1,4,4-Trimethylpiperidine (*9*).—Prepared by the method of Leorard and Hauck,[8] b.p. 137–140°/738 mm. from the N-methylanilide of β,β-dimethylglutaric acid, m.p. 59–61°.[8]

Basicity measurements.—The method developed by Hall[16] was used. Acetonitrile was refluxed over phosphorus pentoxide and distilled. Perchloric acid (60%, 8.42 g.) was made up to 100 ml. with dioxane purified by distillation and passage through an alumina column (concn. *ca.* 0.5 *M*). The acid was standardized against pure 1,4,4-trimethylpiperidine. Titrations were carried out in a 5-cm.-diameter vessel (height *ca.* 5 cm.), capacity, 75 ml., and fitted with a Teflon cover. Titrations were followed with a Beckman Zeromatic pH meter with a glass electrode (no. 41263). Solutions were stirred with a Teflon covered magnet and acid was added from a 1-ml. Gilmont microburet.

Procedure.—About 0.0005 mole of amine was dissolved in 50 ml. of acetonitrile and titrated with perchloric acid, using electrodes standardized against buffer, pH 7 (then rinsed and dried) and using 1000 mv. as the starting point. Stirring was maintained but did not affect the readings. Readings were taken every 0.005 ml. near the end point. The millivolt readings were plotted against the volume of acid and the $E_{1/2}$ values recorded. ($E_{1/2}$ was the millivolt reading at half-neutralization.) The $E_{1/2}$ values were then plotted against known pK_a values. The new pK_a values were read from the plot. The $E_{1/2}$ values are recorded in Table IV.

Nucleophilic Reactions of Morpholine with the Benzoyl Halides. The Presence of an Element Effect[1]

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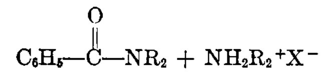
The rate constants for the reactions of morpholine with benzoyl fluoride, chloride, bromide, and iodide have been determined in cyclohexane solution by spectrophotometric means. All the reactions obey second-order kinetics. The kinetic constants for these four reactions differ widely, that for benzoyl iodide being about 10^5 times faster than that for benzoyl fluoride. These results are compared to those for aromatic nucleophilic substitution reactions of aryl halides with amines in which it is found that the halogen atom has relatively little effect on the rate. It is concluded that differences in resonance stabilization of the reactant acid halides and differences in the partitioning of the tetrahedral addition intermediate account for the large differences in rate found here.

Acid chlorides may react with nucleophiles either through an S_N1 reaction with the intermediacy of an acylium ion or *via* a reaction which can be described either as an S_N2 reaction or a carbonyl addition reaction. In highly polar solvents and in the absence of strong nucleophiles, the first mechanism predominates, whereas in nonpolar solvents and in the presence of strong nucleophiles the latter mechanism predominates. The present study is directed to the elucidation of some of the details of the latter (bimolecular) process.

Examination of the bimolecular reaction of benzoyl halides with various nucleophiles has established many of the characteristics of these reactions. The relative rates of solvolysis of various *para*-substituted benzoyl chlorides in 40% ethanol–60% diethyl ether show that electron-attracting groups accelerate the reaction.[3,4] Furthermore, the bimolecular reactions of a series of substituted benzoyl chlorides with aniline in benzene also shows the same substituent effect (Hammett rho = 1.2).[5–7] 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[5,8] [Hammett rho = 2.73[6] (3.12)[7]]. Furthermore, 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.[9,10] Thus the kinetic importance of nucleophilic attack on the carbonyl carbon atom is established for this reaction.

Presumably, the bimolecular reaction of an amine with an acid chloride proceeds through a mechanism similar to that proposed for the saponification of an ester, that is, the addition of the amine to the carbonyl group of the acid chloride leading to a tetrahedral intermediate which can either decompose to products or revert to reactants. The most pertinent evidence concerning such a mechanism is the observation that benzoyl chloride and *p*-toluyl chloride undergo isotopic oxygen exchange concur-



$$C_6H_5\overset{O}{\overset{\|}{C}}—X + R_2NH \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C_6H_5—\underset{+NHR_2}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}—X \xrightarrow[NHR_2]{k_3} C_6H_5—\overset{O}{\overset{\|}{C}}—NR_2 + NH_2R_2{}^+X^- \quad (1)$$

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(2) Alfred P. Sloan Foundation Research Fellow; present address: Department of Chemistry, Northwestern University, Evanston, Ill.

(3) D. A. Brown and R. F. Hudson, *J. Chem. Soc.*, 3352 (1953).

(4) In 50% water–50% acetone, both electron-attracting and electron-withdrawing groups accelerate the reaction, indicating that bond-breaking is starting to assume importance. Therefore, the present experiments were carried out in the nonpolar solvent cyclohexane.

(5) E. G. Williams and C. N. Hinshelwood, *J. Chem. Soc.*, 1079 (1934).

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(7) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. trav. Chim.*, **78**, 815 (1959).

(8) F. J. Stubbs and C. N. Hinshelwood, *J. Chem. Soc.*, 71 (1949).

(9) A. N. Bose and C. N. Hinshelwood, *ibid.*, 4085 (1958).

(10) H. S. Venkataraman and C. N. Hinshelwood, *ibid.*, 4086 (1960).

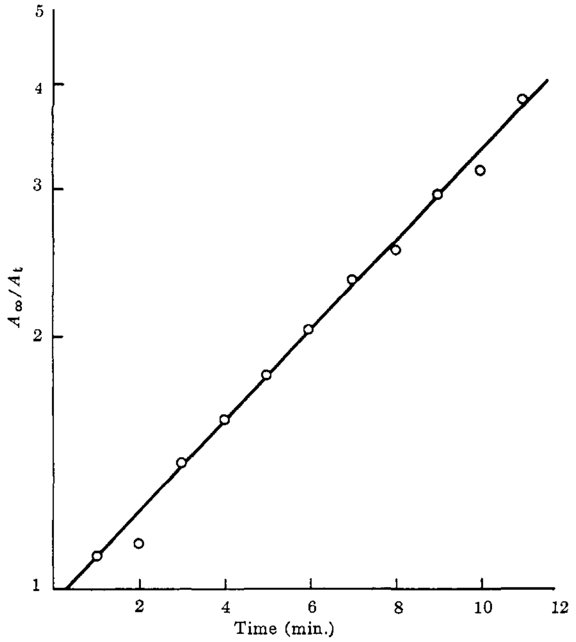

Fig. 1.—The reaction of benzoyl fluoride and morpholine in cyclohexane solution at 25.0°; [benzoyl fluoride] = 1.84×10^{-5} *M;* [morpholine] = 4.10×10^{-3} *M.*

rently with hydrolysis in initially neutral aqueous dioxane solutions,[11] which can be explained most readily by the postulation of a tetrahedral addition intermediate. If one can extrapolate this hydrolytic reaction to the reaction with amines one might expect the same mechanistic pathway for the latter reaction.

A similar mechanistic scheme has been advanced for the aromatic nucleophilic substitution reactions involving amines with activated aryl halides. In this reaction, it has been demonstrated that the mechanism involves the addition of the amine to the aryl halide forming a tetrahedral addition intermediate which decomposes to form the products of the reaction.[12–14] One of the interesting adjuncts to the mechanistic arguments in this system is the demonstration of the absence of an "element effect" in the reactions of a series of nine 1-substituted 2,4-dinitrobenzenes with piperidine in methanol solution.[15] Three substituents, fluorine, nitro, and *p*-toluenesulfonoxy, were shown to be displaced very rapidly while six substituents were displaced more slowly with remarkably little variation in rate among the six. Since displacement of these six substituents involves the breaking of bonds between carbon and five other elements (including bromine, chlorine, and iodine), this result indicates that bond-breaking has not made significant progress in the rate-determining transition states of these reactions.

The question may then be asked as to the presence or absence of an *"element effect" in the analogous* reaction of acid chlorides with amines. The kinetic effect of the departure of the halide ion (bond-breaking) appears to be less important in aqueous media. It has been reported that the second-order rate constants of hydroxide ion with benzoyl fluoride or benzoyl chloride in 50% acetone–water are very close to one another, with that of the fluoride being larger.[16] It was therefore of interest to determine the magnitude of the element effect in the reaction of a complete series of benzoyl halides with a nitrogen nucleophile in a nonaqueous solvent where nucleophilic attack should predominate.

Experimental

Materials.—Benzoyl fluoride was prepared by passing hydrogen fluoride into benzoyl chloride in a copper pot, and was purified according to the directions of Swain and Scott,[16] b.p. 155°; lit.,[16] b.p. 155–157°, $n^{15}\text{D}$ 1.4988. Since the benzoyl fluoride obtained turned pale violet to yellow on standing overnight, a solution in cyclohexane was prepared immediately after distillation. Benzoyl chloride (Eastman Kodak White Label) was fractionally distilled under nitrogen before use, b.p. 196°, $n^{20}\text{D}$ 1.5535. Benzoyl bromide (Eastman Kodak) was fractionally distilled under nitrogen before use, b.p. 218°, $n^{20}\text{D}$ 1.5871; lit.,[16] $n^{25}\text{D}$ 1.5864. *Benzoyl iodide was prepared from benzoyl chloride and hy*drogen iodide according to the directions of Staudinger and Anthes.[17] The crude product was shaken with mercury and purified by fractional distillation under nitrogen. The distillate was initially pale violet, but darkened even on storage under nitrogen in the dark in a refrigerator. Solutions were prepared immediately after distillation and used within a day. Benzoyl morpholine was prepared from benzoyl chloride and morpholine in pyridine. It was recrystallized twice from petroleum ether, m.p. 73.8°; lit.,[18] m.p. 74–75°. Morpholine (Eastman Kodak practical grade) was dried with potassium hydroxide pellets and fractionally distilled under nitrogen from calcium hydride. The middle fraction, b.p. 128° was used. Cyclohexane (Eastman Kodak spectrograde) was used as solvent. Dioxane (Eastman Kodak spectrograde) and also purified according to the method of Fieser[19] was also used as solvent. Tetrahydrofuran was purified by drying with potassium hydroxide pellets, distilling from lithium aluminum hydride, and passing through an activated alumina column.

Kinetics.—The kinetics of the reactions were followed by measurement of the change in absorbance at the absorption maximum of each benzoyl halide. A Beckman DK2 spectrophotometer equipped with a thermostatted cell compartment was used. Cyclohexane solutions were prepared by pipetting measured volumes of benzoyl halide or morpholine into volumetric flasks and filling to the mark in a 25° bath. The concentration of the morpholine solutions was checked, usually by titration with perchloric acid in acetic acid using *p*-naphtholbenzein as indicator. Reaction was initiated by mixing 5-ml. portions of benzoyl halide and morpholine solutions, and quickly transferring the mixture to a 1-cm. stoppered quartz cuvette. When reaction was rapid, 25 μl. of morpholine solution was added to 3 ml. of benzoyl

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(19) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., rev., D. C. Heath and Co., Boston, Mass., 1957, p. 284.

halide solution contained in an unstoppered quartz cuvette in the instrument cell compartment. Mixing in this instance was ensured by adding the morpholine solution by means of a glass rod stirrer.

Rate constants were calculated by first-order or Guggenheim[20] plots when a large excess of morpholine was used, and by second-order kinetic plots in other cases. Figure 1 shows a typical first-order plot for benzoyl fluoride. The stoichiometry used in the calculations was that of the equation

$$C_6H_5COX + 2R_2NH \longrightarrow C_6H_5CONR_2 + R_2NH_2^+X^-$$

The concentration of benzoyl halide had to be maintained below the solubility point of the quaternary morpholine salt formed. The highest chloride concentration used was therefore 2×10^{-5} *M*. The high rate of reaction of benzoyl bromide and iodide further limited the concentration range. Morpholinium fluoride appears to be much more soluble than the other morpholine salts, and was not precipitated at 7×10^{-5} *M*.

Beer's law plots for all the benzoyl halides in cyclohexane were determined at the absorption maximum of each: benzoyl fluoride, 230.4 mμ; benzoyl chloride, 242 mμ; benzoyl bromide 245 mμ; benzoyl iodide, 248.5 mμ. A Beer's law plot of benzoyl morpholine was determined at 240 mμ since the absorption maximum of this compound in cyclohexane is below 218 mμ. Straight lines passing through the origin were obtained in all cases. The spectrum of the product of the reaction of morpholine with each benzoyl halide was examined. In the reaction of the fluoride, chloride, and bromide, it corresponded exactly to the expected amount of benzoyl morpholine. Deviations amounting to 15% at 230 mμ and less than 5% at the absorption maximum were observed with the product from benzoyl iodide, presumably because of the presence of a decomposition product of benzoyl iodide. The benzoyl iodide solution deteriorated markedly in 24 hr., and therefore was always prepared immediately before use.

In preliminary experiments the solvents dioxane and tetrahydrofuran were used. They were abandoned, however, when it was discovered that the Beer's law plots were curves with the curvature convex to the concentration axis.

Results and Discussion

The kinetics of the reactions of morpholine with four benzoyl halides in cyclohexane solution at 25.0° were carried out. Several different concentrations were used in each case; for the reaction of benzoyl fluoride, pseudo first-order conditions were used, whereas for the other benzoyl halides second-order conditions were used. The results are summarized in Table I. The precision of the results of the benzoyl fluoride and chloride reactions is reasonably good; however, the precision of the results of the benzoyl bromide and iodide reactions is less than desirable. The reasons for the imprecision are twofold: one is the high rates of reaction, and the second is the decomposition of the reactants which may affect the kinetics of the morpholine reaction.

The most important conclusion to be drawn from these results is that the rate differences between the reactions of the various benzoyl halides is large. The spread in rate constants found here is in some respects wider than that found by Swain and Scott[16] in 50% acetone–water solution as shown in Table II. The benzoyl chloride/benzoyl fluoride ratio is the most striking one. A likely explanation of the wide spread of the rate ratio of benzoyl chloride/benzoyl fluoride is that electrophilic catalysis of the removal of the fluoride ion which occurs in aqueous solution cannot occur in cyclohexane. In aqueous solvent, the fluorine atom may be solvated by hydrogen bonding, and thus the nucleophilic reaction of benzoyl fluoride will be facilitated. This solvation amounts to acid catalysis, which has been noticed in various fluoride solvolyses, for example with benzoyl fluoride,[21] alkyl fluorides,[22] and benzyl fluorides.[23,24] The importance of the solvation of fluoride ion is shown strikingly in an aromatic nucleophilic substitution reaction involving *p*-nitrofluorobenzene and azide ion in the aprotic solvent dimethylformamide. In this system which cannot solvate the leaving fluoride ion, the initial addition step to produce a tetrahedral intermediate takes place, but the decomposition of this intermediate to produce the organic azide and fluoride ion does not take place until water is added to the system, at which time an instantaneous liberation of fluoride ion is observed.[25,26] It is certainly reasonable to assume that the fluoride ion would be solvated less efficiently in cyclohexane solution than in 50% acetone–water, and thus the difference in solvent can explain the difference in results between the present experiments and those of Swain and Scott.

TABLE I

KINETICS OF THE BENZOYLATION OF MORPHOLINE[a]

Halide	Halide $\times 10^6$, *M*	Morpholine $\times 10^6$, *M*/2[b]	k_2, l./mole sec.
Benzoyl fluoride	9.2	765	1.12[c]
	36.5	765	1.09
	73.6	3060	1.01
			Av. 1.06 ± 0.03
Benzoyl chloride	5.15	19.7	2.83×10^3
	17.8	39.4	2.56×10^3
	39.4	39.4	2.59×10^3
			Av. $2.64 \pm 0.13 \times 10^3$
Benzoyl bromide	0.849	1.97	6.5×10^4
	1.97	1.97	8.3×10^4
	3.94	1.97	5.8×10^4
			Av. $6.66 \pm 0.64 \times 10^4$
Benzoyl iodide	0.754	0.394	2.25×10^5
	.967	.967	2.45×10^5
	.89	.591	1.67×10^5
			Av. $2.39 \pm 0.18 \times 10^5$

[a] Cyclohexane solution at 25.0°. [b] The morpholine concentration divided by two is given so that the real excess of morpholine may be noted. [c] Each run is the average of at least two individual runs.

As stated in the introduction, the nucleophilic reaction of morpholine with the benzoyl halides

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TABLE II

RELATIVE RATES OF REACTIONS OF NUCLEOPHILIC REACTIONS OF BENZOYL HALIDES

Nucleophile	Solvent	C_6H_5COCl/C_6H_5COF	C_6H_5COBr/C_6H_5COCl	Ref.
Morpholine	Cyclohexane	2600	25	[a]
Water	50% acetone–water	39	150	16
Hydroxide ion	50% acetone–water	0.75	21	16
p-Nitroaniline	Benzene		136	10, 9

[a] This work.

may be assumed to occur through the reversible formation of a tetrahedral addition intermediate, followed by expulsion of halide ion, (equation 1). The steady state treatment of the kinetics of this process leads to the expression

$$[k_{obs} = k_1/(k_2/k_3) + 1] \qquad (2)$$

The observed rate constants may therefore be interpreted in terms of the addition step, k_1, and of the partitioning of the intermediate, $k_2/k_3 = \alpha$. In order that the leaving halide ion have no effect on observed rate constant, two conditions must be met: (1) it is necessary that the partitioning of the intermediate be equivalent for all benzoyl halides or be heavily in favor of the decomposition to products (k_2/k_3 be small compared to 1); and (2) the steps k_1 for the different benzoyl halides be equivalent to one another. If the partitioning of the intermediate favors k_3 over k_2, then equation 2 reduces to $k_{obs} = k_1$, and at the same time, the effect of differences in the leaving tendencies of the various halide ions is no longer of kinetic importance.

From the results of the present experiments one or both of the above requirements for an insignificant effect of the halogen atom on the rate are not met. The halogen atom could affect k_1 through steric and electronic effects. Inductively it might be expected that benzoyl fluoride would react the fastest, although from a resonance standpoint, it would be expected that benzoyl fluoride would react the slowest. From a consideration of the relative reactivities of all carboxylic acid derivatives, it appears that the resonance stabilization of the ground state is the most important factor governing the reactivity. Therefore, it may be postulated that part of the difference in reactivities of the various benzoyl halides lies in the difference in resonance stabilization of the ground state of these molecules, with benzoyl fluoride showing the greatest stabilization.[27] It is probable, however, that resonance stabilization in the acid halide groups is of small magnitude, and thus may not account for the rate differences observed here.

Another explanation for the large difference in the reactivities of the benzoyl halides is a large difference in the ratio k_2/k_3 in the reactions of these compounds. If k_2/k_3 varies from zero to one, there will be a relatively small change in k_{obs}. However, if k_2/k_3 varies from one to a large number, the change will be reflected almost completely in k_{obs}. It may therefore be postulated that the ratio k_2/k_3 has a large and variable magnitude, leading to large difference in the observed rate constant. These differences in k_2/k_3 could be accentuated in the present instance by the nonhydroxylic solvent used which could reduce k_3 in a variable fashion depending on the solvation necessary for each halide ion. It is, of course, seen that the observed relative rates are in the order of the relative strengths of the carbon–halogen bonds, which on the surface indicates that the bond-breaking in the decomposition of the tetrahedral intermediate is of major importance. It should be pointed out that the difference between the present results and those of Swain and Scott cannot be explained entirely in terms of differences in resonance stabilization of the ground states of the benzoyl halides, for that factor should remain a constant between the two systems.[28]

In conclusion, there appear to be two avenues by which the halogen atoms could affect the observed rate constant differently—through differential partitioning of the intermediate, and through differences in resonance stabilization of the reactant. With benzoyl fluoride, it is presumed that at least some of its lowered rate with respect to benzoyl chloride is due to the unfavorable partitioning of the tetrahedral addition intermediate. However, the 10^5 difference in rate in going from benzoyl fluoride to benzoyl iodide may be due to combination of both factors outlined above. It should be noted that in the aromatic series, both differences in conjugation of the reactants and differences in the partitioning of the intermediate do not occur, leading to over-all rates of reaction which differ only fifty per cent in going from the chloro compound to the iodo compound.

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(27) L. Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1960, pp. 289, 315.

(28) An argument against differences in the partitioning of the benzoyl halides accounting for differences in the observed rates is that Bunton, *et al.*,[11] have observed that the partitioning ratio k_2/k_3 in the hydrolysis of benzoyl chloride in 75% dioxane–water is approximately $^1/_{12}$. If other partitioning ratios also are less than one, they could have little effect on the observed rate constant.