline to remove the hydrogen chloride by-product of the pyrolysis. The atom fraction of oxygen 18 in mesitamide was calculated from the mass spectrometric data in the same way as that for benzamide.³

Results

The kinetic data for the hydrolyses of 4-substituted-2,6-dimethylbenzoyl chlorides, the substituents being $\text{CH}_3\text{O}-$, CH_3- , $\text{H}-$, $\text{Br}-$ and NO_2- , and for benzoyl chloride in 99% acetonitrile-water solution at 25° are shown in Table I.

Both acids such as perchloric acid and hydrochloric acid, and bases such as tetramethylammonium hydroxide, increase the rate of hydrolysis of the 4-substituted 2,6-dimethylbenzoyl chlorides in 99% acetonitrile-water solution. The product of the acid- or base-catalyzed hydrolysis as well as the spontaneous hydrolysis of the compounds was confirmed to be the 4-substituted-2,6-dimethylbenzoic acid by spectrophotometric analysis. The observed rate constants of the catalyzed hydrolyses can be expressed as

$$k_{\text{obs}} = k_0 + k_{\text{H}}(\text{H}^+) \quad (1)$$

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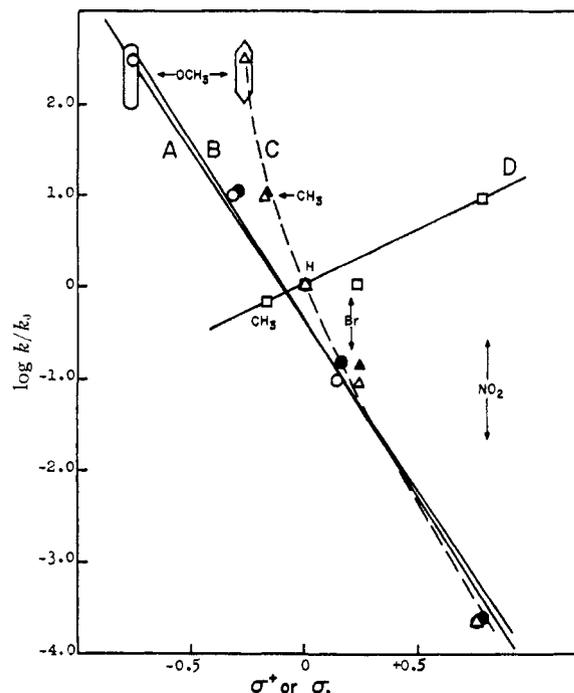


Fig. 2.—Hammett plots for the hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides in 99% aqueous CH_3CN at 25° : A, neutral hydrolysis (vs. σ^+); B, acidic hydrolysis (vs. σ^+); C, neutral and acidic hydrolysis (vs. σ); D, basic hydrolysis (vs. σ).

for acid-catalyzed hydrolysis and

$$k_{\text{obs}} = k_0 + k_{\text{OH}}(\text{OH}^-) \quad (2)$$

for base-catalyzed hydrolysis, where k_{obs} is the observed first-order rate constant, k_0 is the first-order rate constant for the spontaneous hydrolysis, and k_{H} and k_{OH} are the catalytic rate constants for the acid- and base-catalyzed reactions. Knowing the values of k_{obs} , k_0 and the concentration of the catalyst, it is possible to calculate k_{H} and k_{OH} . It is shown later that the perchloric acid-catalyzed and tetramethylammonium hydroxide-catalyzed hydrolyses of mesitoyl chloride adhere to eq. 1 and 2, respectively. In Table I are shown the kinetic results for the hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides in 99% acetonitrile-water containing $1.09 \times 10^{-2} M$ perchloric acid or various concentrations of tetramethylammonium hydroxide at 25° . In contrast to 2,6-disubstituted benzoyl chlorides, the hydrolysis of benzoyl chloride itself is seen not to be catalyzed by acid; however, the hydrolysis of both 2,6-disubstituted benzoyl chlorides and benzoyl chloride are catalyzed by base.

Hammett plots of the kinetic data of the spontaneous hydrolysis, the acid-catalyzed hydrolysis and the base-catalyzed hydrolysis of the 4-substituted-2,6-dimethylbenzoyl chlorides are shown in Fig. 2. The Hammett plot of the rate constants of the spontaneous hydrolyses leads to a straight line with a slope of -3.85 when σ^+ -constants are used, but to a curved line when σ -constants are used. Likewise, the Hammett plot of the rate constants of the acid-catalyzed hydrolyses leads to a straight line with a slope of -3.73 when σ^+ -constants are used, but to a curved line when σ -constants are used. However, the rate constants for the base-catalyzed hydrolyses gives a Hammett plot with a slope of $+1.20$ using σ -constants.

The effects of various substances, including perchloric acid, hydrochloric acid, tetramethylammonium hydroxide, tetra-*n*-butylammonium bromide, chloride and sodium perchlorate, on the hydrolysis of mesitoyl chloride are shown in Table II and Fig. 3. A linear re-

TABLE II
KINETIC EFFECTS OF VARIOUS SUBSTANCES ON THE HYDROLYSIS
OF MESITOYL CHLORIDE^a

Added substance	Concn. of added substance		Added substance	Concn. of added substance	
	$\times 10^3, M$	$k \times 10^3, \text{sec.}^{-1}$		$\times 10^2, M$	$k \times 10^3, \text{sec.}^{-1}$
None		4.45	Bu ₄ N ⁺ Cl ⁻	0.1	3.77
HClO ₄	0.583	32.9	Bu ₄ N ⁺ Cl ⁻	1.0	2.05
HClO ₄	1.09	58.4	Bu ₄ N ⁺ Cl ⁻	1.63	1.44
HCl	0.99	11.3	Bu ₄ N ⁺ Br ⁻	0.115	4.46
HCl	3.55	22.5	Bu ₄ N ⁺ Br ⁻	0.871	4.76
HCl	6.4	31.8	Bu ₄ N ⁺ Br ⁻	1.19	4.70
HCl	11.5	38.9	NaClO ₄	0.455	3.85
Me ₄ N ⁺ OH ⁻	0.149	45.8	NaClO ₄	0.994	4.23
Me ₄ N ⁺ OH ⁻	.288	89.6	NaClO ₄	6.59	4.10
Me ₄ N ⁺ OH ⁻	.344	124.8			

^a 99% acetonitrile-water, 25.0°. ^b Average of at least two runs.

relationship between the observed rate constant and the concentration of the catalyst is demonstrated, with the exception of high concentrations of hydrochloric acid. Thus the validity of the acid- and base-catalysis described above is proved. It should be noted that hydrochloric acid does not have the same effect on the hydrolysis as perchloric acid does. Furthermore, tetra-*n*-butylammonium chloride retards the rate, but there is no significant salt effect by tetra-*n*-butylammonium bromide or by sodium perchlorate.

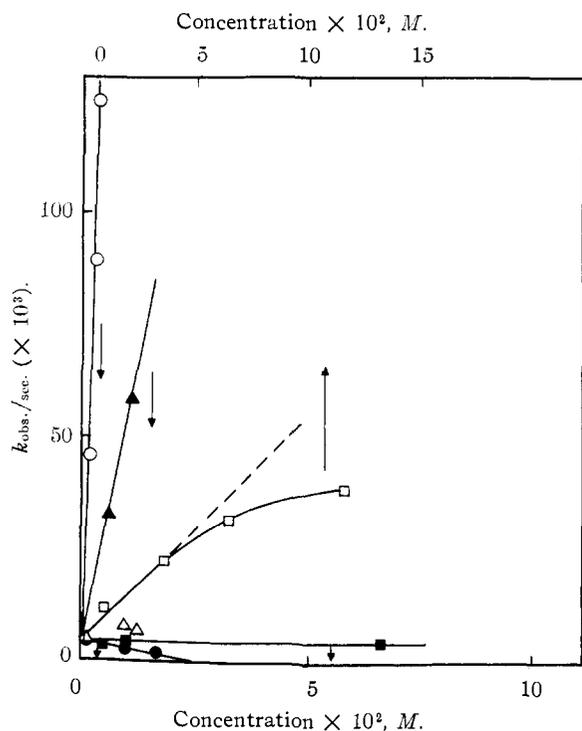


Fig. 3.—Effect of media on the hydrolysis of mesitoyl chloride in 99% aq. CH₃CN at 25°: O, Me₄N⁺OH⁻; ▲, HClO₄; □, HCl; △, Bu₄N⁺Br⁻; ■, NaClO₄; ●, Bu₄N⁺Cl⁻.

Isotopic Oxygen Exchange.—The results of isotopic oxygen exchange experiments during the hydrolysis of mesitoyl chloride in acidic and neutral hydrolysis are shown in Table III. For convenience in analysis, 50–100 mg. of mesitoyl chloride was used in each oxygen exchange experiment, resulting in a concentration of $2.7\text{--}5.4 \times 10^{-2} M$. In this concentration range, the hydrolysis is catalyzed by the hydrochloric acid produced during the reaction. Therefore even in run 3 of Table III, the reaction probably cannot be considered to be a neutral hydrolysis. This conclusion was qualita-

TABLE III
CARBONYL OXYGEN EXCHANGE DURING THE HYDROLYSIS OF
MESITOYL CHLORIDE

Run	Solvent	Time of hydrolysis, sec.	R ₀	R _s	Atom fraction, ¹⁸ O in C=O, X
1	{ 99% CH ₃ CN, H ₂ ¹⁸ O and 5.83×10^{-3} M HClO ₄ }	19	0.00404		0.00203
2		19	0.00405		0.002025
3	99% CH ₃ CN, H ₂ ¹⁸ O	25	0.00404		0.00203
4	Liq. NH ₃			0.00406	0.00204

tively confirmed by the fact that the yield of mesitamide in run 3 was much smaller than that calculated from the rate constant of hydrolysis without any hydrochloric acid present.

Discussion

A number of experimental criteria can be used to delineate a mechanism involving acylium ion formation. These criteria include the use of the Hammett acidity function, entropy and enthalpy data, isotopic oxygen exchange, the effects of substituents on the rate and the effects of salts on the rate of reaction.⁴² In the present study the last three experimental criteria have been used. Isotopic oxygen exchange should be positive in the nucleophilic reaction of a carboxylic acid derivative involving a tetrahedral addition intermediate, but should be negative in a reaction involving an acylium ion intermediate.³ Electron-attracting substituents should facilitate nucleophilic reactions of carboxylic acid derivatives involving tetrahedral addition intermediate formation, but electron-donating substituents should facilitate reactions involving acylium ion intermediates. The primary salt effect should facilitate and the common-ion salt effect should retard reactions proceeding through an acylium ion intermediate, but neither should have a profound effect on a reaction proceeding through a tetrahedral addition intermediate. The bearing of each of these criteria on the hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides will be discussed.

The rate of alcoholysis of benzoyl chlorides is affected by 2,6- and 2,4,6-substituents in the following manner: electron-donating groups enhance the rate whereas electron-withdrawing substituents decrease the rate considerably.¹⁵ The differences in rate caused by these di-*o*-substituents are much greater than the changes caused by monosubstitution. Steric hindrance has been suggested to explain the large reductions in rate of solvolysis and a similar reduction observed in the hydrolysis of 2,6-dibromobenzoyl chloride.⁴³ Steric hindrance, however, is apparently not exhibited in the solvolysis of 2,6-dimethyl- and 2,6-dimethoxybenzoyl chlorides. These results imply that the latter compounds may be solvolyzed with a different, possibly unimolecular mechanism, in which the rate of reaction is not adversely affected by steric hindrance. Arguments involving the effect of various *o*-substituents on the rates of reaction are, however, inherently unsatisfactory because, as has been pointed out by Hammett,⁴⁴ entropies of activation are usually not constant when *o*-substituents are varied. That is, separation of the electronic effect and steric effects of *o*-substituents becomes a difficult problem. In order to obviate this problem, we have investigated electronic effects of substituents on the reactions of *o*-substituted benzoyl chlorides by

(42) M. L. Bender and M. C. Chen, *J. Am. Chem. Soc.*, **85**, 37 (1963).

(43) S. C. G. Olivier, *Rec. trav. chim.*, **48**, 227 (1929).

(44) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

keeping the *o*-substituents constant and varying only the *p*-substituent. Presumably under these conditions, entropies of activation are constant and one can observe solely electronic effects on the rate of reaction.

If the hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides proceeds by a unimolecular mechanism with the formation of an acylium ion intermediate, one may expect that an electron-donating group at the 4-position will accelerate, and an electron-withdrawing group at the 4-position will retard the rate of hydrolysis. Moreover, due to possible resonance interaction between the positively charged transition state and the substituent in the 4-position, one will anticipate in the unimolecular mechanism that a Hammett plot should show a correlation between $\log k/k_0$ and σ^+ values rather than with σ -values, leading to a value of the slope (ρ) which is highly negative.⁴² The kinetic results and the Hammett plot shown in Table I and Fig. 2, respectively, confirm this picture of the mechanism of hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides in 99% acetonitrile-water.

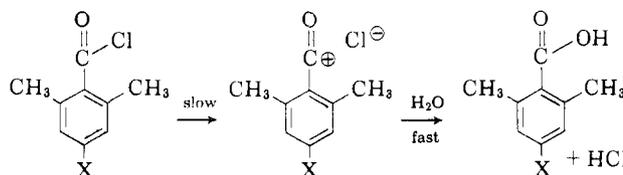
While this research was being carried out, two studies of the influence of steric hindrance on the reactivity of acid chlorides were reported. The sterically hindered acid chloride α -butyl- α -ethyl- γ -carbomethoxybutyryl chloride is very sensitive to traces of moisture whereas the unhindered acid chloride γ -butyl- γ -ethyl- γ -carbomethoxybutyryl chloride is not.⁴⁵ These results may be interpreted on the basis of a unimolecular heterolysis for the sterically hindered acid chloride and a bimolecular displacement for the unhindered acid chloride. In a study of the solvolysis of four 4-substituted-2,6-dimethylbenzoyl chlorides in 89.1% acetone-water at -20° , electron-donating substituents were found to accelerate and electron-attracting substituents were found to retard the hydrolysis,⁴⁶ as in the present work. A Hammett plot of the logarithms of the relative rates shows a correlation with σ^+ with a slope (ρ) of -3.88 close to that found in this investigation ($\rho = 3.85$). This is a surprising result considering that the water content of the two media are considerably different, a condition which should result in differing development of the cationic character in the transition states of the two reactions and thus a different ρ of reaction.

The formation of an acylium ion in the hydrolysis of a sterically hindered benzoyl chloride, *i.e.*, mesitoyl chloride, is strongly suggested by the occurrence of a common-ion salt effect on its hydrolysis shown in Table II and Fig. 3. It is seen that the rate of hydrolysis of mesitoyl chloride is retarded by tetra-*n*-butylammonium chloride in direct proportion to its concentration. Non-common ion salts such as sodium perchlorate and tetra-*n*-butylammonium bromide might be expected to show an enhancement in rate, but do not show any significant effect on the reaction rate. This lack of a primary salt effect cannot eliminate the unimolecular mechanism, however, for in 99% acetonitrile-water, these salts are probably in the form of ion pairs instead of dissociated ions, leading to an additional salt effect. In solvents of such low water content, water may be rendered unavailable for solvation of the transition state because of preferential solvation of the ion pairs, and the hydrolytic rate may thus be retarded. The very slight enhancement of rate of hydrolysis due to the bromide and the very slight retardation of rate due to the perchlorate salt may be attributed to the compensation of the rate-enhancing primary salt effect and the rate-retarding removal of water by salts in a solvent of low water content.⁴⁷ Thus the salt effects on the rate

of the hydrolysis of mesitoyl chloride are consistent with a mechanism involving a rate-determining ionization.

Carbonyl oxygen exchange during hydrolysis is a good indication of a tetrahedral intermediate; its absence is a reasonable although not infallible indication of an acylium ion intermediate.³ The knottiest problem to a consistent picture for the mechanism of the hydrolysis of mesitoyl chloride is the observation that carbonyl oxygen exchange occurs concurrently with hydrolysis of this compound in 95% dioxane-water.²⁰ Carbonyl oxygen exchange during the hydrolysis of mesitoyl chloride in 99% acetonitrile-water was investigated in this research. The results shown in Table III indicate no oxygen exchange, in agreement with the results of other experimental data obtained in this investigation, but not in agreement with the earlier oxygen exchange results. The explanation is not forthcoming for the earlier results in which oxygen exchange was observed with mesitoyl chloride in 95% dioxane-water, a solvent in which benzoyl chloride and *p*-toluyl chloride did not show oxygen exchange. This set of results is confusing since the latter two compounds usually show a greater tendency toward formation of a tetrahedral intermediate and therefore would be expected to show the most oxygen exchange. The most that can be said at the moment is that carbonyl oxygen exchange does not occur in the hydrolysis of mesitoyl chloride in 99% acetonitrile-water, which is consistent with a mechanism involving acylium ion formation in this solvent; however, something else may occur in 95% dioxane-water, which has a lower dielectric constant even though it has a higher water content.

The substituent effects, the salt effects and the lack of carbonyl oxygen exchange are thus consistent with a mechanism for the hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides in which the rate-determining step is the formation of an acylium ion. A mechanism for this process may be written as



Acid Hydrolysis.—The hydrolysis of benzoyl chloride is reported not to be catalyzed by hydrogen ion,^{5,48} a result which has been confirmed in this investigation. However, acid catalysis of the hydrolysis of benzoyl fluoride is known,⁴⁹ presumably proceeding through electrophilic assistance of the removal of fluoride ion by the acid catalyst. The results shown in Table II and Fig. 3 clearly demonstrate the occurrence of perchloric and hydrochloric acid catalysis in the hydrolysis of 4-substituted-2,6-dimethylbenzoyl chlorides. This is the first instance of the demonstration of acid catalysis in the hydrolysis of an acid chloride. Since sodium perchlorate does not enhance the rate, the effect of perchloric acid is a genuine acid catalysis. The finding that perchloric acid catalyzes the hydrolysis more strongly than hydrochloric acid is easily explained: in acid-catalyzed hydrolysis by hydrochloric acid there

in the alcoholysis of mesitoyl chloride in 80% acetone-ethanol solution because the rate was not affected by the addition of 0.1 M lithium chloride, but was increased twofold in the presence of 0.1 M lithium bromide. The apparent lack of a common-ion salt effect with lithium chloride in this reaction can be attributed to the (often noted) compensation of the rate-retarding common-ion salt effect and the rate-enhancing primary salt effect. On this ground it would be predicted that lithium bromide would have a rate-enhancing primary salt effect which indeed is the experimental result.

(48) G. Berger and S. C. G. Olivier, *Rec. trav. chim.*, **46**, 516 (1927).

(49) C. W. L. Bevan and R. F. Hudson, *J. Chem. Soc.*, 2187 (1953).

(45) J. Cason and K. W. Kraus, *J. Org. Chem.*, **26**, 2624 (1961).

(46) I. Ugi and F. Beck, *Chem. Ber.*, **94**, 1839 (1961).

(47) Peeling²¹ concluded that a unimolecular heterolysis did not occur

