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Nucleophilic Substitution at Centers Other Than Carbon. 2. Reaction at the Chlorine of *N*-Chloroacetanilide with Substituted Phenoxides

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The importance of *N*-chloroamides as a synthetic reagent for organic chemists is well documented.[2] They are a commonly used reagent for oxidations[3] and chlorinations.[2,4] It appears that many of these reactions can be explained by a mechanism involving a substitution at the nitrogen-bound chlorine. We have demonstrated that *N*-chloroacetanilide is an excellent compound for studying reactions involving substitutions at the chlorine bonded to the nitrogen of an amide.[5]

We have previously reported[5] nucleophilic displacement reactions at the chlorine of *N*-chloroacetanilides, the nucleophile being triethylamine. As described in the preceding paper,[5] the nucleophile was maintained constant and the substrate was modified in order to assess the amount of charge buildup in the transition state. The large positive ρ value (3.87 ± 0.29) for the reaction suggests that there is significant heterolytic bond breakage of the nitrogen-chlorine bond in the transition state.[5]

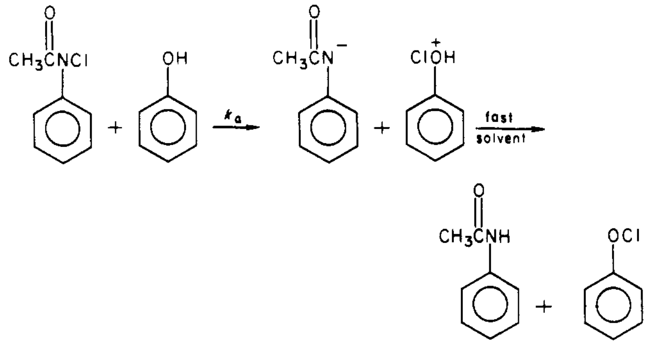
In our continuing study of substitution reactions at the chlorine of *N*-chloroacetanilides, we now report the results for the reaction of various meta- and para-substituted phenoxides with *N*-chloroacetanilide (see Scheme II). All reactions were carried out in buffered 10% aqueous acetonitrile brought to an ionic strength of 1.350 M with $NaClO_4$ at 39.36 °C.

Results

A series of meta- and para-substituted phenols (H, *p*-CH_3, *m*-Cl, *m*-NO_2, and *p*-NO_2) were allowed to react with *N*-chloroacetanilide under pseudo-first-order conditions with the phenol in an 11- to 16-fold excess. The pseudo-first-order rate constants, k_{obsd}, were obtained by monitoring the disappearance of the *N*-chloroacetanilide as a function of time. It was observed that if no phenol was present in the reaction medium, then k_{obsd} was zero. There are four reasonable modes by which a phenol might react with *N*-chloroacetanilide under the reaction conditions: (1) Reaction of phenol with *N*-chloroacetanilide. (2) Reaction of phenoxide with *N*-chloroacetanilide. (3) Reaction of phenol with protonated *N*-chloroacetanilide. (4) Reaction of phenoxide with protonated *N*-chloroacetanilide.

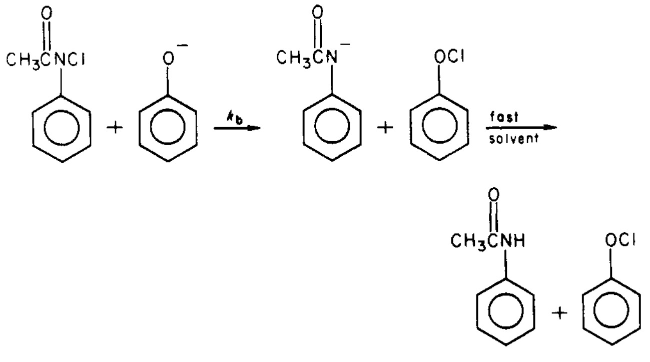
The gross structural changes and expressions for the apparent pseudo-first-order rate constant for each of these reactions, k_1–k_4, is shown in Schemes I–IV. In these reaction schemes, equilibrium constants are defined as K_{AE} = [phenoxide][H^+]/[phenol] and K_{BS} = [protonated *N*-chloroacetanilide]/[*N*-chloroacetanilide][H^+].

Scheme I[a]



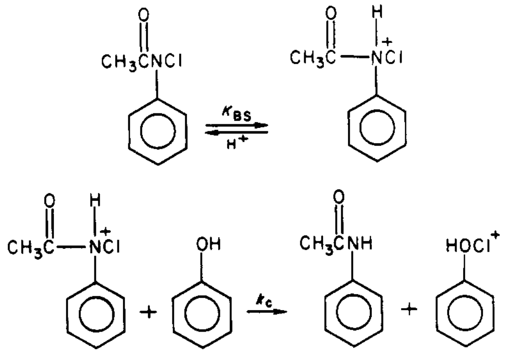
[a] $k_1 = k_a$[phenol].

Scheme II[a]



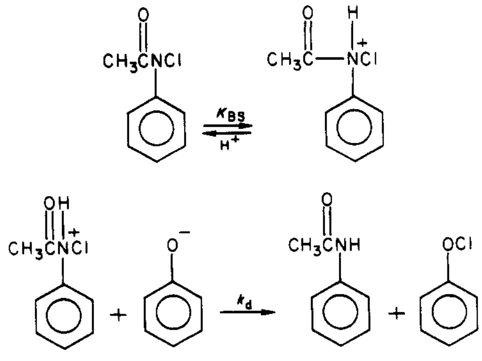
[a] $k_2 = k_b$[phenoxide].

Scheme III[a]



[a] $k_3 = k_cK_{BS}$[H^+][phenol].

Scheme IV[a]



[a] $k_4 = k_dK_{AE}K_{BS}$[phenol].

Mechanisms 1 and 4 have identical kinetic forms and cannot be distinguished kinetically. The pseudo-first-order rate constant, k_{obsd} for the disappearance of *N*-chloro-

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(1) (a) Earlham College. (b) New York University.

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Table I. A Summary of the Rate Constant for Reaction of Phenoxides with *N*-Chloroacetanilide (k_b), the pK_a of the Phenols, and σ^- and σ Values for the Substituents

substituent	pK_a[a] in water	pK_a[b] under reactions conditions	σ[c]	σ^-[a]	k_b, L mol^{-1} min^{-1}
p-CH_3	10.19	10.28 ± 0.11	0.16	0.16	$(1.09 \pm 0.07) \times 10^3$
none	9.95	9.81 ± 0.04	0.00	0.00	$(5.33 \pm 1.5) \times 10^2$
m-Cl	9.02	9.42 ± 0.13	0.37	0.37	$(3.58 \pm 1.14) \times 10^2$
m-NO_2	8.35	8.52 ± 0.11	0.74	0.74	(8.46 ± 1.3)
p-NO_2	7.14	7.13 ± 0.13	0.78	1.25	$(4.07 \pm 0.88) \times 10^{-1}$

[a] From ref 13. [b] 10% aqueous acetonitrile of ionic strength 1.350 M at 39.36 °C. [c] From ref 14.

acetanilide can be written as the sum of the k's for each individual process:

$$k_{obsd} = k_a[\text{phenol}] + k_b[\text{phenoxide}] + k_cK_{BS}[\text{phenol}][\text{H}^+] + k_dK_{AE}K_{BS}[\text{phenol}] \quad (1)$$

Rewriting eq 1 yields:

$$k_{obsd} = A[\text{phenol}] + B[\text{phenol}][\text{H}^+] + C[\text{phenoxide}] \quad (2)$$

where

$$A = k_a + K_{AE}K_{BS}k_d \qquad B = k_cK_{BS} \qquad C = k_b$$

The constants A, B, and C can be evaluated by using a multiparameter least-squares analysis since the terms k_{obsd}, [phenol], [H$^+$], and [phenoxide] are all experimentally obtainable. The phenol and phenoxide concentrations were determined by using the Henderson–Hasselbach equation, the measured pH, and the pK_as of the phenols determined under the experimental conditions.

Values for k_b, the rate constant for attack of phenoxide on unprotonated *N*-chloroacetanilide, the pK_as of the phenols, and σ and σ^- values for the substituents are given in Table I. The values for k_{obsd} and the specific reaction conditions for reaction of each phenol with *N*-chloroacetanilide are available as supplementary material.

Discussion

As expected, the plot of log k_b (Figure 1) correlated better with σ^- than with σ (correlation coefficient 0.982 compared with 0.904). This suggests that the attacking atom of the phenol is oxygen and not an aromatic carbon.[6] The oxygen-bound chlorine then presumably rearranges to the ring-chlorinated phenol. The only products that could be detected by HPLC when phenol was the nucleophile were ring-chlorinated phenols and acetanilide.

The Hammett ρ value for the reaction is −2.54 ± 0.35, indicating that the phenoxide undergoes substantial change in charge distribution on progressing from the starting material to the transition state. The Hammett ρ value for phenol dissociations was determined to be 2.80 ± 0.18 by using the pK_as obtained under the reaction conditions.[7] The large ρ value for this reaction is consistent with our earlier observation[5] from the reaction of various para- and meta-substituted *N*-chloroacetanilides with triethylamine, the nitrogen–chlorine bond is substantially broken in the transition state. Thus the transition state can be depicted as in 1, in which there is considerable chlorine–oxygen bonding and the majority of the charge has been transferred from oxygen to nitrogen.

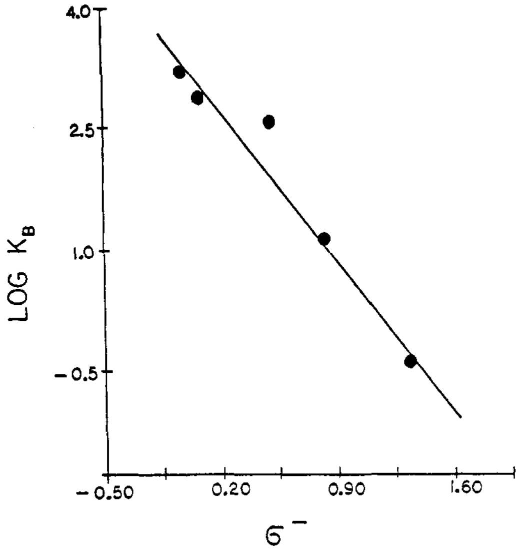
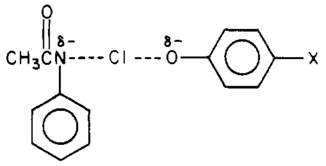


Figure 1. Plot of the logarithm of the second-order rate constant (k_b) for the reaction of various meta- and para-substituted phenoxides with *N*-chloroacetanilide vs. the substituent constant.



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The classical Brønsted plot of log k_b vs. the pK_a of the phenol nucleophiles is an alternate but equivalent measures of the sensitivity of the reaction to basicity. The slope B of this plot was 1.16 ± 0.11 (correlation coefficient 0.986). Brønsted values for reactions involving proton abstractions often have values between 0.0 and 1.0, the larger the B value the more the transition state resembles the products.[8] However, for reactions that do not involve proton transfers, B is frequently larger than 1.0.[9] A linear relationship between log k_b and the nucleophiles pK_a should be expected in this case since the nucleophiles all have similar structures.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. The pH measurements were made with an Altex Model 3500 digital pH meter equipped with a Corning Model 476051 combination electrode. The pH meter was standardized at the temperature of the reaction before each measurement by using pH 7.00 NBS standard. The pH of all kinetic runs was monitored at at least three well-chosen intervals during the reaction. The pH of each kinetic run remained constant within the accuracy of the measurements. The high-performance liquid chromatography system used to monitor the kinetics has been described previously.[5]

The monobasic and dibasic sodium phosphate used to prepare buffers was Baker Analyzed Reagent Grade of established purity.

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(6) If the attacking atom of the phenol had been an aromatic carbon, attack would have occured by the carbon ortho to the hydroxy group. Such attack would allow for the favorable resonance stabilization of the transition state by the hydroxy group. However, resonance stabilization of the transition state by substituents para to the hydroxy group would not be possible. Since these are the substituents whose σ and σ^- values are being used in the Hammett linear free-energy relationships, correlations would have been better with σ.

(7) Our ρ value of 2.80 for phenol dissociation may seem large considering the ρ value for aqueous phenol dissociation at 25 °C is 2.229 (see ref 10). However, ρ values can differ in magnitude depending on solvent and temperature (for example, see reaction 23 of Table I in: Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191).

(8) Chapman, N. B.; Shorter, J. "Correlation Analysis in Chemistry"; Plenum Press: New York, 1978; p 75.

(9) Grunwald, E.; Leffler, J. E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963.

Sodium perchlorate monohydrate was Fischer Purified (98%+) and for the purpose of ionic strength calculation was assumed to be 99% pure.

N-Chloroacetanilide [mp 91.0–92.0 °C (lit.[10] mp 91.0 °C)] was prepared as previously described.[5]

All phenols were commercially available. *p*-Nitrophenol and *m*-nitrophenol were recrystallized from benzene. *m*-Nitrophenol: mp 96.0–98.0 °C (lit.[11] mp 97 °C). *p*-Nitrophenol: mp 112.0–114.0 °C (lit.[11] mp 114.9 °C). Phenol: mp 41.5–43.5 °C (lit.[11] mp 43 °C). All phenols showed only one peak by HPLC analysis under conditions identical with those used in kinetic runs.[12]

Kinetics were monitored under pseudo-first-order conditions with phenol in at least an 11-fold excess. All kinetic runs were monitored to greater than 85% reaction with 10–20 data points being obtained for each run. The pseudo-first-order rate constant, k_{obsd}, for each phenol was evaluated at several different pHs between 5.4 and 7.3. For each reaction two stock solutions were made, one that was 0.500 M in monobasic sodium phosphate and the other 0.500 M in dibasic sodium phosphate. The ionic strength of both buffers was maintained at 1.500 M by adding appropriate amounts of sodium perchlorate monohydrate. Two phenol stock solutions were accurately made of approximately 1.0 M and approximately 0.6 M in acetonitrile. Both phenol stock solutions contained nitrobenzene as an internal standard. The desired pH was obtained by mixing appropriate volumes of the stock buffer solutions. To 9.0 mL of a buffer solution was added 1.0 mL of the phenol solution. The test tube was covered, shaken, and placed in a constant-temperature bath at 39.36 ± 0.005 °C. After thermal equilibration approximately 0.01 g (6.0×10^{-3} mol) of solid *N*-chloroacetanilide was added to initiate the reaction. The test tube was sealed, shaken, and returned to the constant-temperature bath. Aliquots of the reaction mixture were withdrawn periodically and injected on to the HLPC in order to obtain the concentration of *N*-chloroacetanilide as a function of time. The pseudo-first-order rate constants, k_{obsd}, were obtained from the equation

$$\ln [H_0/(H_t - H_\infty)] = k_{\text{obsd}}$$

where H_0 = initial HPLC peak height of *N*-chloroacetanilide, H_t = peak height at time t, and H_∞ = peak height at t_∞.

The pK_a of substituted phenols at 39.36 °C under the reaction conditions was determined by adding a known volume of 0.0858 M sodium hydroxide in 10% aqueous acetonitrile at an ionic strength of 1.350 M (sodium perchlorate monohydrate added as necessary) to 2.0 mL of an accurately weighed phenol solution (approximately 0.1 M) dissolved in 10% aqueous acetonitrile of ionic strength 1.350 M. The sodium hydroxide was standardized according to accepted procedure by titration of standard-grade potassium acid phthalate.

The pH of the phenol solution was determined after each addition of sodium hydroxide. (The pH of a given solution when measured 5 times had an average error of ±0.06 pH unit.) The concentration of phenoxide and phenol were determined by knowing the total amount of phenol and the amount of sodium hydroxide added. The pK_a values were then determined by using the Henderson–Hasselbach equation. The pK_a was calculated from the average of at least five measurements determined at different phenoxide/phenol ratios. The phenoxide/phenol ratio was varied from approximately 0.2 to 2.0 for each phenol.

In order to examine the products from the reaction of phenol with *N*-chloroacetanilide the reaction was repeated on a larger scale by doubling all reagents. The reaction was allowed to proceed for at least 10 half-lifes. The reaction mixture was cooled to room temperature and acidified with 30% H_2SO_4 and extracted twice with ethyl ether (40 mL). The ether layer was washed twice with 10% NaOH to remove any phenols. The ether layer was dried ($MgSO_4$) and removed under reduced pressure. The residue was dissolved in 20 mL of methanol and injected on the HPLC by using conditions identical with those used in a kinetic experiment.[12] Only one peak could be detected corresponding to acetanilide.

The aqueous layer was acidified with 10% H_2SO_4 and extracted twice with ethyl ether (50 mL). The ether layer was dried ($MgSO_4$) and removed under reduced pressure. The solid residue was dissolved in 20 mL of methanol and injected on the HPLC under identical conditions with those used in a kinetic run.[12] One large peak was detected corresponding to phenol and two smaller peaks that corresponded to the ortho- and para-chlorinated phenols. Also two very small peaks were detected that were identified as the *o*- and *p*-hydroxyacetanilides. HPLC peaks were identified by comparison of retention times with authentic samples and by spiking the extracted samples with authentic samples.

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Registry No. *N*-Chloroacetanilide, 579-11-3; *p*-methyl phenoxide, 22113-51-5; phenoxide, 3229-70-7; *m*-chlorophenoxide, 18938-14-2; *m*-nitrophenoxide, 16554-54-4; *p*-nitrophenoxide, 14609-74-6.

Supplementary Material Available: Summary of the specific reaction conditions and pseudo-first-order rate constants, k_{obsd}, for the reaction of various substituted phenols with *N*-chloroacetanilide and a summary of the HPLC conditions used to monitor the reaction rates of various phenols with *N*-chloroacetanilide (2 pages). Ordering information can be found on any current masthead page.

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New Procedures for Preparation of Potassium 3-Aminopropylamide

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Potassium 3-aminopropylamide, KAPA, is well-known as an efficient reagent in isomerizing internal acetylenes to the terminal position.[1] KAPA has been used in the synthesis of pheromones[2] and fatty acids.[3] The reagent was first prepared by C. A. Brown,[1] from 1,3-propanediamine and potassium hydride. The main disadvantages of using potassium hydride are that it is hazardous,[4] is expensive, and has a short shelf stability. An alternative route was developed by Brandsma,[4] who reacted potassium amide made in liquid ammonia with 1,3-propanediamine at 80 °C. Since we frequently employ KAPA for synthesis of pheromone analogues, it was essential to develop an alternative route. We report herein a direct, safe, and cheap procedure.

In preliminary experiments it was found that no reaction took place when molten potassium was stirred in 1,3-propanediamine for 2 h at 80 °C, perhaps due to its lack of solubility in amines.[5] Since potassium does dissolve

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