Cyclic Imides. 14.[1] Kinetics of the Reaction of 3-Fluoro-*N*-methylphthalimide with Secondary Amines. An Example of Imide-Activated Aromatic Nucleophilic Substitution

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The kinetics of the reactions of 3-fluoro-*N*-methylphthalimide with pyrrolidine, piperidine, and morpholine in acetonitrile and in benzene have been measured under pseudo-first-order conditions at 25 °C on the basis of the rate of increase of absorbance of the aminophthalimide end product. The reactions display kinetic behavior typical of the S_NAr bimolecular addition–elimination mechanism of aromatic nucleophilic substitution. Base catalysis of the reaction is observed for all three amines in benzene and for pyrrolidine and piperidine in acetonitrile. Although these reactions are much slower than the reactions of 1-fluoro-2,4-dinitrobenzene with these amines under similar conditions, they appear to be identical with them in mechanism. The apparent base catalysis with both fluoro compounds may be attributed to removal of fluoride ion by the secondary amine acting as a hydrogen-bond donor, rather than as a proton acceptor. The results of these measurements clearly establish the cyclic imide moiety as an activating group for the S_NAr mechanism in anhydrous aprotic media. In hydroxylic solvents, base-catalyzed solvolysis of the imide ring is a competing, and often dominating, reaction.

There have been extensive investigations of the scope, synthetic utility, and the kinetics and mechanism of the nucleophilic substitution reactions of aromatic halides and nitro compounds. When these reactions occur under mild conditions as the result of activation by electron-withdrawing groups, such as nitro or heterocyclic nitrogen ortho and/or para to the leaving group, they proceed by the bimolecular addition–elimination process, or S_NAr mechanism. Reactions of these types have been the subject of several comprehensive reviews[2-5] published during the last decade.

None of these reviews nor the subsequent literature of aromatic nucleophilic substitution describe examples in which the activating group was a cyclic imide moiety. Like other activating groups, the cyclic imide moiety withdraws electrons from the benzene ring by resonance; and dipole moment measurements[1,6] have shown that it is also strongly electron-withdrawing by induction, though less strong than a nitro group. It should thus show at least moderate activation of a nucleofugal substituent to displacement by a nucleophile under S_NAr conditions.

The first examples of apparent imide-activated aromatic nucleophilic substitution were actually reported over 20 years ago.[7,8] Subsequent investigations of these reactions by Williams, Relles, Markezich, and their co-workers[9-13] considerably extended their scope and synthetic utility. The only mechanistic study of the imide-activated process so far published[14] demonstrated that this nucleophilic substitution does not occur by a radical mechanism. The transient, deep-red coloration which has been observed[7,9] in some examples of reactions of alkoxides with nitrophthalimides is instead characteristic of the Meisenheimer–Jackson type of σ-adduct which is formed in the first step of the S_NAr mechanism of nucleophilic displacement of the nitro group by strong bases.[15] The detection of nitrite ion[7] in the final reaction mixture is also in accord with this mechanism. The order of reactivity leaving groups has been found[8] to be $F > NO_2 > Cl$, which is characteristic of activated aromatic nucleophilic substitution.[16]

We have undertaken an investigation of the kinetics of nucleophilic substitution of a halogenated phthalimide derivative under conditions at which the S_NAr mechanism should occur. As the substrate, 3-fluoro-*N*-methylphthalimide (1) was chosen. This compound, unlike many halogenated phthalimides, is quite soluble in solvents suitable for such measurements, and the 3-fluorophthalimides are the substituted phthalimides most suceptible to nucleophilic substitution.[8] Amines were chosen as nucleophiles because aminophthalimides are strongly colored in the visible range of the spectrum[17] where the reagents and solvents are completely transparent, thus providing a reaction whose rate can be measured photometrically, following the model provided by Bunnett[18-20] in his studies of the reactions of amines with 2,4-dinitrohalobenzenes.

The general form of the S_NAr bimolecular addition–elimination mechanism[19] is adapted to the reaction of 1 with secondary amines in Scheme I. The intermediate σ-adduct may decompose to products either directly or with the assistance of a base, which in this case is a second molecule of the nucleophile. The choice of route by which the product is formed is dependent not only upon the

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Scheme I

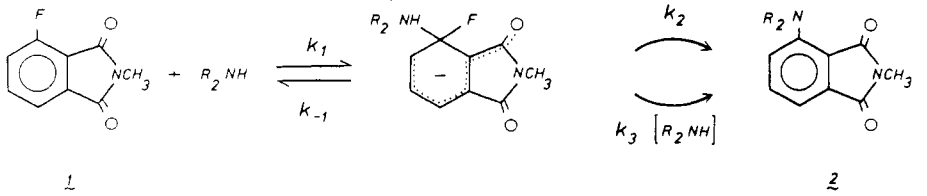

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Table I. Rate Constants for the Reaction of 3-Fluoro-*N*-methylphthalimide with Secondary Amines

amine	solvent	$10^3k'$,[a] L mol^{-1} min^{-1}	$10^3k''$,[a] L^2 mol^{-2} min^{-1}	k''/k'	r
pyrrolidine	MeCN	21.5 ± 0.3	16.7 ± 0.7	0.777	0.996
pyrrolidine	C_6H_6	1.7 ± 0.6	11.7 ± 0.4	6.9	0.995
piperidine	MeCN	5.04 ± 0.06	2.35 ± 0.09	0.466	0.997
piperidine	C_6H_6	0.81 ± 0.04	1.80 ± 0.06	2.2	0.996
morpholine	MeCN	0.202 ± 0.006	0		
morpholine	C_6H_6	0.034 ± 0.002	0.081 ± 0.001	2.4	0.999

[a] ± one standard deviation.

nature of the nucleophile and the halide upon which it acts, but also upon the solvent.

Steady-state treatment[19] of the mechanism of Scheme I provides eq 1 in which k_A is the observed second-order rate constant for the reaction. Three possible situations

$$k_A = \frac{k_1(k_2 + k_3[R_2NH])}{k_{-1} + k_2 + k_3[R_2NH]} \quad (1)$$

exist. (1) If $k_{-1} \ll k_2 + k_3[R_2NH]$, then $k_A = k_1$ and base catalysis is not observed. (2) If $k_{-1} \gg k_2 + k_3[R_2NH]$, then $k_A = (1/k_{-1})(k_1k_2 + k_1k_3[R_2NH])$ and k_A increases rectilinearly with nucleophile concentration. (3) Where neither of these conditions exists, k_A decreases curvilinearly with increasing nucleophile concentration.

Nucleophilic attack can also occur at a carbonyl group of the imide with subsequent base-catalyzed opening of the imide ring. This reaction must be considered as competition to the nucleophilic substitution. The base-catalyzed hydrolysis of the imide ring is in fact the only reaction which occurs if water is present in the reaction medium.[7] Base-catalyzed methanolysis as a competing reaction may well be responsible for the rather poor yields in the reactions of substituted phthalimides with methoxide in methanol.[8] The work of Williams[9] has shown that imide ring opening does not occur to any detectable extent in aprotic solvents. Aprotic anhydrous media have therefore been chosen for the present study.

Results and Discussion

The rates of the reactions of 1 with pyrrolidine, piperidine, and morpholine in benzene and acetonitrile under anhydrous conditions were measured photometrically as the rate of formation of 2 at 25.0 °C. Initial amine concentrations were at least a hundred times greater than the initial concentration of 1, so that pseudo-first-order conditions existed. Plots of the experimental second-order rate constants, k_A (L mol^{-1} min^{-1}), against initial amine concentrations are presented in Figures 1–3. These plots are represented by eq 2 in which the intercept k' =

$$k_A = k' + k''[R_2NH] \quad (2)$$

k_1k_2/k_{-1}, the experimental rate constant for the uncatalyzed reaction, and the slope $k'' = k_1k_3/k_{-1}$, the experimental third-order rate constant for the catalysis. Values of k' and k'' with one standard deviation, the ratios k''/k', and the correlation coefficient r are given in Table I.

The plots presented in Figures 1 and 2 and the rate constants in Table I for the reactions with pyrrolidine and

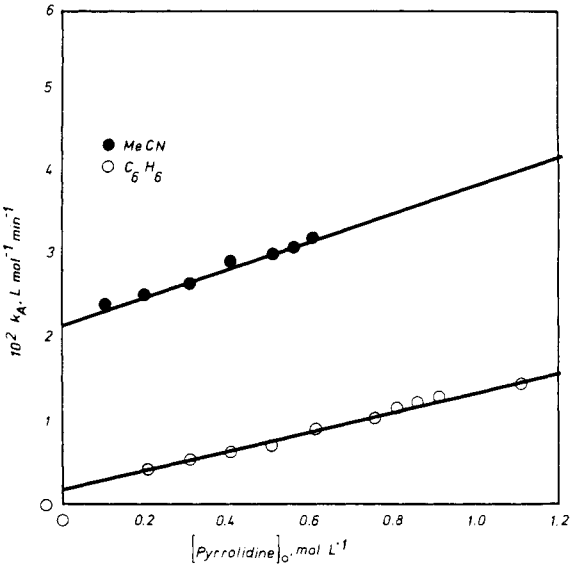

Figure 1. Observed rate constants as a function of pyrrolidine concentration.

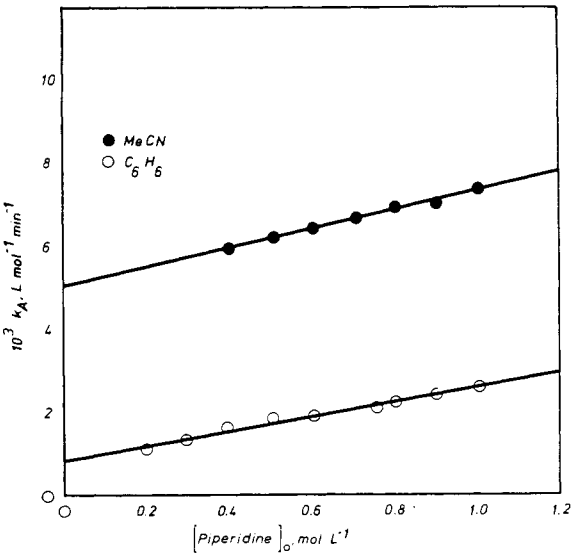

Figure 2. Observed rate constants as a function of piperidine concentration.

piperidine are quite typical of S_NAr reactions with base-catalyzed decomposition of the σ-adduct.[15] This kinetic evidence, together with the observations cited above, leaves

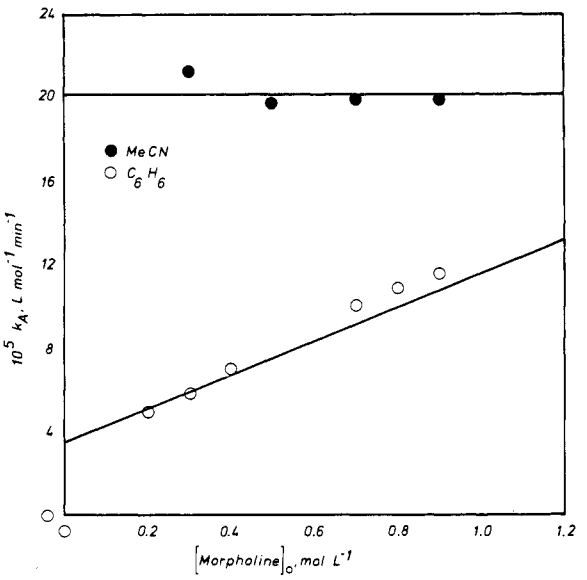

Figure 3. Observed rate constants as a function of morpholine concentration.

no doubt as to the validity of assignment of the mechanism of Scheme I for nucleophilic substitution reactions of 3-fluorophthalimide derivatives.

The differences in behavior between the three amines can be ascribed to differences in base strength and to differences in molecular size and shape. In aqueous media pyrrolidine and piperidine have almost the same base strength,[21] pK_b 2.73 and 2.78, respectively, at 25 °C. If this similarity of basicities exists for solutions in the solvents of the present study, then the faster rate of reaction of pyrrolidine is attributable to the smaller size of this molecule, which can more easily approach the reaction site.

The morpholine molecule has essentially the same size and shape as the piperidine molecule, but the base strength of morpholine is much weaker,[22] pK_b 5.30 in water at 25 °C. The slower rates for the reaction with morpholine, and the absence of base catalysis in the reaction of morpholine in acetonitrile, are therefore attributable to its weaker basicity.

All reaction rates were faster in acetonitrile than in benzene. The greater solvating ability of the polar solvent enhances the rate of departure of both the proton and the fluoride ion. The uncatalyzed decay of the σ-adduct, with rate constant k_2, is thus more important in acetonitrile than is the catalyzed decay with rate constant k_3. This is evident from the ratios k''/k' in Table I, which are much larger for benzene than for acetonitrile, indicating the greater importance of the catalyzed route in the nonpolar solvent. The ratio k''/k' in fact reduces to k_3/k_2, the ratio of the catalyzed to uncatalyzed rate constants for the second step of the reaction.

Solvent effects upon the rates of reaction of nitro- and dinitrophenyl halides with amines have been recently investigated by Hirst[23,24] and Nudelman.[25-27] These authors have also reviewed earlier work on such solvent effects. In the reaction of morpholine with 1-fluoro-2,4-dinitrobenzene, Hirst has found that there is no base catalysis in polar aprotic solvents,[23] but such catalysis was observed when the solvent was benzene.[24] Nudelman[27] has obtained similar results in the reaction of piperidine with 1-fluoro-2,4-dinitrobenzene. The fact that base catalysis is observed with piperidine in acetonitrile in our study, while it was not observed in Nudelman's, may be attributed to the relatively weaker reactivity of 1 as compared with 1-fluoro-2,4-dinitrobenzene. Otherwise, our results are quite in agreement with those of Hirst and Nudelman.

It has been shown frequently that the addition of non-nucleophilic bases or of hydrogen-bond acceptors will enhance the rates of S_NAr reactions in which the base catalysis is observed.[15,24] In the expectation of observing such enhancement, we repeated the measurements of the rates of the reaction of 1 with morpholine in benzene with the addition of *N*-methylpyrrolidine at concentrations equal to those of the morpholine. This amine was chosen because it is a significantly stronger base than morpholine, having a pK_b of 3.54 in aqueous solution at 25 °C.[21] This addition had no significant effect on the rates. All of the rates measured with this additive were either identical with the rates in its absence or within one standard deviation of them. A possible interpretation of this result is that the base-catalyzed process does not involve deprotonation of the σ-adduct, at least in the case of the reaction of morpholine with 1 in benzene. The apparent base catalysis would instead have to be the result of hydrogen bonding of the departing fluoride ion to the catalyzing molecule of the morpholine. Such a conclusion is consistent with the finding by Nudelman[27] that the rate of reaction of piperidine with 1-fluoro-2,4-dinitrobenzene is enhanced in proportion to the hydrogen bond donating ability of the solvent. Since this effect was not observed with 1-chloro-2,4-dinitrobenzene, it was concluded that the rate-limiting step was the departure of the fluoride ion. Such also appears to be the case in the reaction of 1 with morpholine. It must be recognized, however, that an absence of base catalysis by *N*-methylpyrrolidine could be attributed to steric effects, but these effects should not completely suppress it.

Since hydrogen-bonding solvents should enhance the rate of fluoride ion departure through hydrogen bonding, efforts were mad to measure the rates of reaction of piperidine with 1 in anhydrous methanol. The absorbance scan did indeed increase very rapidly during the first 15–30 s of the reaction, beyond which the absorbance became constant. A possible explanation of this finding is that a steady state had been achieved at which the nucleophilic substitution and a base-catalyzed methanolysis of the 3-piperidino-*N*-methylphthalimide were occurring at equal rates. The characteristic aminophthalimide band in the visible disappears when the imide ring is opened.[17]

The results with methanol as solvent came as a surprise, considering that methanol at reflux temperature was a more satisfactory solvent than either acetonitrile or benzene for the synthesis of the aminophthalimides from 1. Evidently the rates of the substitution and solvolysis reactions increase with temperature at quite different rates. The mechanism of the substitution may also change with increasing temperature. This should be examined in the future.

A few kinetic runs were made with pyrrolidine and with morpholine at initial concentrations between 1.0 and 4.0

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mol L^{-1}, that is, between 300 and 1300 times the concentration of 1. Beginning at 1.2 mol L^{-1}, the values of k_A declined at an increasing rate as the concentration of the amine increased. In this range, then, neither of the simplifying conditions for eq 1 existed; that is $k_{-1} \approx k_2 + k_3[R_2NH]$.

Experimental Section

Procedures and Materials. Melting points were determined with an Electrothermal apparatus and are not corrected. Absorption spectral measurements were made with a Cary Model 15 recording spectrophotometer using 1-cm rectangular quartz cells. Infrared spectra were measured by a Pye-Unicam SP-1100 infrared spectrophotometer and nuclear magnetic resonance spectra with a Varian EM 390 nuclear magnetic resonance spectrometer. Microanalyses were done by Atlantic Microlab Inc., Norcross, GA, or by Midwest Microlab Ltd., Indianapolis, IN.

Reagents and solvents were the highest purity commercially available and were maintained pure by established methods. Piperidine, pyrrolidine, morpholine, and *N*-methylpyrrolidine were obtained from Aldrich Chemical Co. and stored over KOH pellets. They were distilled over Na metal and stored under nitrogen within 24 h of use.[28] Benzene, acetonitrile, and methanol were Burdick and Jackson "distilled in glass" grade. They were stored over Type 4A molecular sieves.[29] Acetonitrile was distilled over P_2O_5 and stored under nitrogen within 24 h of use.[29] 3-Fluorophthalic acid was obtained from Columbia Organic Chemicals Co.

3-Fluoro-*N*-methylphthalimide (1). In typical runs, 18.4 g (0.100 mol) of 3-fluorophthalic acid and 18 mL (25 g, 0.12 mol) of trifluoroacetic anhydride were heated under reflux for 1.5 h, followed by concentration of the mixture to half volume by distillation. To the residue were added 8.50 g (0.126 mol) of methylamine hydrochloride, 10.2 g (0.126 mol) of anhydrous sodium acetate, and 50 mL of glacial acetic acid. The mixture was refluxed 1.5 h, cooled to room temperature, and filtered. The filtrate was diluted with 100 mL of water, precipitating 1 in yields of 60–75%. The material to be used in kinetic studies was recrystallized twice from cyclohexane, giving glittering white crystals: mp 111–112 °C; UV (C_6H_6) 300 nm (ϵ = 3190 M^{-1} cm^{-1}); UV (MeCN) 299 nm (ϵ = 3230 M^{-1} cm^{-1}); UV (MeOH) 300 nm (ϵ = 3150 M^{-1} cm^{-1}); IR (Nujol) 1782, 1733, 1261, 1014, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.07 (s, 3 H), 7.80 (m, 3 H). Anal. Calcd for $C_9H_6FNO_2$: C, 60.34; H, 3.38; F, 10.60; N, 7.82. Found: C, 60.52; H, 3.51; F, 10.75; N, 7.86.

Derivatives of 3-Amino-*N*-methylphthalimide. Mixtures of 3.6 g (0.020 mol) of 1, 0.050 mol of a secondary amine, and 50 mL of methanol were refluxed for 1–3 h. The solutions were concentrated to half volume under reduced pressure and neutralized with 0.2 M H_2SO_4. The crude products were removed by filtration, dried, and twice recrystallized from cyclohexane, giving bright yellow crystals in yields of 55–65%.

3-Pyrrolidino-*N*-methylphthalimide (2a): mp 99.5–100 °C; vis (C_6H_6) 416 nm (ϵ = 5320 M^{-1} cm^{-1}); vis (MeCN) 416 nm (ϵ = 5040 M^{-1} cm^{-1}); vis (MeOH) 421 nm (ϵ = 5050 M^{-1} cm^{-1}); IR (Nujol) 1753, 1700, 1271, 1010, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.93 (quintet, 4 H), 2.97 (s, 3 H), 3.53 (t, 4 H), 7.07 (unsymmetrical quartet, 2 H), 7.52 (unsymmetrical triplet, 1 H). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.15; N, 12.16. Found C, 67.69; H, 6.15; N, 12.16.

3-Piperidino-*N*-methylphthalimide (2b): mp 111–111.5 °C; vis (C_6H_6) 402 nm (ϵ = 3440 M^{-1} cm^{-1}); vis (MeCN) 402 nm (ϵ = 3230 M^{-1} cm^{-1}); vis (MeOH) 405 nm (ϵ = 3040 M^{-1} cm^{-1}); IR (Nujol) 1764, 1716, 1247, 1013, 743 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.97 (m, 6 H), 3.00 (s, 3 H), 3.18 (t, 4 H), 7.27 (unsymmetrical triplet, 2 H), 7.63 (unsymmetrical triplet, 1 H). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.84; H, 6.62; N, 11.45.

3-Morpholino-*N*-methylphthalimide (2c): mp 137.5–138.5 °C; vis (C_6H_6) 391 nm (ϵ = 3330 M^{-1} cm^{-1}); vis (MeCN) 389 nm (ϵ = 3140 M^{-1} cm^{-1}); vis (MeOH) 392 nm (ϵ = 3120 M^{-1} cm^{-1}); IR (Nujol) 1762, 1718, 1250, 1125, 1020, 747 cm^{-1}; NMR (DMSO-d_6) δ 3.00 (s, 3 H), 3.33 (t, 4 H), 3.78 (t, j H), 7.32 (unsymmetrical quartet, 2 H), 7.68 (unsymmetrical triplet, 1 H). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found C, 63.46; H, 5.74; N, 11.35.

Kinetic Measurements. All kinetics measurements were made at the absorption maximum of the reaction product for the solvent in which the reaction was carried out, using a Cary Model 15 recording spectrophotometer fitted with thermostated cuvette holders for 1-cm rectangular cells in both the sample and reference compartments, with sensitivity at 4, and slit widths set manually at 0.10. Solutions of 1 and the amine at double the concentrations to be used in a run were prepared and brought to 25.0 °C in a constant-temperature bath. The cuvettes were maintained at 25.0 °C by means of a circulating thermostat. A 1.50-mL sample of the solution of 1 was injected into the sample cell with a syringe, followed by injection of 1.50 mL of the amine solution at time zero. The initial concentration of 1 in the reaction mixture was 3.00×10^{-3} mol L^{-1}. Initial concentrations of amines ranged from 0.100 to 1.000 mol L^{-1}. The absorbance was recorded on the recorder chart as a function of time. In the cases of pyrrolidine and piperidine a run was discontinued at 2 h or when the absorbance reached 1.0, whichever came first. In the case of morpholine the absorbance was recorded at intervals until 72 h had elapsed or until it reached 0.5, whichever came first. Pseudo-first-order rate constants were obtained as the slopes of plots of ln $[A_\infty/(A_\infty - A_t)]$ versus t by linear least-squares curve fittings, where A_∞ is the absorbance calculated for 100% reaction and A_t is the absorbance at time t in minutes.[30] Pseudo-first-order rate constants were accepted only for those kinetic runs which gave a correlation coefficient of 0.998 or better. The second-order rate constants k_A were obtained by dividing the pseudo-first-order rate constants by the initial amine concentrations. Each point in the graphs presented in Figures 1–3 represents a second-order rate constant from a single kinetic run.

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